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Manual of Cardiovascular Medicine



FIFTH EDITION

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CONTENTS

Preface xv
Contributors xvii

SECTION I

Ischemic Heart Disease 1
Editor: Venu Menon

1 Acute Myocardial Infarction 2
Michael J. Johnson, Venu Menon

2 Non–ST-Segment Elevation Acute Coronary Syndrome 27
Bhuvnesh Aggarwal, Venu Menon

3 Complications of Acute Myocardial Infarction 42
Samuel E. Horr, Venu Menon

4 Cardiogenic Shock Complicating Acute Myocardial Infarction 55
Jayendrakumar S. Patel, Venu Menon

5 Post–Myocardial Infarction Risk Stratification and Management 62
Terence Hill, Venu Menon

6 Stable Angina 71
Jimmy L. Kerrigan, Venu Menon

7 Other Ischemic Syndromes: Silent Ischemia, Microvascular Angina, and Stress Cardiomyopathy 90
Chetan P. Huded

SECTION II

Heart Failure and Transplant 97
Editor: W.H. Wilson Tang

8 Heart Failure with Systolic Dysfunction 98
Julie L. Rosenthal, W. H. Wilson Tang

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9 Heart Failure with Preserved Ejection Fraction and Restrictive Cardiomyopathy 120
Antonio L. Perez, W. H. Wilson Tang

10 Hypertrophic Cardiomyopathy 130
Albree Tower-Rader, Milind Desai

11 Myocarditis 142
Nael Hawwa, W. H. Wilson Tang

12 Nontransplantation Surgical Treatment for Chronic Heart Failure and Durable Mechanical Circulatory Support 152
Forum Kamdar, Nader Moazami, Mazen Hanna

13 Cardiac Transplantation 164
Julie L. Rosenthal

14 Pulmonary Hypertension 184
Kenneth D. Varian, Miriam Jacob, W. H. Wilson Tang

SECTION III

Valvular Heart Disease 195
Editor: Brian P. Griffin

15 Aortic Valve Disease 196
James L. Gentry III

16 Mitral Valve Disease 223
Serge C. Harb, Brian P. Griffin

17 Tricuspid Valve Disease, Pulmonary Valve Disease, and Drug-Induced Valve Disease 251
Sneha Vakamudi, Brian P. Griffin

18 Prosthetic Heart Valves 263
Paul C. Cremer

19 Infective Endocarditis 279
Sneha Vakamudi, Brian P. Griffin

20 Rheumatic Fever 296
Rayji S. Tsutsui, Brian P. Griffin

Copyrighted Material

SECTION IV

Arrhythmias 305
Editor: Thomas D. Callahan

21 Tachyarrhythmias 306
Todd Senn

22 Bradyarrhythmias, Atrioventricular Block, Asystole, and Pulseless Electrical Activity 336
Erich L. Kiehl

23 Sudden Cardiac Death 355
Chonyang L. Albert

24 Atrial Fibrillation 366
Newton B. Wiggins, Thomas D. Callahan

SECTION V

Vascular Disease 375
Editor: Esther S. H. Kim

25 Venous Thromboembolism and Hypercoagulable States 376
Donald Clark III

26 Aortic Aneurysm and Aortic Dissection 389
Bhuvnesh Aggarwal, Maran Thamilarasan

27A Peripheral Arterial Disease 407
Joseph Campbell

27B Carotid Artery Disease 419
Joseph Campbell

SECTION VI

Adult Congenital Heart Disease 433
Editor: David Majdalany

28 Atrial Septal Defect and Patent Foramen Ovale 434
Jayendrakumar S. Patel, David Majdalany

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29 Ventricular Septal Defect 443
Baran Aksut, David Majdalany

30 Patent Ductus Arteriosus and Coarctation of the Aorta 449
Khendi White Solaru, David Majdalany

31 Complex Congenital Heart Disease 459
Baran Aksut, David Majdalany

SECTION VII

Clinical Cardiology 477
Editor: Brian P. Griffin

32 Syncope 478
Aldo L. Schenone, Brian P. Griffin

33 Assessing and Managing Cardiac Risk in Noncardiac Surgical Procedures 490
Donald Clark III

34 Hypertensive Crisis 498
Jeffrey Rossi

35 Cardiac Trauma 510
Jeffrey Rossi

36 Cardiovascular Manifestations of Systemic Disease 515
Kenneth D. Varian, Brian P. Griffin

37 Pericardial Disease 523
Aldo L. Schenone, Amav Kumar, Allan Klein

38 Cardiac Tumors 546
Serge C. Harb, Brian P. Griffin

39 Common Genetic Issues in Cardiovascular Disease 555
Mary T. Quinn Griffin

40 Heart Disease in Women 572
Ann Gage, Leslie Cho, Russell Raymond

41 The Athlete's Heart 595
Philip Aagaard, Dermot Phelan

SECTION VIII

Preventive Cardiology 607
Editor: Leslie Cho

42 Dyslipidemia 608
Mohamed B. Elshazly, Leslie Cho

43 Nonlipid Cardiovascular Risk Factors 627
Donald Clark III

44 Diabetes and the Heart 639
Khendi White Solaru, Haitham Ahmed, Venu Menon

SECTION IX

Noninvasive Assessment 655
Editor: Brian P. Griffin

45 Exercise Electrocardiographic Testing 656
Rayji S. Tsutsui

46 Nuclear Cardiac Imaging 675
Brett W. Sperry, Wael A. Jaber

47 Stress Echocardiography 692
Jimmy L. Kerrigan

48 Testing for Myocardial Viability 707
Terence Hill, Patrick Collier

49 Cardiovascular Computed Tomography Including Calcium Scoring 714
Bo Xu, Christine Jellis

50 Cardiovascular Magnetic Resonance Imaging 726
Serge C. Harb

SECTION X

Electrophysiologic Procedures 737
Editor: Thomas D. Callahan

51 Electrophysiologic Studies 738
Newton B. Wiggins, Thomas D. Callahan

52 Cardiac Resynchronization Therapy 763
Mohamed B. Elshazly, John Rickard

53 Cardiac Pacing 771
Joseph M. Bumgarner

54 Antitachycardia Devices 796
Joseph M. Bumgarner

55 Catheter Ablation 804
Corey M. Coleman, Thomas D. Callahan

SECTION XI

Common Cardiology Procedures 819
Editors: Brian P. Griffin, Thomas D. Callahan, Venu Menon

56 Common ECG Patterns 820
Salim H. Ahmed, Thomas D. Callahan, Chetan P. Huded, Donald Underwood

57 Temporary Cardiac Pacing 851
Erich L. Kiehl, Bryan J. Baranowski

58 Electrical Cardioversion 855
Corey M. Coleman

59 Right Heart Catheterization 862
Grant W. Reed, Venugopal Menon

60 Endomyocardial Biopsy 877
Antonio L. Perez, W. H. Wilson Tang

61 Short-Term Mechanical Circulatory Support Devices 881
Grant W. Reed, Forum Kamdar, Maria Mountis, Amar Krishnaswamy

62 Left Heart Catheterization 905
Samuel E. Horr, Amar Krishnaswamy

63 Percutaneous Coronary Intervention 927
Daniel M. Shivapour, Amar Krishnaswamy, Samir R. Kapadia

64 Percutaneous Structural Heart Disease Procedures 949
Michael J. Johnson, Amar Krishnaswamy

65 Transthoracic Echocardiography 962
Albree Tower-Rader

66 Transesophageal Echocardiography 985
Jorge Betancor, Maran Thamilarasan

67 Pericardiocentesis 999
Carlos L. Alviar, Brian P. Griffin

68 Commonly Used Cardiovascular Formulae 1007
Willis M. Wu, Brian P. Griffin

Index 1013

CHAPTER 1

Acute Myocardial Infarction

Michael J. Johnson
Venu Menon

I. **EPIDEMIOLOGY.** Acute myocardial infarction (MI) is the leading cause of death in North America and Europe. Each year, an estimated 650,000 Americans will sustain a new MI, and another 300,000 will have a recurrent MI. Coronary artery disease is the leading cause of death in the United States and has been for the past 90 years. However, the incidence of and mortality associated with acute MI have declined dramatically over the last 30 years with the advent of the coronary care unit, fibrinolytic therapy, catheter-based reperfusion, and lipid-modifying therapy. The aging of the population in advanced economies and the global increased incidence of diabetes and obesity will, however, increase the burden of atherosclerotic coronary artery disease in the future.

II. **PATHOPHYSIOLOGY.** In most patients, coronary plaque rupture is the initiating event of acute MI. **Rupture of the thin fibrous cap of a coronary atheroma exposes the underlying subendothelial matrix to formed elements of circulating blood, leading to activation of platelets, thrombin generation, and thrombus formation.** Erosion of a coronary plaque without rupture can also lead to thrombus formation and is estimated to cause up to 25% of MIs. Acute coronary syndrome (ACS) is a dynamic process that involves cyclical transitioning among complete vessel occlusion, partial vessel occlusion, and reperfusion. Occlusive thrombus in the absence of significant collateral vessels most often results in acute ST-segment elevation myocardial infarction (STEMI). The pathophysiology of STEMI and non-STEMI (NSTEMI) is similar, and this explains the substantial overlap in ACSs with regard to ultimate outcome, extent of necrosis, and mortality rates. The recognition of ST-segment elevation is particularly important because it generally mandates the need for emergent reperfusion therapy.

III. **DEFINITION.** A 2012 expert consensus document defined acute MI as evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. This concept was further described as the detection of **a rise and/or fall in cardiac troponin (cTn) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of ischemia**. Ischemia was defined as any symptom supportive of ischemia, electrocardiographic changes suggestive of new ischemia, development of pathologic Q-waves on electrocardiogram (ECG), and imaging evidence of infarction or identification of an intracoronary thrombus on angiography or autopsy. Included in the definition were sudden cardiac death (SCD) with evidence of myocardial ischemia (new ST-elevation, left bundle branch block [LBBB], or coronary thrombus), documented stent thrombosis by angiography or autopsy, and biomarker elevation >5×

URL for post–percutaneous coronary intervention (PCI) patients with normal baseline values or a rise of >20% if baseline values are stable or falling and biomarker elevation >10× URL for post–coronary artery bypass grafting (post-CABG) patients (Table 1.1). Established MI was defined as any one criterion that satisfies the following: development of new pathologic Q-waves on ECG with or without symptoms in the absence of nonischemic causes, imaging evidence of MI, or pathologic findings of healed or healing MI.

TABLE 1.1 Clinical Classification of Different Types of MI

Type 1	Spontaneous MI related to ischemia from a coronary plaque rupture, erosion, or dissect
Type 2	MI because of ischemia resulting from increased oxygen demand or decreased supply
Type 3	SCD with symptoms of ischemia, new ST-elevation, or LBBB, but biomarkers are unava
Type 4a	MI associated with PCI
Type 4b	MI associated with stent thrombosis
Type 5	MI associated with CABG

IV. CABG, coronary artery bypass grafting; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCD, sudden cardiac death.

V. Adapted from Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation.* 2012;126(16):2020–2035; American Heart Association, Inc.

VI. CLINICAL DIAGNOSIS. In any patient with a clinical history of chest pain suspected to be of cardiac origin, an ECG should be promptly obtained. Ideally, this should be within 10 minutes of presentation to an emergency room or outpatient center or first medical contact and interpreted promptly to determine eligibility for reperfusion therapy. If the **ECG demonstrates acute ST-segment elevation or new LBBB, emergent reperfusion treatment with primary PCI or fibrinolysis is indicated**. During this evaluation period, a targeted medical history and physical examination should be performed. If the patient's history is compatible with cardiac ischemia and the ECG does not meet the criteria for emergent reperfusion therapy, the patient may have unstable angina or NSTEMI. These syndromes are discussed in Chapter 2.

A. Signs and symptoms

1. The classic symptoms of an acute MI is characterized by severe, **crushing substernal chest pain** described as a squeezing or constricting sensation with frequent radiation to the left arm, often associated with an impending sense of doom. The discomfort is similar to that of angina pectoris, but it is typically more severe, of longer duration (usually >20 minutes), and is not relieved with rest or nitroglycerin. Peak intensity is usually gradual and not instantaneous, as it would be with other cardiac emergencies like a pulmonary embolism (PE) or acute aortic syndrome.

a. The chest discomfort may radiate to the neck, jaw, back, shoulder, right arm, and epigastrium. Pain in any of these locations without chest pain is possible. Myocardial ischemic pain localized to the epigastrium is often misdiagnosed as indigestion. Symptoms may be atypical in the elderly, in women, and in patients with diabetes mellitus.

b. If the pain is sudden, radiates to the back, and is described as tearing or knifelike, aortic dissection should be considered.

2. Associated symptoms may include diaphoresis, dyspnea, fatigue, lightheadedness, palpitations, acute confusion, indigestion, nausea, or vomiting. Gastrointestinal symptoms are especially common with inferior infarction. Ischemic chest pain rarely radiates below the umbilicus.

B. Physical examination. Although the physical examination does not add much to the diagnosis of acute MI, the presence of heart failure on examination identifies patients at heightened clinical risk. The examination is also extremely important in excluding other diagnoses that may mimic acute MI, in risk stratification, and in serving as a baseline examination to monitor for mechanical complications of acute MI that may develop. The **mechanical complications** of papillary muscle rupture with acute mitral regurgitation and ventricular septal defect are often heralded by a new systolic murmur (see Chapter 3). Early diagnosis of these complications relies on well-documented examination findings at baseline and during the hospital course.

VII. DIFFERENTIAL DIAGNOSIS.

The differential diagnosis of ST-elevation on a surface ECG includes conditions with comorbid ischemia such as acute aortic dissection involving the root, conditions with ST-elevation but no ischemia such as left ventricular (LV) hypertrophy or early repolarization abnormality, and conditions with chest pain but no ischemia such as myopericarditis (Table 1.2). The most common differential diagnostic considerations are discussed in the following text.

TABLE 1.2 Differential Diagnostic Considerations for STEMI

Comorbid Ischemia	ST-Elevation but No Ischemia	Ches
Aortic dissection	Early repolarization	Aorti
Stress cardiomyopathy	LV hypertrophy	Stres
Systemic arterial embolism	LBBB	Myop
Hypertensive crisis	Hyperkalemia	Pleur
Aortic stenosis	Brugada syndrome	PE
Cocaine use		Costo
Arteritis		Gastr

VIII. LBBB, left bundle branch block; LV, left ventricular; PE, pulmonary embolism; STEMI, ST-segment elevation myocardial infarction.

IX. Adapted with permission from Christofferson RD. Acute ST-elevation myocardial infarction. In: Shishehbor MH, Wang TH, Askari AT, et al, eds. *Management of the Patient in the Coronary Care Unit*. New York, NY: Lippincott Williams & Wilkins; 2008.

A. Pericarditis. Chest pain that is worse when the person is supine and improves when the person is sitting upright or slightly forward is typical of pericarditis. Care must be taken in excluding acute MI, however, because pericarditis can complicate acute MI. The electrocardiographic abnormalities of acute pericarditis may also be confused with acute MI. Diffuse ST-segment elevation is the hallmark of acute pericarditis, but this finding may be

seen in acute MI that involves the left main coronary artery or a large "wraparound" left anterior descending artery. PR-segment depression, peaked T-waves, or electrocardiographic abnormalities out of proportion to the clinical scenario may favor the diagnosis of pericarditis. The ST-segment elevations in pericarditis are often concave, whereas the ST-segment elevations in acute MI are usually convex. Reciprocal ST-depression does not occur in pericarditis, except in leads aVR and V_1. Early T-wave inversion is not a feature of acute pericarditis. Echocardiography may be useful, not in evaluating for pericardial effusion, which may occur in either condition, but in documenting the lack of regional wall motion abnormalities in a coronary distribution in the setting of ongoing pain and ST-elevation.

B. **Myocarditis.** As with pericarditis, the symptoms and electrocardiographic findings of myocarditis may be similar to those of acute MI. Echocardiography is less useful in differentiating this syndrome from acute MI, because segmental LV dysfunction may be encountered in either condition. With myocarditis, a complete history may reveal a more insidious onset and an associated viral syndrome. The diagnosis of myocarditis can be confirmed with cardiac magnetic resonance imaging (MRI) with gadolinium. A patchy distribution of delayed hyperenhancement in the epicardium and mid-myocardium with sparing of the endocardium is the characteristic MRI finding with myocarditis.

C. **Stress cardiomyopathy (Takotsubo).** Following an acute emotional or physical stress, patients may present with typical chest pain, ischemic ECG changes, a mild troponin elevation and new onset, transient regional LV wall motion abnormalities. In **the absence of obstructive epicardial coronary artery disease, this clinical presentation may be explained by a stress-induced cardiomyopathy**. The presenting signs and symptoms of this syndrome can be identical to an acute MI, making stress cardiomyopathy a diagnosis of exclusion. Stress cardiomyopathy is also called apical ballooning syndrome as the regional wall motion abnormalities tend to preferentially affect the apex while sparing the basal and mid-ventricular segments, although many other variants have been described. The term "takotsubo" comes from the Japanese word for "octopus pot" as the apical ballooning as seen on imaging represents the shape of this octopus trap. Stress cardiomyopathy occurs most commonly in women and in older adults. In addition to an ECG and an echo, the evaluation of stress-induced cardiomyopathy generally requires coronary angiography to document the absence of obstructive coronary artery disease. The LV wall motion usually but not invariably returns to normal over time and recurrence may occur following another stressful event.

D. **Acute aortic dissection.** Sharp, tearing chest pain that radiates through the chest to the back is typical of aortic dissection. Chest pain with new neurologic deficits or symptoms may also be a presenting sign of an aortic dissection with both coronary and carotid involvement. This type of chest pain pattern should be investigated thoroughly before administration of antithrombotic, antiplatelet, or fibrinolytic therapy. Proximal extension of the dissection into either coronary ostium can account for acute MI. A chest radiograph may reveal a widened mediastinum. Transthoracic echocardiography (TTE) may reveal a dissection flap in the proximal ascending aorta. If aortic dissection is suspected, a computerized tomography (CT) scan of the chest with contrast should promptly be obtained. In the presence of acute renal failure or if CT is unavailable, transesophageal echocardiography is an alternative imaging modality to evaluate for aortic dissection.

E. **PE.** Shortness of breath associated with pleuritic chest pain but without evidence of pulmonary edema is suggestive of PE. Echocardiography helps to rule out wall motion

abnormalities and may identify right ventricular (RV) dilatation and dysfunction in the setting of PE. A clot in transit may rarely be seen on TTE. In the absence of renal dysfunction, a CT PE protocol helps confirm the diagnosis.

F. Esophageal disorders. Gastroesophageal reflux disease, esophageal motility disorders, and esophageal hyperalgesia can cause chest pain, the character of which can mimic cardiac ischemic pain. These disorders can often coexist in patients with coronary disease, thereby complicating the diagnosis. A workup for coronary disease should precede evaluation of esophageal disorders. Symptoms that may be suggestive but not diagnostic of chest pain of an esophageal origin include postprandial symptoms, relief with antacids, and a lack of radiation of the pain.

G. Acute cholecystitis can occasionally mimic the symptoms and ECG findings of inferior acute MI, but rarely can the two coexist. Tenderness in the right upper quadrant, fever, and an elevated leukocyte count favor cholecystitis. Confirmatory imaging should be obtained if acute cholecystitis is suspected.

H. Brugada syndrome. In this setting, a genetic defect in myocardial sodium channels predisposes patients to ventricular fibrillation and SCD. Patients with Brugada do not typically present with acute chest pain, but may present with SCD. Twelve lead ECG may show a pseudo-right bundle branch block (RBBB) pattern and ST-elevation in V_1–V_2, typical findings for type 1 Brugada pattern. The mechanism of SCD in Brugada is not intracoronary thrombus, but believed to be secondary to the altered sodium channels and variability in refractory periods in adjacent myocardium.

X. LABORATORY EXAMINATION (FIG. 1.1)

A. Cardiac troponin. Both fourth-generation and high-sensitivity troponin T and troponin I assays are particularly useful in the diagnosis and management of non–ST-elevation ACS because of their high sensitivity to detect myocardial injury. In the setting of ST-elevation on ECG, waiting for confirmatory testing with cTn is not indicated. A single troponin fourth-generation T concentration measured 72 hours after acute MI may be predictive of MI size, independent of reperfusion. Troponin elevation in the absence of ischemic heart disease can be found in a number of clinical settings including congestive heart failure (CHF), aortic dissection, hypertrophic cardiomyopathy, PE, acute neurologic disease, cardiac contusion, or drug toxicity.

B. High-sensitivity cardiac troponin (hs-cTn). Recently approved in the United States, the development of hs-cTn has increased our ability to detect myocardial injury early and accurately. By definition, hs-cTn must be able to detect concentrations below the 99th percentile above the assay's lower limit of detection for more than 50% of healthy population and should have a coefficient of variance of <10% at the 99th percentile value. Hs-cTn assays are, however, best utilized to rapidly and reliably rule out myocardial ischemia, especially in patients presenting acutely with chest pain because of the test's high negative predictive value. If the initial hs-cTn value is negative, a second value can be measured as early as 1 to 3 hours without compromising sensitivity or negative predictive value. The shortened time interval to a second biomarker measurement can translate into a more rapid rule out for acute MI and shorten emergency room stays for patients presenting with suspected acute chest pain.

C. **Creatine kinase and creatine kinase myocardial band (CK and CK-MB).** An elevated level of CK and CK-MB is rarely helpful in making the diagnosis of acute MI for a patient with ST-segment elevation, and both assays are now of historical significance. All major societal guidelines recommend the use of cTn over both CK and CK-MB as the preferred marker of myocardial injury. Because it usually takes 4 to 6 hours to see an appreciable rise in CK levels, an initial normal value does not exclude recent complete occlusion. **CK levels remain helpful in gauging the size and timing of acute MI.** CK levels peak at 24 hours, but early peaking is noted among patients who undergo successful reperfusion of the infarct-related artery. The presence of a positive CK, CK-MB assay in the setting of negative troponin almost certainly indicates a noncardiac source, including skeletal muscle disease or trauma (e.g., rhabdomyolysis).

FIGURE 1.1 Timing of biomarker release after acute myocardial infarction. AMI, acute myocardial infarction; CK, creatine kinase; CK-MB, creatine kinase myocardial band; CV, coefficient of variation; MI, myocardial infarction. (Reprinted from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction—executive summary. *J Am Coll Cardiol*. 2007;50(7):652–726. Copyright © 2007 American College of Cardiology Foundation and the American Heart Association, Inc. With permission.)

XI. DIAGNOSTIC TESTING

A. Electrocardiography

1. **Definitive electrocardiographic diagnosis** of acute MI requires ST-elevation of 1 mm or more in two or more contiguous leads, often with reciprocal ST-depression in the contralateral leads. In leads V_2–V_3, ST-elevation of at least 2 mm in men ≥40 years, 2.5 mm in men <40 years, and 1.5 mm in women are required for accurate diagnosis.

2. **ECG subsets.** ST-segment elevations can be divided into subgroups that may be correlated with the infarction-related artery and risk of death. These five subgroups are listed in Table 1.3 and illustrated in Figure 1.2.

TABLE 1.3 Acute MI: ECG Subsets and Correlated Infarct-Related Artery and Mortality

Category	Anatomy of Occlusion	ECG Findings
1. Proximal LAD	Proximal to first septal perforator	ST ↑ V_1–V_6, I, aVL, and fascicular or bundle branch block
2. Mid-LAD	Proximal to large diagonal but distal to first septal perforator	ST ↑ V_1–V_6, I, aVL
3. Distal LAD or diagonal	Distal to large diagonal or diagonal itself	ST ↑ V_1–V_4, or I, aVL, V_5, V_6
4. Moderate to large inferior (posterior, lateral, RV)	Proximal RCA or left circumflex	ST ↑ II, III, aVF, and any of the following: (a) V_1, V_3R, V_4R; (b) V_5, V_6; (c) R > S in V_1, V_2

TABLE 1.3 Acute MI: ECG Subsets and Correlated Infarct-Related Artery and Mortality

5. Small inferior	Distal RCA or left circumflex branch	ST ↑ II, III, aVF only

3. ECG, electrocardiogram; LAD, left anterior descending (coronary artery); MI, myocardial infarction; RCA, right coronary artery; RV, right ventricular; ↑, increased.

4. [a] Mortality rate based on GUSTO I cohort population in each of the 5-year categories, all receiving reperfusion therapy.

5. Reprinted with permission from Topol EJ, Van de Werf FJ. Acute myocardial infarction: early diagnosis and management. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. 1st ed. New York, NY: Lippincott-Raven; 1998.

6. **FIGURE 1.2** Electrocardiographic subsets of acute myocardial infarction (MI). **A:** Large anterior MI with conduction disturbance (proximal left anterior descending [LAD] coronary artery). **B:** Anterior MI without conduction disturbance (mid-LAD). **C:** Lateral MI (distal LAD, diagonal branch, or left circumflex branch). **D:** Large inferior MI with reciprocal changes (proximal right coronary artery [RCA]). **E:** Small inferior MI (distal RCA). (Reprinted with permission from Topol EJ, Van de Werf FJ. Acute myocardial infarction: early diagnosis and management. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. 2nd ed. New York, NY: Lippincott-Raven; 2002.)

7. **Left bundle branch block**

a. **New LBBB in the setting of symptoms consistent with acute MI** may indicate a large, anterior wall, acute MI involving the proximal left anterior descending coronary artery and should be managed as acute STEMI.

b. **In the absence of an old ECG or in the presence of LBBB at baseline**, the diagnosis of acute STEMI can be made with >90% specificity on the basis of the criteria listed in Table 1.4 and illustrated in Figure 1.3.

c. **RBBB may** challenge interpretation of ST-elevation in leads V_1 through V_3. RBBB does not, however, obscure ST-segment elevation, and criteria for ST-elevation apply.

B. **Echocardiography** may be helpful in the evaluation of LBBB of undetermined duration in that the lack of regional wall motion abnormality in the presence of continuing symptoms makes the diagnosis of acute MI unlikely. It is worth noting that abnormal septal motion is often observed in the setting of LBBB even in the absence of ischemia. Echo may also be useful in detecting extensive wall motion abnormalities in the posterior circulation when the presenting electrocardiogram (EKG) is normal or reveal ST-depression consistent with the presence of a true posterior infarction.

XII. RISK STRATIFICATION. Early risk stratification in patients with acute MI is crucial, especially in those being considered for fibrinolysis, because the risks of therapy must be weighed against the potential benefits. Five simple baseline parameters have been reported to account for >90% of the prognostic information for 30-day mortality. These characteristics are given in descending order of importance: age, systolic blood pressure,

Killip classification (Table 1.5), heart rate, and location of MI (Table 1.3; Fig. 1.2). Timely, optimally performed primary PCI is the preferred reperfusion strategy for all patients with STEMI, but patients with evidence of acute heart failure or cardiogenic shock are especially well suited for treatment with primary PCI. In addition, various risk models have been created to improve risk prediction.

A. **The Global Registry of Acute Coronary Events score** is used to predict in-hospital mortality and postdischarge to 6-month mortality in all patients with ACS. Risk is calculated based on Killip class, heart rate, systolic blood pressure, serum creatinine, age, presence of cardiac arrest at admission, presence of cardiac biomarkers, and ST-segment deviation. Patients with a score of ≤60 have a ≤0.2% probability of in-hospital mortality, whereas patients with a score of ≥250 have a ≥52% probability of in-hospital mortality.

B. **The thrombolysis in myocardial infarction (TIMI) risk score** was developed in patients with ST-elevation who received fibrinolysis and incorporates eight variables obtained from the history, physical examination, and ECG (Table 1.6). In patients treated with fibrinolysis, a TIMI score of 9 or greater predicts a 30-day mortality of approximately 35%. In patients with a TIMI score of 0 or 1, the 30-day mortality rate is <2%. The strongest predictor of poor prognosis is advanced age (where age ≥75 years receives 3 points and age 65 to 74 years receives 2 points). Other variables that predict a poor prognosis include hypotension, Killip class II–IV at presentation, tachycardia, history of diabetes or hypertension, anterior ST-elevation (also complete LBBB), low body weight, and a time to treatment of >4 hours.

TABLE 1.4 Electrocardiographic Criteria for the Diagnosis of Acute MI in the Presence of LBBB

Criterion
ST-segment elevation ≥ 1 mm concordant with QRS
ST-segment depression ≥ 1 mm in leads V_1, V_2, or V_3
ST-segment elevation ≥ 5 mm discordant with QRS

C. LBBB, left bundle branch block; MI, myocardial infarction.

D. [a] Point scores for each criterion met are added. Total point score of 3 yields ≥90% specificity and an 88% positive predictive value.

E. From Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. *N Engl J Med*. 1996;334:481–487. Copyright © 1996 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.

F. **FIGURE 1.3** Electrocardiogram displays all of the criteria for the diagnosis of acute myocardial infarction (MI) in the setting of left bundle branch block: ST-segment elevation > 1 mm, concordant with QRS in lead II (5 points); ST-segment depression > 1 mm in leads V_2 and V_3 (3 points); and ST-segment elevation > 5 mm, discordant with QRS in leads III and VF (2 points). A score of 10 points indicates an extremely high likelihood of inferior MI. (From Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic Diagnosis of Evolving Acute Myocardial Infarction in the Presence of Left Bundle-Branch Block. *N Engl*

J Med. 1996;334:481–487. Copyright © 1996 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

TABLE 1.5 30-Day Mortality Based on Hemodynamic (Killip) Class

Killip Class	Characteristics	Patients (%)	M
I	No evidence of CHF	85	5
II	Rales, ↑JVD, or S_3	13	1
III	Pulmonary edema	1	3
IV	Cardiogenic shock	1	5

G.CHF, congestive heart failure; ↑, increased; JVD, jugular venous distention; S_3, third heart sound.

H.Adapted with permission from Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation*. 1995;91(6):1659–1668.

XIII. THERAPY

A. Prior to reperfusion

1. **Aspirin.** Immediate administration of aspirin is indicated for all patients with suspected acute MI, unless there is a clear history of true aspirin allergy (not intolerance). Aspirin therapy conveys as much mortality benefit as streptokinase (SK) and the combination provides additive benefit. The dose should be four 81 mg chewable tablets (for more rapid absorption) or one 325 mg nonchewable tablet. If oral administration is not possible, a rectal suppository can be given. If true aspirin allergy is present, clopidogrel monotherapy is the best alternative.

2. **Oxygen.** The routine administration of supplemental oxygen via nasal cannula to all patients with suspected MI is no longer warranted as there is some emerging data regarding the deleterious effects of supplemental oxygen. Instead, arterial oxygen saturations should be checked in all patients and if <94%, oxygen therapy should be initiated. Supplemental oxygen should also be supplied to patients who are visibly cyanotic or are in respiratory distress. Administration through a face mask or endotracheal tube may be necessary for patients with severe pulmonary edema or cardiogenic shock.

TABLE 1.6 TIMI Risk Model for Prediction of Short-Term Mortality in STEMI Patients

History
Age 65–74 y
Age ≥ 75 y
Angina or DM/HTN
Physical Examination
HR > 100 beats/min
SBP < 100 mm Hg

TABLE 1.6 TIMI Risk Model for Prediction of Short-Term Mortality in STEMI Patients

Killip class II–IV
Weight < 67 kg
Presentation
Anterior ST-elevation or LBBB
Time to treatment > 4 h
TIMI risk score = Total points (0–14)

3.DM, diabetes mellitus; HR, heart rate; HTN, hypertension; LBBB, left bundle branch block; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

4.Adapted with permission from Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. 2000;102(17):2031–2037.

5. **Nitroglycerin.** Nitroglycerin can be useful in the management of acute MI complicated by heart failure, persistent chest pain, or hypertension. Nitroglycerin should not be administered to patients who are hypotensive, to patients in whom RV infarction is suspected, or to those with recent use of phosphodiesterase inhibitors (24 to 48 hours). Administration of sublingual nitroglycerin may also identify whether the ST-segment elevation represents coronary artery spasm while arrangements for reperfusion therapy are being initiated. A meta-analysis performed before the age of routine reperfusion suggested a mortality benefit with intravenous nitroglycerin, although routine use of oral nitrates after MI had no benefit in two large randomized trials in the modern era. A 30% reduction in systolic blood pressure can be expected with appropriately aggressive dosing (10 to 20 µg/min with 5 to 10 µg/min increases every 5 to 10 minutes). Intravenous therapy may be continued for up to 24 to 48 hours.

6. **Oral platelet $P2Y_{12}$ receptor antagonists** should be used routinely in all patients with STEMI, regardless of whether or not primary PCI is performed. Currently, the three agents available for treatment of STEMI are clopidogrel, prasugrel, and ticagrelor. Clopidogrel and prasugrel are thienopyridines that irreversibly inhibit the platelet adenosine diphosphate $P2Y_{12}$ receptor, and ticagrelor is a reversible direct inhibitor of this same receptor. In patients in whom PCI is planned, a loading dose should be given as early as possible or at the time of PCI. The Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction, or ATLANTIC, trial demonstrated that the administration of ticagrelor in the prehospital setting (ambulance) is safe, may prevent postprocedural acute stent thrombosis, but does not improve preprocedural coronary reperfusion. In contrast, the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction, or ACCOAST trial, studied the administration of prasugrel before or after diagnostic angiography in patients with NSTEMI. Pretreatment with prasugrel in these patients did not reduce major ischemic events within the first 30 days, but did increase the risk of bleeding. The recommended loading dose of clopidogrel is 600 mg. The recommended loading dose of prasugrel is 60 mg and ticagrelor is given as a 180 mg loading dose. The

absorption of prasugrel and ticagrelor may be significantly impaired in patients with STEMI. This may be overcome by crushing these tablets prior to administration for more rapid absorption. Current U.S. guidelines do not endorse one agent over another except in patients receiving fibrinolysis. In fibrinolysis patients, clopidogrel is the thienopyridine of choice, at a loading dose of 300 mg if the patient is ≤75 years and a loading dose of 75 mg if age >75 years. The duration of clopidogrel following fibrinolysis should be at least 14 days and ideally up to 12 months. The maintenance dose of clopidogrel and prasugrel is 75 mg daily and 10 mg daily, respectively. The maintenance dose for ticagrelor is 90 mg twice a day. It is currently recommended that clopidogrel and ticagrelor be held for 5 days and prasugrel be held for 7 days prior to CABG, unless the need for urgent revascularization outweighs the risk of potential excessive bleeding. Following CABG, dual antiplatelet therapy (DAPT) should be reintroduced and continued for at least a year in this setting (Class I). In patients with STEMI receiving DAPT following stent implantation, it is reasonable to use ticagrelor or prasugrel over clopidogrel for maintenance, especially in patients with diabetes. Prasugrel should, however, not be utilized in patients with a prior history of stroke or transient ischemic attack. The planned duration for DAPT following STEMI should be for 12 months (class I) at which point the risk and benefit for further continuation may be reassessed. For patients at recognized high risk for bleeding, discontinuation of DAPT at 6 months may be considered (class IIb).

7. **Intravenous platelet $P2Y_{12}$ receptor antagonists.** Cangrelor is the only available intravenous $P2Y_{12}$ inhibitor and binds reversibly to the receptor. Cangrelor is given as a 30 µg/kg IV bolus followed by an infusion of 4 µg/kg/min and provides potent platelet inhibition almost immediately (<2 minutes). The short plasma half-life of <5 minutes allows for near complete restoration of platelet function within 1 to 2 hours after stopping the infusion. The Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events, or CHAMPION PHOENIX Trial, showed that preprocedural cangrelor reduced ischemic events including stent thrombosis at 48 hours compared with a loading dose of clopidogrel in patients undergoing urgent or elective PCI. Cangrelor currently has a Food and Drug Administration indication for patients undergoing PCI who have not yet been treated with an oral $P2Y_{12}$ inhibitor and are not receiving glycoprotein (GP) IIb/IIIa inhibitors. This may be most effective in patients with extremely short door-to-balloon times because administration in this setting will ensure reliable platelet inhibition.

8. **Parenteral anticoagulants.** Unless there is a contraindication, all STEMI patients should receive intravenous antithrombotic therapy. Traditionally in patients who are undergoing primary PCI, this has been accomplished with unfractionated heparin (UFH). The dose of UFH is 70 to 100 U/kg as a bolus (maximum 4,000 U), followed by 12 U/kg/h infusion (maximum 1,000 U/h) to achieve a therapeutic activated clotting time (ACT). Routine administration of GP IIb/IIIa inhibitors is no longer warranted, but can be used as a bailout strategy in patients with a large thrombus burden, inadequate DAPT, loading or poor reflow. If GP IIb/IIIa inhibitors are used, the dose of UFH is reduced to 50 to 70 U/kg (maximum 4,000 units). The current guidelines allow for the use of bivalirudin, a direct thrombin inhibitor, as an alternative with or without prior administration of UFH. Bivalirudin is given as a 0.75 mg/kg intravenous bolus, followed by a 1.75 mg/kg/h infusion. Additional boluses of 0.3 mg/kg can be given to maintain therapeutic ACT. However, the recent How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention trial randomized patients scheduled for emergent angiography to receive upstream UFH or bivalirudin. The results of the trial demonstrated that the rate of major adverse cardiovascular events (all-cause mortality, stroke, reinfarction, or

unplanned target-lesion revascularization) was significantly lower in the UFH group (5.7%) versus the bivalirudin group (8.7%) with no difference in major bleeding at 28 days. Overall data suggest that the use of bivalirudin is associated with lower bleeding risk (this advantage is reduced by adopting radial access) in PCI STEMI while being associated with increased risk of ischemic complications, especially acute stent thrombosis. Enoxaparin and fondaparinux are alternative options in patients undergoing fibrinolysis, but fondaparinux is contraindicated in patients undergoing primary PCI because it has been associated with catheter thrombosis.

B. Reperfusion therapy. The primary goal in the management of acute MI is to institute reperfusion therapy as quickly as possible. All patients with ST-segment elevation or new LBBB MI who seek treatment within 12 to 24 hours from onset of continuous symptoms should be considered for immediate reperfusion therapy. Persistent ischemic symptoms after 12 hours may indicate a stuttering course of occlusion, spontaneous reperfusion, and reocclusion and may indicate potential continued benefit for early therapy.

1. **Benefit.** The benefit of reperfusion therapy has been well documented in the management of acute MI, regardless of age, gender, and most baseline characteristics. However, the patients who derive the most benefit are those treated earliest and those at highest risk, such as those with anterior MI.

2. **Time to treatment is paramount.** Although the current guidelines focus on door-to-balloon times, total ischemic time is the most important parameter. Patients treated in the first hour have the highest mortality benefit. **There is an inverse relationship between time to treatment and survival benefit**. This relationship appears more consistent with fibrinolytic therapy than with direct PCI. After 12 hours of continuous symptoms, there is little net benefit to pharmacologic reperfusion with fibrinolytics. The therapeutic window for PCI extends beyond that of fibrinolysis, but is not infinite. The Occluded Artery Trial (OAT) suggests that stenting of an occluded infarct-related artery >72 hours after the initial event is not associated with benefit and may be harmful. Currently, the American Heart Association (AHA) recommends against PCI of an occluded infarct-related artery >24 hours after STEMI if the patient is hemodynamically stable and does not have signs of severe ischemia.

3. **Fibrinolysis versus direct PCI.** After it has been determined that a patient is a candidate for reperfusion therapy, the decision to use fibrinolytic or direct PCI therapy must be made quickly. Optimally performed primary PCI is the preferred strategy in all patients who present with STEMI. Patients presenting with cardiogenic shock or those presenting late (>2 hours after symptom onset) are especially well suited for primary PCI, given the relative lack of efficacy of fibrinolysis in these settings. Pooled data from several large trials show a significant (22%) reduction in short-term mortality for patients treated with primary angioplasty. This benefit was durable because there were significant reductions in the incidence of death, nonfatal MI, and recurrent ischemia at long-term follow-up. PCI is also associated with a reduction in the incidence of intracerebral hemorrhage compared with fibrinolytic therapy.

a. If a patient presents to a PCI-capable facility, **a door-to-device time of 90 minutes or less is recommended.** If a patient presents to a non–PCI-capable hospital, immediate transfer to a PCI-capable one is recommended if the door-to-device time can be achieved within 120 minutes. If primary PCI or transfer for PCI cannot be performed within 120 minutes of presentation, fibrinolysis should be administered within 30 minutes assuming no contraindications to fibrinolysis (Table 1.7).

b. Several trials, including the Danish Multicenter Randomized Study on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI)-2, the Air-Primary Angioplasty in Myocardial Infarction, and the Primary Angioplasty in Patients Transferred from a General Community Hospital to Specialized PTCA Units, have investigated the benefit of on-site fibrinolysis compared with transfer to tertiary centers for direct PCI. These studies have found improved outcomes in patients randomized to a transfer strategy and direct PCI even after taking into account the increased time for patient transfer. For example, patients in DANAMI-2 randomized to transfer for PCI had a significantly lower 30-day incidence of death, MI, or stroke (8.5% vs. 14.3%; $p = 0.002$) despite a median time from randomization to balloon inflation of 112 minutes.

TABLE 1.7 Contraindications and Cautions for Use of Thrombolytic Agents to Manage MI

Absolute Contraindications
Previous hemorrhagic stroke at any time or ischemic stroke within 3 mo
Known intracranial neoplasm, structural cerebral vascular lesion, or closed head injury within 3 mo
Active bleeding or bleeding diathesis (excluding menses)
Suspected aortic dissection
Intracranial or intraspinal surgery within 2 mo
Severe uncontrolled hypertension, unresponsive to medical therapy
For SK, prior exposure within 6 mo
Relative Contraindications
Severe, uncontrolled hypertension at presentation (blood pressure > 180/110 mm Hg), or history of chroni
History of ischemic stroke > 3 mo, dementia, or known intracerebral pathologic condition not covered in co
Oral anticoagulant therapy
Traumatic or prolonged (>10 min) CPR or major surgery (<3 wk)
Noncompressible vascular punctures
Recent internal bleeding (2–4 wk)
Pregnancy
Active peptic ulcer

CPR, cardiopulmonary resuscitation; MI, myocardial infarction; SK, streptokinase.

Adapted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol*. 2004;44(3):E1–E211. Copyright © 2004 American College of Cardiology Foundation. With permission.

4. **Primary PCI.** Once the decision has been made to perform reperfusion with primary PCI, the patient should be moved to the cardiac catheterization laboratory and undergo angiography as rapidly as possible. After the culprit lesion has been identified, reperfusion should be achieved with standard PCI techniques.

a. **Radial approach:** The benefits of a radial over a femoral approach in STEMI have been noted in the Radial Versus Femoral Access for Coronary Intervention, Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome, and Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of angioX trials. Consequently, radial access should be the default approach when performing primary PCI as it is associated with decreased rates of access site bleeding, vascular complications, and need for blood transfusion and has been associated with an overall decrease in mortality.

b. **Culprit versus multivessel PCI:** Performing PCI on a flow-limiting lesion in a noninfarct artery in the setting of a hemodynamically stable STEMI was considered a contraindication in the recent past (class IIIb). Advances in pharmacology, stent technology, and safety of interventional procedures have led to a series of small randomized controlled trials (RCTs) that have shown both safety and superior clinical outcomes with a multivessel over culprit-alone strategy. Consequently, PCI of a noninfarct artery may now be considered in select patients either immediately following revascularization of the culprit lesion or in a staged manner later in the index hospitalization, or on an elective basis following discharge (class IIb). A number of clinical trials are currently underway that will clarify this matter further.

c. **Platelet GP IIb/IIIa inhibitors.** There is no current role for routine GP IIb/IIIa inhibitors in this setting. The historical efficacy of GP IIb/IIIa inhibitors was largely demonstrated in the era prior to potent DAPT. Three major trials have evaluated the efficacy of GP IIb/IIIa therapy in STEMI patients receiving oral DAPT: bavarian reperfusion alternatives evaluation-3 (BRAVE-3), ongoing tirofiban in myocardial infarction evaluation (On-TIME-2), and harmonizing outcomes with revascularization and stents in acute myocardial infarction (HORIZONS-AMI). These studies did not demonstrate benefit of the routine administration of GP IIb/IIIa inhibitors in addition to DAPT in patients with STEMI undergoing primary PCI. It remains reasonable to consider the utilization of GP IIb/IIIa therapy as a bailout strategy in the presence of large thrombus burden, slow or no reflow, or inadequate oral $P2Y_{12}$loading. The risk of bleeding is significantly increased with use of these agents but this can be significantly reduced by adopting radial access for the procedure. Abciximab, tirofiban, and eptifibatide are GP IIb/IIIa inhibitors currently available in the United States and are considered equivalent options.

d. **Thrombus aspiration.** Although thought to be useful mechanistically in small trials, two large randomized trials (Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction [TASTE] and the trial of routine aspiration thrombectomy with PCI versus PCI alone in patients with STEMI [TOTAL]) have failed to show any benefit with routine use of thrombus aspiration in patients with STEMI. Consequently, societal guidelines provide a class III recommendation against the routine use of aspiration thrombectomy, but do allow for its use as a bailout strategy if reperfusion cannot be successfully established with initial attempts.

e. **Distal embolic protection devices (EPDs)** have failed to show any benefit in multiple trials. These devices are not routinely recommended for acute PCI of native coronary arteries. If the culprit vessel is a saphenous vein bypass graft, an EPD should be used because it has been shown

to reduce a 30-day composite outcome of death, MI, emergency CABG, and target-lesion revascularization.

f. Coronary stenting. Primary PCI is the preferred modality for all patients presenting with STEMI. Historically, primary PCI was initially achieved with balloon angioplasty, but with the development of intracoronary stents, the use of balloon angioplasty is extremely limited in STEMI. Bare-metal stents (BMSs) were the first stents developed and reduced the high rates of acute closure and long-term restenosis associated with balloon angioplasty. The STENT-Primary Angioplasty in Myocardial Infarction study found that coronary stenting significantly reduced the need for target vessel revascularization at 6 months (7.7% vs. 17.0%; $p < 0.001$). These findings were confirmed in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial, which found that coronary stenting significantly reduced the incidence of restenosis at 6 months (40.8% vs. 22.2%; $p < 0.0001$), independent of abciximab use. BMS are also prone to in-stent restenosis (ISR), which led to the development of drug-eluting stents (DESs). DESs have antiproliferative agents attached to the struts that reduce neointimal hyperplasia and thus ISR. DESs have reduced the rates of long-term restenosis but they do require longer duration of DAPT because of concern for in-stent thrombosis. The placement of DES should be considered first-line therapy for all STEMI patients who are candidates for primary PCI unless they have a strong contraindication to or inability to comply with prolonged DAPT. New-generation DESs have proven superior to use of BMS in STEMI patients in the Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction as well as Everolimus-Eluting Stents versus Bare Metal Stents in ST Segment Myocardial Infarction trials mainly because of reduced reintervention rates.

5. Fibrinolysis

a. Fibrinolytic therapy. Fibrinolysis is considered a second-line option for patients presenting with STEMI when timely, optimally performed primary PCI is not available. In this context, it is worthwhile to review the data and clinical considerations associated with fibrinolysis. The lifesaving capability of early fibrinolytic therapy has been well established, beginning with the Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico (GISSI) 1 trial in 1986. Pooled data show a relative reduction in mortality of 18% and an absolute reduction of nearly 2%.

b. Contraindications. As discussed previously (Table 1.7), the only **absolute contraindications to fibrinolytic therapies are recent cerebrovascular accident (CVA), hemorrhagic CVA, intracranial neoplasm, active internal bleeding, and suspected aortic dissection**. The presence of one of these or one or more of the relative contraindications would favor PCI, even if it meant delaying reperfusion.

c. Choice of agent

1. **(1) Alteplase (tPA).** The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial I showed that use of accelerated tPA significantly reduced 30-day mortality rate by 15% relative to SK plus subcutaneous or intravenous heparin. This mortality reduction correlated with significantly higher rates of TIMI 3 flow at 90 minutes compared with SK (54% vs. 31%; $p < 0.001$). The benefit was seen across all subgroups, although the patients at highest risk derived the most benefit. The accelerated protocol consisted of an intravenous bolus dose of 15 mg followed by 0.75 mg/kg (up to 50 mg) over 30 minutes and then 0.5 mg/kg over 60 minutes. tPA is considered a fibrin-specific agent because of its relative selectivity for clot-bound fibrin. The use of continuous infusion fibrinolytics has been replaced by bolus-dosed fibrinolytics,

such as reteplase and tenecteplase, because of the ease of administration of bolus-dosed agents and a lower risk of medication error.

2. **(2) Reteplase.** The first of the third-generation fibrinolytic agents approved for use in the United States, reteplase is a less fibrin-specific mutation of tPA. Reteplase has a longer half-life than tPA and can be administered in a double bolus (10 mg each, 30 minutes apart). The GUSTO III trial showed no mortality benefit of reteplase over tPA, but its ease of use may help to reduce time to administration.
3. **(3) Tenecteplase (TNK)**, another third-generation fibrinolytic, is characterized by its improved fibrin specificity, enhanced resistance to plasminogen activator inhibitor 1, and decreased plasma clearance. These properties allow it to be administered as a single bolus and it is **the currently preferred agent**. The Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction 2 (ASSENT 2) trial found no mortality difference between TNK and tPA at 30 days. However, TNK was associated with significantly less noncerebral bleeding and improved mortality in patients treated for >4 hours after symptom onset. The weight-adjusted dose of TNK is 30 to 40 mg (ASSENT 1). The recent Strategic Reperfusion Early after Myocardial Infarction (STREAM) trial compared primary PCI to prehospital fibrinolysis with TNK in early presenting (within 3 hours) STEMI patients who were unable to undergo primary PCI within 1 hour of first medical contact. Prehospital fibrinolysis coupled with timely angiography was found to be an effective reperfusion strategy in this select group of patients with similar rates of the primary end point (composite of death, shock, CHF, and reinfarction up to 30 days) in both groups, but there was a slightly higher risk of intracranial bleeding associated with fibrinolysis.
4. **(4) SK** is no longer commercially available in the United States and is of historical significance. Because of the possible development of antibodies, SK should not be administered to a patient who has received it in the past. Because the overall rate of intracerebral hemorrhage is lower with SK (0.5%) than with tPA (0.7%), some cardiologists advocate its use, if commercially available, in the care of high-risk patients, such as elderly patients with a history of a cerebrovascular event or severe hypertension. SK is a nonfibrin-specific agent capable of lysing circulating and clot-bound plasminogen to plasmin. This process results in substantial systemic fibrinogenolysis, fibrinogenemia, and elevation in fibrin degradation products.

d. **Bleeding complications after fibrinolysis.** The most serious **complication** of fibrinolytic therapy is **intracerebral hemorrhage, which occurs in approximately 0.5% to 0.7% of patients receiving such therapy. The major risk factors for intracranial hemorrhage include age >75 years, hypertension, low body weight, female gender, and coagulopathy** (e.g., prior Coumadin use). The diagnosis must be considered if a patient has severe headache, visual disturbances, new neurologic deficit, acute confusional state, or seizure. If the clinical suspicion is high, fibrinolytic, antithrombin, and antiplatelet therapy should be interrupted while emergency CT or MRI is performed and neurosurgical consultation is obtained. Surgical evacuation may be lifesaving. Even with prompt recognition and treatment, the mortality rate is higher than 60% and elderly patients (>75 years) have a mortality rate greater than 90%. There is controversy regarding the risk of fibrinolytic therapy in elderly patients. An observational study from the Medicare database found that patients older than 75 years had an increased risk of death at 30 days with fibrinolytic therapy (RR = 1.38; 95% confidence interval [CI] 1.12 to 1.71; $p = 0.003$). However, an updated meta-analysis of nine randomized trials found that the risk reduction with fibrinolysis in patients older than 75 years was 16% (odds ratio = 0.84; 95% CI 0.72 to 0.98; $p < 0.05$). There appears to be a decreasing relative benefit with fibrinolysis in the elderly, but an absolute gain in lives saved. The only randomized trial to specifically study management of STEMI in the elderly found that patients

treated with PCI had significantly lower 30-day and 1-year mortality rates than patients treated with fibrinolysis. However, the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)-TIMI 25 study suggested that fibrinolytic therapy may be safe in the elderly if a reduced dose of enoxaparin is used. The previously discussed STREAM trial noted an increased rate of intracranial hemorrhage (ICH) (8.1%) in patients older than 75 years early in the study enrollment period. This led to a study amendment and a dose reduction of TNK by 50%, which lowered the rate of ICH in patients >75 years to 0%. Gastrointestinal, retroperitoneal, and access site bleeding may also complicate fibrinolytic therapy but are usually not life-threatening if promptly recognized and managed. In any case, the best treatment of acute STEMI in elderly patients appears to be primary PCI.

6. **Rescue percutaneous revascularization** is defined as the use of PCI when fibrinolytic therapy has proved unsuccessful. Despite the proven mortality benefit, >30% of patients who received lytic therapy have TIMI 0 to 1 flow at 90 minutes, whereas patency at 90 minutes has been shown to correlate with long-term survival. If reperfusion is not clearly evident 90 minutes after initiation of lytic therapy, particularly among patients with a large acute MI, the decision to perform emergency angiography and mechanical reperfusion should be made promptly. Patients in cardiogenic shock, with severe heart failure, or with compromising arrhythmias after lytic therapy should undergo immediate coronary angiography and should not await clinical assessment of reperfusion.

a. **Clinical determination of successful reperfusion.** It can be difficult to determine clinically whether a patient has successful reperfusion with fibrinolytic therapy. Resolution of chest pain is an inaccurate measure of reperfusion, because the pain may be blunted by narcotic analgesia or the partial denervation that is known to occur among some patients with MI. Serial assessment of 12-lead ECGs is a more reliable indicator of reperfusion, although it is also suboptimal. An accelerated idioventricular rhythm (AIVR) is fairly specific for reperfusion, but arrhythmias other than AIVR are not reliable indicators because a variety of ventricular and supraventricular arrhythmias may be observed in patients with nonreperfused infarction-related artery. The complete resolution of chest pain and electrocardiographic changes (defined as >70% resolution of ST-segment elevation), accompanied by a run of AIVR, is highly specific for successful reperfusion, but it occurs in <10% of patients receiving lytic therapy. Resolution of ST-segment elevation by >70% is correlated with effective tissue-level reperfusion, and this finding has been correlated with better clinical outcomes and angiographic reperfusion.

b. **Benefit.** It has been shown in the Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints trial that patients with anterior MI who have unsuccessful thrombolysis (TIMI 0 or 1 flow) have a significant benefit from rescue angioplasty. In addition, the Rapid Early Action for Coronary Treatment trial demonstrated that among patients with failed reperfusion with lytics, treatment with rescue angioplasty with or without PCI is associated with a ~50% reduction in death, reinfarction, stroke, and severe heart failure. The Grupo de Aálisis de la Cardiopatía Isquémica Aguda I trial evaluated an early invasive strategy (within 24 hours) versus an ischemia-guided approach among patients with STEMI treated with fibrinolytic therapy. This trial primarily demonstrated a reduction in revascularization events with the early invasive approach, although a trend was seen toward fewer deaths and reinfarctions. Based on the above data, an early angiography strategy (within 24 hours) is a reasonable approach in all patients who receive lytic therapy.

7. **Pharmacoinvasive strategy.** Although it is clear that routine fibrinolysis prior to transfer for PCI in all patients who present with STEMI (facilitated PCI) results in worse outcomes, fibrinolysis is still necessary to achieve early reperfusion in some patients who present to non–PCI-capable facilities. More recent data suggest that high-risk patients who receive fibrinolytic therapy benefit from immediate transfer for PCI. The Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction trial randomized patients presenting to a non–PCI-capable facility, who received half-dose fibrinolytics and abciximab, to either immediate transfer for PCI or rescue PCI. Patients who were transferred immediately for PCI had a significant reduction in the primary end point of death, reinfarction, or refractory ischemia at 30 days. In addition, the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction study showed that high-risk patients benefit from this pharmacoinvasive strategy. This trial looked at 1,059 high-risk patients with STEMI who presented to a non–PCI-capable facility within 12 hours of symptom onset. All patients received fibrinolysis with TNK and were then randomized to immediate transfer for PCI or rescue PCI dictated by continued chest pain, <50% resolution of ST-elevation, or hemodynamic instability. The primary end point was 30-day composite of the first occurrence of death, MI, recurrent ischemia, new or worsening heart failure, and cardiogenic shock. The primary end point was significantly less common in the pharmacoinvasive group compared with the group who received rescue PCI (11% vs. 17.2%; RR = 0.64; 95% CI 0.47 to 0.87; $p = 0.004$). Immediate transfer to a PCI-capable hospital should occur for all patients with cardiogenic shock or acute severe heart failure. Urgent transfer to a PCI-capable hospital should occur for patients with evidence of failed reperfusion or acute reocclusion. Hemodynamically stable patients with evidence of successful reperfusion should be transferred to a PCI-capable hospital for coronary angiography to be performed within 24 hours.

8. **The late open artery hypothesis** postulates that benefit in terms of improved ventricular function, increased electrical stability, and provision of collaterals can be gained by late patency of occluded infarct arteries. However, OAT failed to show benefit of angioplasty for late total occlusion within 3 to 28 days after MI. It should be noted that the OAT excluded high-risk patients with New York Heart Association (NYHA) class III or IV heart failure, rest angina, clinical instability, multivessel disease (left main or three-vessel disease), or severe inducible ischemia on stress testing. Patients in OAT were hemodynamically stable, were asymptomatic, and had TIMI 0 flow in the infarct-related artery. This study has led to a **class III recommendation against PCI of a totally occluded artery >24 hours after STEMI in OAT-eligible patients (asymptomatic without the previously noted high-risk criteria**).

9. **Emergency coronary bypass surgery** may be the treatment of choice for patients in whom the intent is to perform direct or rescue percutaneous mechanical reperfusion but who are found to have a critical left main or severe three-vessel disease unapproachable with percutaneous revascularization. Studies of this strategy are fairly encouraging, especially when patients can be taken to the operating room early in the course of infarction, before severe myocardial necrosis has occurred. RV infarction is a relative contraindication to bypass surgery because it complicates the discontinuation of cardiopulmonary support.

10. **PCI in hospitals without surgical backup.** Several trials and two meta-analyses have shown no difference in in-hospital or 30 day mortality in patients undergoing primary PCI at sites with or without surgical backup. Consensus guidelines recommend that primary PCI without on-site

surgical backup is reasonable with the intent of providing timely, high-quality STEMI care (class IIa, *Level of Evidence B*).

C. Adjuvant therapy

1. **β-Blockers.** Extensive data from the era before reperfusion established the usefulness of β-blockers in reducing recurrent ischemia, arrhythmias, and mortality. Several small randomized trials performed in the fibrinolytic reperfusion era confirmed the anti-ischemic and antiarrhythmic benefits, although short-term mortality was not affected. As a result, prior recommendations have stated that β-blockers should be administered to all patients within the first 24 hours of acute MI, unless contraindicated by severe reactive airway disease, hypotension, bradycardia, or cardiogenic shock. However, more recent data from the PCI era have shown no difference in mortality and no difference in the composite end point of death, reinfarction, or ventricular fibrillation arrest. The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study trial, a large (n = 22,929) RCT, found that the metoprolol group had more ventricular fibrillation arrest (2.5% vs. 3.0%; p = 0.001) and shock (5.0% vs. 3.9%; $p < 0.001$). The incidence of shock was most notable in patients with Killip class II and III heart failure. This has led to a change in guidelines recommending more judicious use of early (<24 hours) β-blockers, avoiding use in patients with significant signs of heart failure, low cardiac output, risk of cardiogenic shock, or other relative contraindications to their use.

a. **For ongoing ischemia with tachycardia or hypertension**, after rapid evaluation of ventricular function, intravenous metoprolol may be given (5 mg every 5 minutes until the desired blood pressure and pulse are achieved). Patients who tolerate the intravenous loading can begin moderate oral doses (12.5 to 50 mg of metoprolol, two to four times daily). The dose should be subsequently titrated upward to the maximally tolerated dose (200 mg of sustained-release metoprolol, once daily). Use of β-blockers should be avoided in patients with tachycardia of unclear origin, as this can represent decompensated heart failure with a compensatory tachycardia.

2. **Angiotensin-converting enzyme (ACE) inhibitors** can be started orally in the first 24 hours for all patients without hypotension, acute renal failure, or other contraindications. These medications were shown to reduce mortality in the GISSI 3 and International Study of Infarct Survival-4 trials. ACE inhibitors should be continued indefinitely in patients with LV dysfunction or clinical CHF, because these patients have been shown to derive a mortality benefit. In addition, the Heart Outcomes Prevention Evaluation study found that high-risk patients, including those with prior MI but normal LV function, still had long-term benefit from ramipril. Intravenous formulations of these agents should not be used because they have not demonstrated benefit and may increase mortality. Rather, a graded oral regimen is advised. Angiotensin-receptor blockers remain a viable option for ACE inhibitor–intolerant patients.

3. **Calcium channel blockers.** Evidence for a potential increase in mortality has limited the use of calcium channel blockers in the care of patients with acute MI. They are indicated for the management of supraventricular tachyarrhythmia, cocaine-induced MI, or relief of postinfarction angina unresponsive to β-blockade. Otherwise, these agents should be avoided. Short-acting agents, such as nifedipine, are contraindicated because of their reflex sympathetic activation. Verapamil and diltiazem should be avoided in patients with LV dysfunction or heart failure. Amlodipine is an effective antianginal agent and appears safe to use for this indication in patients with CHF.

4. **Aldosterone antagonists.** The use of aldosterone-blocking agents has been shown to be beneficial in post-MI patients. The Randomized Aldactone Evaluation Study found a reduction in all-cause mortality with the use of aldactone in patients with ischemic cardiomyopathy and NYHA class III or IV heart failure. However, the only randomized trial to address the use of such agents among patients with ventricular dysfunction after STEMI is the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, where eplerenone was found to reduce death, cardiovascular death, and hospitalization for heart failure.

5. **Diabetes control.** The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study found a significantly lower mortality rate at 1 year compared with standard therapy (8.6% vs. 18.0%; $p = 0.020$) in diabetic patients treated with aggressive blood glucose reduction with an insulin infusion during hospitalization, followed by multidose subcutaneous insulin injections. However, a small trial Organization to Assess Strategies in Ischemic Syndromes-6 Glucose-insulin-potassium (OASIS-6 GIK) and a large (>20,000 patients) randomized trial (CREATE-ELCA) failed to show any benefit to glucose–insulin–potassium (GIK) infusions. As a result, it appears prudent to institute sound glucose control, but it is not necessary to aggressively pursue glucose control with GIK infusions. Current guidelines suggest insulin therapy to achieve and maintain blood glucose levels <180 mg/dL while avoiding hypoglycemia.

6. **Antiarrhythmics.** The use of lidocaine or other antiarrhythmic agents is not warranted for the prophylactic suppression of ventricular tachycardia (VT) and fibrillation. Although lidocaine may decrease tachyarrhythmias, there is no survival benefit. There is also evidence to suggest an increase in mortality related to an increased incidence of bradycardia and asystole. The Resuscitation Outcomes Consortium recently published the "Amiodarone, Lidocaine or Placebo in Out-of-Hospital Cardiac Arrest," a randomized trial comparing intravenous amiodarone versus lidocaine versus placebo in adults with nontraumatic out-of-hospital cardiac arrest with VT or ventricular fibrillation. Neither lidocaine nor amiodarone significantly improved survival or favorable neurologic outcomes compared to placebo.

7. **Intra-aortic balloon pump (IABP).** The utility of IABP to provide circulatory support in patients with cardiogenic shock complicating acute MI is now uncertain. A mortality benefit of IABP for MI complicated by cardiogenic shock was not demonstrated in the IABP-II trial which randomized 600 patients with MI and cardiogenic shock to IABP or no IABP. Subsequently, the guideline recommendation for IABP in patients with cardiogenic shock after MI was downgraded to a class IIa recommendation (*Level of Evidence B*). The counterpulsation to reduce infarct size pre-PCI acute myocardial infarction CRISP-AMI study evaluated 337 patients with anterior STEMI without shock and randomized them to a prophylactic IABP prior to primary PCI versus primary PCI alone. The primary end point was infarct size as measured by cardiac MRI and there was no demonstrable benefit for a prophylactic IABP in these patients.

8. **Implantable cardioverter–defibrillators (ICDs).** Posited to reduce the risk of sudden death following acute MI, the utility of ICDs implanted at an average of 18 days following the index MI was tested in patients with reduced ventricular function and autonomic dysfunction Defibrillator in Acute Myocardial Infarction (DINAMIT trial). Although there was a decrease in cardiovascular death, this study failed to demonstrate any reduction in all-cause mortality. Similarly, no difference in overall mortality was noted in the Immediate Risk Stratification Improves Survival trial that randomized 898 patients with recent MI (5 to 31 days) and either left ventricular ejection fraction (LVEF) <40% with initial heart rate >90 beats/min, or non

sustained ventricular tachycardia (NSVT) >150 beats/min over a mean follow-up of 37 months. The Multicenter Automatic Defibrillator Implantation Trial II evaluated the benefit of delayed ICD insertion in patients with prior MI. The trial enrolled 1,232 patients with a history of MI at least 1 month prior to enrollment (90 days if bypass surgery was performed) and an LVEF ≤30%. Patients were randomized to prophylactic ICD insertion or standard medical therapy. At an average follow-up of 20 months, prophylactic insertion of an ICD significantly reduced all-cause mortality (14.2% vs. 19.8% for standard therapy; HR = 0.69; 95% CI 0.51 to 0.93; p = 0.016). According to the current American College of Cardiology/AHA guidelines, an ICD should be inserted in patients with ventricular fibrillation or hemodynamically significant sustained VT that occurs 48 hours after acute MI, assuming there is no recurrent ischemia or MI. Patients with an EF ≤35% and NYHA class II or III heart failure secondary to an MI that occurred at least 40 days prior should also receive an ICD. In addition, patients who are 40 days post-MI with NYHA class I heart failure and an EF ≤30% are candidates for ICD insertion. Lastly, any patient with a prior MI, nonsustained VT, EF ≤ 40%, and inducible ventricular fibrillation or sustained VT during an electrophysiologic study are candidates for an ICD. Patients who have received CABG should have their LVEF and NYHA functional class reassessed 90 days after the procedure to determine ICD candidacy.

9. **Wearable cardioverter–defibrillators.** Patients who are considered at risk for SCD but do not meet the above criteria, such as patients waiting for reassessment of LVEF after percutaneous or surgical revascularization, can be given the option of a wearable cardiac defibrillator as a bridge to ICD implantation or recovery of LVEF. The results of the randomized VEST Prevention of Early Sudden Death trial, however, showed no benefit utilizing this approach in post-MI survivors with LVEF <35% over 90 days of follow-up.

10. **Anticoagulation for large anterior wall MIs.** Historical teaching (not based on randomized data) has advocated anticoagulating patients for 6 weeks after a large anterior wall MI, with the goal of preventing LV thrombus development. However, in the era of primary PCI, the rates of LV thrombus have been reduced. Therapeutic anticoagulation is recommended in the presence of objective imaging evidence of LV thrombus. Prophylactic anticoagulation, however, is not currently recommended, because the routine addition of oral anticoagulation in all patients with STEMI would lead to "triple therapy"—warfarin and DAPT—leaving patients at an increased risk of bleeding without any demonstrable benefit.

XIV. ACUTE MI ASSOCIATED WITH COCAINE ABUSE.

The pathophysiologic process and management of acute MI associated with cocaine use differ from those of classic MI.

A. Pathophysiology

1. **The underlying pathophysiologic factor** in acute MI associated with cocaine abuse is believed to be coronary spasm or thrombus formation caused by α-adrenergic stimulation. This can occur in a normal segment of artery or be superimposed on mild to moderate atherosclerosis. Atherosclerosis is accelerated by chronic cocaine use.

2. **Increased oxygen demand** caused by β-adrenergic stimulation of heart rate and contractility also contributes to the onset of ischemia.

B. Clinical presentation.

Chest pain caused by infarction after cocaine ingestion typically occurs within 3 hours, although it can vary from minutes to days, and depends on the route of administration (median of 30 minutes with intravenous cocaine, 90 minutes with crack

smoking, and 135 minutes with nasal inhalation). More than 80% of persons with infarction are also cigarette smokers. Studies with animals have demonstrated a synergistic effect between cigarette smoking and cocaine use.

C. Therapy

1. The **initial management** of ST-segment elevation associated with cocaine use includes the routine administration of antiplatelets and heparin. Aggressive use of sublingual and intravenous nitroglycerin or intravenous calcium channel blockers is advised in an effort to relieve coronary spasm. Intravenous benzodiazepines can also be given because they not only relieve cocaine-induced chest pain but can also improve cardiac hemodynamics.

2. **β-Blockers are contraindicated in patients with cocaine-induced acute MI.** Although they block undesirable β-adrenergic effects, these agents allow unopposed α-adrenergic stimulation and have been associated with increased mortality in nonrandomized analyses.

3. **Reperfusion therapy must be considered if vasodilator therapy is unsuccessful** in relieving symptoms and ST-segment changes.

4. **Immediate angiography and mechanical revascularization as appropriate** may be even more beneficial in cocaine-induced MI patients. Many patients who use cocaine have contraindications to thrombolysis, such as severe hypertension or persistent vasospasm without thrombosis, which is not amenable to thrombolytic therapy.

XV. POSTOPERATIVE ACUTE MI

A. Etiology and pathophysiology. Acute MI following noncardiac operations most commonly occurs on the third or fourth postoperative day. Conventional theory was that MI was caused by a combination of increased oxygen demand and arterial shear stress associated with the increased adrenergic drive that accompanies pain and ambulation in the postoperative period. Intravascular volume shifts caused by redistribution of fluids, intravenous administration of fluids, and decreased enteral intake all contribute to the risk of postoperative MI. It is apparent that there is a postoperative inflammatory state associated with hypercoagulability, marked by an increase in fibrinogen and other acute-phase reactants. Significant myocardial injury has been observed in postoperative patients in the absence of traditional signs and symptoms of ACS, often labeled as a “troponin leak” or demand ischemia. These events are termed myocardial injury after noncardiac surgery (MINS) and are associated with an increase in long-term mortality when compared with patients without evidence of myocardial injury. There are currently no identifiable therapeutic targets for patients with MINS.

B. Therapy. Management of true postoperative MI is complicated by limitations on the use of fibrinolytic agents and anticoagulant therapies. Therapy relies more heavily on the intravenous use of β-blockers and urgent angiography and mechanical reperfusion. The optimal antiplatelet or anticoagulation regimen for recent (<1 year) DES patients undergoing noncardiac surgery is not known.

XVI. SIMPLIFIED REPERFUSION STRATEGY.

The wealth of data regarding reperfusion strategies and adjunctive therapies in acute MI detailed previously may lead to confusion regarding the optimal approach. Based on guideline recommendations, a simplification of the STEMI management strategy can be achieved.

A. **For patients presenting with STEMI where primary PCI is available with 90 minutes**, a reasonable strategy would involve administration of aspirin, parenteral anticoagulation, and an oral platelet $P2Y_{12}$ receptor inhibitor, as well as nitrates and β-blocker therapy if not contraindicated, and immediate transfer to the catheterization laboratory for primary PCI with DES.

B. **For patients presenting to a hospital where primary PCI is not available, but immediate transfer (medical contact to balloon time<120 minutes) to a PCI facility is available**, a similar strategy is employed, with initiation of aspirin, platelet $P2Y_{12}$ receptor inhibitors, and anticoagulation prior to transfer to the PCI facility.

C. **If anticipated transfer times will exceed the medical contact-to-PCI time of 120 minutes**, then fibrinolytic therapy should be instituted in eligible patients within 30 minutes of first medical contact in addition to therapy with aspirin, clopidogrel, and parenteral anticoagulation. The choice of UFH or enoxaparin remains operator dependent, with either option reasonable. Among patients receiving fibrinolytics, immediate transfer to a PCI facility is preferable, and early angiography (<24 hours) is recommended. Following the administration of fibrinolytics, any patient with cardiogenic shock, ventricular arrhythmias causing hemodynamic compromise, or evidence of failed reperfusion should be immediately transferred for urgent coronary angiography.

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CHAPTER 2

Non–ST-Segment Elevation Acute Coronary Syndrome

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I. INTRODUCTION.

Non–ST-elevation acute coronary syndrome (NSTE-ACS) remains a leading cause of morbidity and mortality across the globe. NSTE-ACS may be subclassified into unstable angina (UA) or non–ST-elevation myocardial infarction (NSTEMI). These clinical entities cannot be differentiated on the basis of chest pain characteristics or electrocardiogram (ECG) abnormalities alone. **The only way this determination can be made is with evidence of myocardial necrosis by measurement of cardiac biomarkers.** With improvements in the diagnosis and risk stratification of patients, therapeutic approaches to NSTE-ACS have continued to evolve.

II. CLINICAL PRESENTATION

A. Signs and symptoms. Chest pain described as heaviness or pressure usually lasting >20 minutes is the typical symptom in NSTE-ACS. Chest pain may be triggered with minimal exertion and can be new-onset or increased in severity and frequency or precipitated with less effort than prior angina. Compared with stable angina, **chest pain in NSTE-ACS** is usually more **severe and protracted**, often requiring several doses of sublingual nitroglycerin or extended periods of rest for relief.

B. Demographics. Compared with ST-elevation myocardial infarction (STEMI), patients with **NSTE-ACS** tend to be **older** and have a higher incidence of **cardiac risk factors or comorbid conditions (e.g., diabetes, hypertension, and hypercholesterolemia)** and a greater likelihood of **prior myocardial infarction (MI) and revascularization procedures** (i.e., percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]).

C. Differential diagnosis. It is crucial to determine the clinical probability that the chest pain or presenting symptom(s) represent ACS resulting from obstructive coronary artery disease (CAD). The exclusion of other diagnoses that mimic angina such as costochondritis, pneumonia, or pericarditis, as well as other life-threatening conditions such as aortic dissection, pneumothorax, and pulmonary embolus, is essential. Hypertensive urgency or emergency, thyrotoxicosis, systemic infection, anemia because of blood loss, and other precipitating causes of myocardial ischemia should also be sought.

D. Physical findings. Physical examination is often noncontributory in making the clinical diagnosis. **Signs of heart failure** (elevated jugular venous pressure, S_3), impaired myocardial

performance (S_4), or peripheral vascular disease (i.e., bruits over major vessels) may be present. The presence of hemodynamic instability identifies a patient at extreme risk.

E. Risk factors

1. **Clinical characteristics indicative of high risk.** Symptoms may include an **acceleration of ischemic symptoms within the preceding 48 hours, angina at rest (>20 minutes), congestive heart failure (CHF; S_3 gallop, pulmonary edema, and rales), known reduced left ventricular (LV) function, hypotension, new or worsening mitral regurgitation murmur, age > 75 years, diffuse ST-segment changes on an ECG (≥0.5 to 1 mm), and the presence of elevated serum cardiac biomarkers**. Patients at intermediate or low risk have angina of short duration, have no ischemic ST-segment changes on ECG, are negative for cardiac biomarkers, and are hemodynamically stable (Table 2.1).

2. **ECG.** The initial ECG can help risk-stratify patients with NSTE-ACS. Ideally, this should be performed within 10 minutes of arrival to the emergency department (ED). Patients with ST-segment deviation (i.e., ST-depression or transient ST-elevation) ≥ 0.5 mm or with preexisting left bundle branch block (LBBB) are at increased risk for death or MI at 1 year after presentation. ST-segment elevation ≥0.5 mm in lead aVR raises the possibility of left main or three-vessel CAD. **T-wave inversions alone are generally not predictive of adverse ischemic events.** It is important to compare the presenting ECG to a prior one for the presence of new ECG changes. When the diagnosis is suspect, serial ECG tracings should be performed and analyzed for dynamic ECG changes.

3. **NSTEMI.** NSTEMI predicts a poorer prognosis among patients with NSTE-ACS. Multivariate predictors of NSTEMI in patients with ACS include **prolonged chest pain** (>60 minutes), **ST-segment deviations** (depression or transient elevation), and **new or recent onset of angina** (in the past month). Elevations in the levels of troponin I or troponin T, contractile proteins released from necrotic cardiac myocytes, help establish the diagnosis when NSTE-ACS is suspected and remain independently predictive of morbidity and mortality.

4. **Clinical risk classification systems.** Numerous scores have been derived to facilitate risk assessment and guide medical therapy in patients with NSTE-ACS. It is important to note that these scores can also be used to determine which patients may benefit most from early invasive therapy as opposed to a more conservative approach. The thrombolysis in myocardial infarction (TIMI) risk score, based on the TIMI II-B and Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) trials, incorporates **the combination of age, clinical characteristics, ECG changes, and cardiac markers for risk stratification** (Table 2.2). A higher risk score correlated with an increase in the incidence of death, new or recurrent MI, and recurrent ischemia requiring revascularization. The global registry of acute coronary events (GRACE) prediction score, which incorporates nine clinical variables derived from the medical history and clinical findings on initial presentation and during hospitalization, can be used to estimate the in-hospital and 6-month outcomes for patients hospitalized with any form of ACS. Together, these various clinical risk stratification systems help identify high-risk patients likely to benefit most from more aggressive therapy.

TABLE 2.1 Initial Risk Stratification of Patients with Unstable Angina

High Risk[a]	Intermediate Risk

TABLE 2.1 Initial Risk Stratification of Patients with Unstable Angina

One of the following must be present:	No high-risk feature but must have one of th following:
Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease
Prolonged ongoing rest pain (>20 min): moderate or high likelihood of CAD	Prolonged rest pain (>20 min) that resolves
Pulmonary edema: most likely caused by ischemia	Rest angina (>20 min or relieved with rest o sublingual NTG)
Rest angina with dynamic ST-changes ≥0.5 mm	Nocturnal angina
New or worsening rales, S_3, or MR murmur	New-onset, severe angina within 2 wk with moderat or high likelihood of CAD
Hypotension, bradycardia, tachycardia	
Bundle branch block, new or presumed new	T-wave changes
Sustained ventricular tachycardia	Pathologic Q-waves or resting ST-depression (< mm) in multiple lead groups
Positive serum cardiac biomarkers	Normal cardiac markers
	Age older than 70 y

5.CAD, coronary artery disease; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; NTG, nitroglycerin.

6. [a] Risk stratification involves considering clinical characteristics and ECG findings to make early triage decisions.

III. PATHOPHYSIOLOGY. The pathophysiology of ACS encompasses a complex interplay of plaque erosion or rupture, platelet activation and aggregation leading to thrombus formation, endothelial dysfunction, vasospasm, and vascular remodeling eventually leading to imbalance between myocardial oxygen consumption and demand.

A. Plaque erosion and rupture. UA, NSTEMI, and STEMI share a common initiating event: atheromatous plaque fissure or rupture. Plaque rupture or erosion exposes thrombogenic components stimulating platelet deposition, activation, and aggregation at the site of vascular injury, followed by activation of the coagulation cascade and thrombus formation. Factors contributing to plaque instability include lymphocyte and macrophage activation and increased inflammation.

B. Thrombus formation. Exposure of circulating platelets to subendothelial contents results in platelet adhesion, aggregation, and, ultimately, thrombus formation. With platelet activation, the glycoprotein (GP) IIb/IIIa receptor on the platelet surface undergoes a conformational

change, facilitating further platelet activation and aggregation. This markedly increases thrombin production, further expanding and stabilizing the thrombus.

C. **Vasospasm** can be induced by the local production of vasoactive substances released from the subendothelial matrix or propagating thrombus or it can occur as a primary phenomenon. Severe localized spasm of a coronary artery segment (i.e., Prinzmetal angina) may also result in ACS. This vasospasm frequently occurs at sites of unstable plaque and is thought to contribute to thrombus formation. Even angiographically, normal coronary arteries with underlying endothelial dysfunction may be subject to vasospasm.

TABLE 2.2 Thrombolysis in Myocardial Infarction Risk Score

Score	Incidence of Death, New or Recurrent Myocardial Infarction, and Recurrent Ischemia R
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9
Scoring System	
One point when risk factor is present, zero points if absent (a total of seven points are possible): Age	
Presence of more than three risk factors for coronary artery disease	
Prior coronary stenosis ≥ 50%	
Presence of ST-segment deviation on admission electrocardiogram	
More than two episodes of angina within the past 24 h	
Prior use of aspirin in past 7 d	
Elevated cardiac markers	

D. **Multiple lesions.** Although a single culprit lesion is often found at angiography, multiple culprit lesions are not uncommon in patients presenting with NSTE-ACS, attesting to the systemic nature of the disease. An intravascular ultrasound study of patients with NSTEMI undergoing angiography and possible PCI revealed an average of 2.1 plaque ruptures per patient, with 79% of patients having a lesion in a location different from that of the culprit lesion.

E. **Secondary causes.** NSTE-ACS can occasionally result from a supply–demand mismatch of oxygen delivery to the myocardium. With stable obstructive coronary lesions, precipitants of NSTE-ACS include **increased myocardial oxygen demand** (i.e., tachycardia, severe hypertension, cocaine use, hyperthyroidism, fever, or sepsis) and **decreased oxygen supply** (i.e., anemia, active bleeding, or hypoxemia).

IV. INITIAL EVALUATION AND MANAGEMENT

A. Initial triage and clinical assessment recommendations

1. Patients with symptoms suggestive of ACS should be instructed to call 911 immediately. It is recommended that the patient be transported to the hospital by ambulance rather than by friends or relatives.
2. Prehospital emergency service providers should perform an ECG at first medical contact. Aspirin at a dosage of 162 to 325 mg of aspirin should be administered to patients who have symptoms suggestive of ACS, unless it is contraindicated. The patient should be instructed to chew the aspirin rather than swallow it whole so as to facilitate rapid absorption.
3. Patients who have been prescribed nitroglycerin should be instructed to take only one dose in response to chest pain. If the symptoms have not improved or are worsening within 5 minutes, then the patient should call 911 immediately before taking additional nitroglycerin. If the patient is known to have chronic stable angina and the chest pain is significantly improving after taking a dose of nitroglycerin, it is appropriate to instruct the patient to take additional doses of nitroglycerin every 5 minutes for a total of three doses and then call 911 if symptoms have not completely resolved.
4. Patients with suspected ACS who have had anginal symptoms at rest for greater than 20 minutes, hemodynamic instability, or recent syncope should be referred immediately to the ED.

B. Early risk stratification recommendations

1. Patients who present with suspected ACS should be quickly assessed and should undergo risk stratification. This should include a history and physical examination focused on high-risk features of ACS (prolonged chest pain at rest, syncope, signs of CHF, etc.), an ECG, and laboratory biomarkers of cardiac injury, preferably troponin I or T.
2. **A 12-lead ECG should be performed immediately.** Common ECG findings in NSTE-ACS include ST-segment depression, transient ST-segment elevation, and T-wave inversion. However, approximately 20% of patients with an NSTEMI confirmed by cardiac enzymes have no ischemic ECG changes. Moreover, a "normal" ECG pattern is not sufficient to rule out NSTE-ACS in patients with chest pain (>4% of patients presenting with chest pain and normal ECG patterns are diagnosed with UA). Persistent ST-segment elevation of ≥1 mm in two or more contiguous leads or new LBBB suggests acute STEMI and should be considered for emergency reperfusion therapy (see Chapter 1). As previously mentioned, ST-segment elevation ≥0.5 mm in lead aVR raises the possibility of left main or three-vessel CAD. T-wave inversions are the least specific of ECG changes in ACS. However, new, deep, symmetric T-wave inversions of ≥2 mm across the precordium in patients presenting with suspected NSTE-ACS (Wellens syndrome) often correspond to acute ischemia, usually related to a severe proximal left anterior descending artery stenosis.
3. **In patients in whom the initial ECG is not diagnostic** but the anginal symptoms persist, serial ECGs should be performed in 15- to 30-minute intervals. This is done in order to detect the development of ST-segment depression or elevation. Posterior circulation ischemia/infarction should be suspected and the use of posterior ECG leads and echo imaging should be considered.
4. **Cardiac biomarkers should be measured in all patients presenting with symptoms suggestive of ACS.** The preferred and recommended biomarker is a cardiac-specific troponin (troponin I or T).

a. **Troponins.** Cardiac troponin I and T are contractile proteins found only in cardiac myocytes and are the **preferred assays to document the presence of cardiac necrosis**. Patients with clinical suspicion for NSTE-ACS should have serial troponins measured. When utilizing a fourth-generation assay, cardiac troponins I and T typically rise within 3 to 6 hours after myocardial necrosis. Elevated troponin levels are a marker of myocyte necrosis and not specific for ischemic mechanism of injury. As a result, elevated troponin levels can also be seen in a number of other nonischemic cardiac conditions and in the setting of renal insufficiency. A rise and fall in troponin levels above the 99th percentile is highly suggestive of ischemic injury. **In the setting of NSTE-ACS, the presence and magnitude of troponin elevation has important prognostic significance beyond that specified by clinical criteria.** In the **Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries IIb (GUSTO IIb)** trial of patients with ACS, the 30-day mortality rate for patients with an elevated troponin T level (>0.1 ng/mL) was 11.8%, compared with 3.9% for patients with normal troponin levels. Elevated troponin levels in the setting of NSTE-ACS have also been associated with increased likelihood of multivessel disease, high-risk culprit lesions, and intracoronary thrombus visible at the time of angiography.

b. **Highly sensitive (Hs) troponin** assays are currently utilized worldwide and are now approved for use in the United States. These assays enable diagnosis of MI within 1 to 3 hours of symptom onset. Because of the high sensitivity and precision of the assay, Hs troponin use results in approximately 4% absolute increase and 20% relative increase in the rates of MI and a resultant decrease in UA. Suspected NSTE-ACS patients with negative protocol–directed Hs troponin assays can be promptly discharged from the ED as the negative predictive value is >99%. Clinicians, however, need to closely evaluate suspected NSTE-ACS patients in the intermediate and high range to distinguish those with a true NSTE-ACS and others with alternate etiologies of troponin elevation. The delta increase in Hs troponin levels along with the clinical history helps facilitate decision making because it distinguishes between ongoing acute and chronic cardiac myocyte injury. A Hs troponin greater than five times the upper reference limit of the assay is 90% predictive of an ACS, but a level up to three times above the upper reference limit has a limited 50% to 60% positive predictive value. As a result, additional testing may be indicated to risk-stratify patients in whom the diagnosis remains ambiguous.

c. **Creatine kinase (CK).** Historically CK and the myocardial band (MB) isoenzyme of CK (CK-MB), measured serially every 6 to 8 hours for the first 24 hours was utilized to measure cardiac necrosis. Following an MI, CK levels peak at 12 to 24 hours and CK-MB levels peak at 10 to 18 hours after the onset of symptoms. **However, with the development of contemporary troponin assays, these agents are no longer utilized for diagnosis of ACS.**

5. The initial evaluation should include consideration and appropriate evaluation of noncoronary causes of the unexplained symptoms.

C. **Recommendations for immediate management and triage.** The initial management of patients with suspected NSTE-ACS is dependent on the predicted risk of adverse ischemic cardiovascular outcomes. Patients can be initially categorized as low, intermediate, or high risk depending on the historical and clinical findings (Table 2.1). The use of risk stratification models such as the TIMI (Table 2.2) and GRACE risk scores can also assist in determining which patients are at increased risk. In addition, it is very useful to simultaneously assess the patients' risk for bleeding, especially in those being considered for coronary angiography. A number of acute bleeding risk scores are available, but the Can rapid risk stratification of

unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines (CRUSADE) and acute catheterization and urgent intervention triage strategy (ACUITY) bleeding scores are commonly utilized. Patients with probable or possible ACS whose initial 12-lead ECG and cardiac biomarker levels are normal should be monitored on telemetry. Repeat ECGs and repeat cardiac biomarker measurements should be performed. When a fourth-generation troponin is utilized, **low- and intermediate-risk patients** (Table 2.1) whose serial ECGs and cardiac biomarkers are normal may be managed conservatively. **Cardiac stress testing** or computed tomography (CT) coronary angiography may be performed in the ED or monitoring facility or as an outpatient. The optimal time for testing may be determined at the discretion of the physician. When performed in the ED, the use of multidetector CT (MDCT) compared to stress testing was associated with a decreased cost and length of stay. However, MDCT was associated with increased rates of referral for angiography without favorable clinical outcomes. MDCT has the advantage of being able to exclude other etiologies of chest discomfort like pulmonary embolism, pneumothorax, and dissection, but has technical limitations in patients with rapid and irregular heart rate, underlying stents, and extensive calcification. For such patients who are referred for outpatient stress testing, the initiation of antiplatelet and anti-ischemic pharmacotherapy (nitroglycerin and β-blockers) should be strongly considered. In the absence of medical contraindications, **high-risk patients** (Table 2.1) should have coronary angiography performed with a plan for revascularization with PCI or CABG when indicated.

When an Hs troponin assay is utilized, patients with a negative assay can be safely discharged with an outpatient follow-up as early as 1 to 3 hours depending on the assay and protocol utilized. Rates of UA have decreased significantly with the use of these sensitive assays but, when strongly suspected based on history and ECG findings, these rare patients should be admitted for further evaluation. Patients with typical clinical symptoms, ECG changes, and elevated Hs troponin levels above the 99th percentile for the assay have a confirmed NSTE-ACS and should be considered for coronary angiography and revascularization. The remainder of subjects with intermediate and elevated Hs troponin levels of uncertain etiology in whom the clinical diagnosis remains ambiguous may be considered for further evaluation with stress testing, CT angiography, or coronary angiography.

Noninvasive stress testing. When a conservative strategy is adopted, patients who have **normal myocardial perfusion scan** without fixed or reversible perfusion defects can be safely **discharged** from the hospital and followed up on an outpatient basis. **Cardiac catheterization** should be considered for patients found to have high-risk features on stress testing because they are at increased risk for adverse ischemic events. If patients are unable to exercise, **pharmacologic stress testing** can be performed with a vasodilator such as adenosine or regadenoson. In appropriate patients without concerns for renal failure, a CT coronary angiogram can accurately identify coronary artery anatomy.

V. EARLY HOSPITAL CARE.

The mainstay of treatment for ACS is directed at anti-ischemic therapy and antithrombotic (antiplatelet and anticoagulation) therapy.

A. Anti-ischemic therapy

1. **Oxygen therapy.** Routine use of supplemental oxygen is not recommended in this setting. It should be administered in patients noted to be in respiratory distress or with resting oxygen saturation <94%.

2. **Nitrates.** Nitrates are endothelium-independent vasodilators that increase myocardial blood flow and reduce myocardial demand (by reducing preload and afterload). Despite a lack of randomized clinical trial data, nitrates remain the mainstay of treatment for patients with suspected spontaneous ischemia.

a. **Dosing.** Sublingual nitroglycerin or nitroglycerin spray (0.4 mg) should be administered immediately and repeated every 5 minutes (three times) to relieve anginal discomfort. If angina persists or in the setting of heart failure or significant hypertension, intravenous nitroglycerin may be started (at 10 to 20 µg/min). Intravenous nitroglycerin can be quickly titrated (5 to 10 µg/min increases every 5 to 10 minutes) to relieve angina. Caution must be exercised because it may cause profound hypotension. Topical (nitroglycerin transdermal patch, 0.2 to 0.6 mg/h, or nitropaste, 1 to 2″, replaced every 6 hours) or oral (isosorbide dinitrate, 10 to 40 mg orally three times daily, or isosorbide mononitrate, 30 to 120 mg orally each day) nitrates can also be used in patients to prevent recurrent anginal symptoms. Tolerance to nitrates is dose and interval dependent and can occur within 24 hours of initiation, requiring higher doses of nitrates. After symptoms are controlled, changing from intravenous to topical or oral formulations with nitrate-free intervals can limit this phenomenon.

b. **Contraindications.** Contraindications are known **hypersensitivity to nitrates and hypotension. Sildenafil (Viagra) use** within the prior 24 hours has been associated with hypotension, MI, and death.

3. **β-Blockers.** These agents relieve myocardial ischemia by lowering myocardial oxygen demand through their effects on blood pressure, heart rate, and contractility. In a meta-analysis from the pre-PCI era, the use of β-blockade was associated with a substantial 13% relative reduction in death following presentation with NSTE-ACS. Cardioselective β-blockers (e.g., metoprolol and atenolol) are typically used to minimize side effects.

a. **Dosing.** Oral β-blockers should be initiated within 24 hours of presentation in the absence of heart failure, low output-state, and risk for cardiogenic shock or other contraindications to β-blockade. β-Blockers with proven benefit in heart failure such as sustained-release metoprolol succinate, carvedilol, and bisoprolol should be given in patients with NSTE-ACS, heart failure, and reduced systolic function once they are stabilized.

b. **Contraindications.** Contraindications to β-blocker therapy include **advanced atrioventricular block, active bronchospasm, cardiogenic shock, hypotension, baseline bradycardia,** and **CHF**.

4. **Calcium channel blockers.** Calcium channel blockers have diverse physiologic effects, including vasodilation, decreased or slowed atrioventricular conduction, and negative inotropy and chronotropy. Data from several trials indicate no effect on death or nonfatal MI with calcium channel blocker trials in NSTE-ACS. Several agents have shown harm such as short-acting nifedipine that increased the risk of MI or recurrent angina compared with metoprolol. In addition, patients with LV dysfunction or pulmonary congestion on physical examination are reported to have worse outcomes when treated with diltiazem.

a. **Indications.** Calcium channel blockers are recommended for patients with NSTE-ACS, but **only in patients with contraindications to β-blockers or when β-blockers and nitrates fail to fully relieve symptoms of ischemia**. Calcium channel blockers are preferred in patients with variant angina or cocaine-induced vasospasm.

b. **Contraindications.** Contraindications to calcium channel blockers include LV dysfunction or signs and symptoms of CHF, hypotension, or atrioventricular conduction abnormalities.

5. **Morphine.** Morphine acts as an anxiolytic and analgesic and potentially reduces ventricular preload by venodilation. Morphine can be considered in patients with continued chest pain after maximally tolerated nitrates and β-blockers. It should be administered at a dosage of 1 to 5 mg intravenously and may be repeated with close monitoring. In a retrospective evaluation of the CRUSADE registry, the use of morphine in NSTE-ACS was associated with increase in hospital mortality.

B. **Antiplatelet and anticoagulant therapies.** There are many different antiplatelet and antithrombotic agents currently available for the treatment of ACS. As such, the decision of which combination of medications to use and when to administer them can be challenging. In general, the decision of which agents to use depends on (1) whether an early invasive strategy is used and (2) what postangiography management strategy is employed. Regardless of which strategy is chosen, all patients presenting with ACS should receive a loading dose of aspirin (162 to 325 mg) to be chewed and swallowed; if the patient is aspirin intolerant, then a loading dose of clopidogrel (300 to 600 mg) should be given. The antiplatelet and anticoagulant therapies available for each of the following strategies are listed below. The specific doses, adverse effects, and pharmacokinetics of these agents are then listed separately.

1. **Initial conservative strategy.** After receiving aspirin, patients who undergo an initial conservative strategy should receive an **anticoagulant** and be started on **clopidogrel or ticagrelor** therapy. Enoxaparin and fondaparinux are the anticoagulants of choice; unfractionated heparin (UFH) is an acceptable alternative. Of note, if fondaparinux is used and an invasive strategy is ultimately employed, then another anticoagulant with factor IIa activity must be initiated to prevent catheterization-associated thrombosis.

2. **Initial invasive strategy.** After receiving aspirin, patients who undergo an initial invasive strategy should receive **anticoagulation with enoxaparin, UFH, or bivalirudin**. All patients should be treated with dual antiplatelet therapy (DAPT). These agents include clopidogrel or ticagrelor. Prasugrel may also be utilized after angiographic definition. A GP IIb/IIIa inhibitor such as eptifibatide or tirofiban may be considered in selected patients with breakthrough angina despite medical therapy if coronary angiography and revascularization is delayed.

3. **Once angiography is performed, the appropriate subsequent therapy depends on the management plan.**

a. For patients undergoing **CABG surgery**, it is recommended to **continue aspirin therapy**. Clopidogrel or ticagrelor therapy should be discontinued 5 days and prasugrel 7 days prior to CABG. GP IIb/IIIa inhibitors should be discontinued 4 hours prior to CABG. UFH can be continued until CABG; however, enoxaparin should be discontinued 12 to 24 hours prior to CABG and bivalirudin should be discontinued 3 hours prior to CABG.

b. Percutaneous coronary intervention. All patients undergoing PCI should be on DAPT. Routine GP IIb/IIIa inhibitor prior to PCI is not warranted and is utilized only as bailout during PCI.

c. Medical therapy. Patients who are medically managed should continue aspirin therapy and either clopidogrel or ticagrelor. UFH should be continued for 48 hours; enoxaparin or fondaparinux should be continued for the duration of the hospitalization. Bivalirudin should be discontinued after angiography if medical therapy is pursued.

4. Aspirin. There are several pathways that lead to platelet activation, of which aspirin blocks only the cyclooxygenase-1–derived thromboxane A_2 pathway. Aspirin therapy for NSTE-ACS has been studied in five major clinical trials at doses ranging from 75 to 325 mg/d. Overall, treatment with aspirin reduced the combined end point of death or nonfatal MI by 50%.

a. Pharmacokinetics. The onset of aspirin's antiplatelet effect is quite rapid, with substantial inhibition of thromboxane A_2 production within 15 minutes, translating into measurable platelet inhibition within 60 minutes. It should be administered at first medical contact. Aspirin's inhibition of cyclooxygenase is irreversible and its antiplatelet effect is durable, lasting 7 to 10 days.

b. Dosing. Unless contraindicated (e.g., active bleeding and documented hypersensitivity to aspirin), an initial dose of 162 to 325 mg of nonenteric-coated aspirin (chewed and swallowed) should be given to all patients with suspected NSTE-ACS followed by a maintenance dose of 75 to 100 mg daily indefinitely. This is based on results from several trials that compared a higher dose of aspirin (300 to 325 mg) to low dose (75 to 100 mg) and showed no reduction in death, stroke, or MI but an increased risk of gastrointestinal (GI) bleeding with higher dose of aspirin. Those patients allergic or intolerant to aspirin should receive clopidogrel loading dose as soon as possible followed by a daily maintenance dose.

5. $P2Y_{12}$ (adenosine diphosphate) inhibitors. Current guidelines recommend addition of a second antiplatelet agent in addition to aspirin in all patients with ACSs including those with NSTE-ACS. Several options are currently available and approved for this indication.

a. Clopidogrel. Clopidogrel is the most extensively studied member of this group. As evidence, in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, addition of clopidogrel to aspirin led to a 20% reduction in incidence of cardiovascular death, nonfatal MI, or stroke in both low-and high-risk patients with NSTE-ACS regardless of revascularization strategy (PCI, CABG, or medical therapy alone). An increased rate of major bleeding (3.7% vs. 2.7% for aspirin) was seen in patients receiving clopidogrel, predominantly in those undergoing CABG. In a substudy of the CURE trial, PCI-CURE, pretreatment with clopidogrel resulted in lower rates of cardiovascular death, nonfatal MI, or urgent target-vessel revascularization at 30 days (4.5% vs. 6.4%) in patients with NSTE-ACS undergoing PCI. Long-term treatment with clopidogrel also resulted in lower rates of cardiovascular death, nonfatal MI, or revascularization, without a significant increase in major bleeding. The benefit of clopidogrel pretreatment in PCI was further confirmed in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial in which patients receiving a 300-mg loading dose plus 1 year of 75 mg daily maintenance therapy of clopidogrel had a 26.9% relative reduction in death, nonfatal MI, or stroke at 1 year compared with those receiving only 1 month of maintenance therapy without any loading dose of clopidogrel.

1. (1) Pharmacokinetics. Clopidogrel is a prodrug that is metabolized to a pharmacologically active metabolite. Clopidogrel has a shorter onset of action than ticlopidine when 300 mg is given, with antiplatelet activity being detected within 2 hours after administration. Loading with 600 mg has been shown to have an even more rapid onset of action.

2. **(2) Side effects.** Clopidogrel is generally well tolerated. Exposure can rarely produce an allergic reaction typically resulting in diffuse urticaria. Rare case reports of thrombotic thrombocytopenic purpura with clopidogrel therapy have been reported.
3. **(3) Dosing.** Clopidogrel loading dose can be 300 to 600 mg although the latter leads to a faster onset of steady-state plasma concentration. The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events— Seventh Organization to Assess Strategies in Ischemic Symptoms-7 (CURRENT OASIS-7) trial compared 600-versus 300-mg loading dose clopidogrel in patients presenting with ACS. Although the results were neutral, subgroup analysis in patients undergoing PCI noted a lower rate of cardiovascular death, MI, and stroke with the 600-mg dose. Results of large meta-analysis including more than 25,000 patients undergoing PCI confirmed this finding, making 600 mg the preferred loading dose in patients with NSTE-ACS undergoing PCI. Clopidogrel maintenance therapy is 75 mg daily.

b. Prasugrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial evaluated the efficacy of prasugrel versus clopidogrel in patients presenting with ACS with planned PCI. In this study of 13,608 patients, use of prasugrel as compared with clopidogrel resulted in a significant reduction in the primary efficacy end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (9.9% vs. 12.1%, $p < 0.001$). The benefit was even more pronounced (30% relative reduction) in patients with diabetes receiving prasugrel. However, the salutary benefits in reduction of ischemic events with prasugrel came at the expense of an increase in bleeding events, including a significant increase in rates of both major bleeding (2.4% vs. 1.1%, $p = 0.03$) and fatal bleeding (0.4% vs. 0.1%, $p = 0.002$). It is an absolute contraindication to use prasugrel in patients with a history of transient ischemic attack or stroke (because of high risk of intracranial hemorrhage) and a relative contraindication in patients ≥75 years of age or <60 kg because of higher incidence of bleeding in these patient subgroups. Prasugrel was also compared with clopidogrel in patients being managed medically after NSTE-ACS in The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial. There were no differences in incidence of ischemic or bleeding end points between the two groups. The Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction trial compared pretreatment with prasugrel 30 mg with an additional 30 mg given during PCI to prasugrel 60 mg admitted during angiography but prior to PCI in the setting of NSTE-ACS. Pretreatment with prasugrel in this trial (median 4.3 hours before angiography) was not associated with clinical benefit but resulted in increased TIMI major bleeding (2.6% vs. 1.4%, $p = 0.006$). As a result, pretreatment with prasugrel is not recommended in this setting.

1. **(1) Pharmacodynamics.** Like clopidogrel, prasugrel is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites. After a 60-mg loading dose of prasugrel is given, 90% of patients achieve ≥50% inhibition of platelet aggregation within 1 hour, with maximum achieved platelet inhibition being approximately 80%. The mean steady-state inhibition of platelet aggregation with prasugrel is 70% after 3 to 5 days of treatment. Platelet aggregation returns to baseline 5 to 9 days after discontinuation of therapy.
2. **(2) Side effects.** Prasugrel is generally well tolerated. Allergic reactions to prasugrel are rare; however, bleeding-related complications such as epistaxis or easy bruising are not uncommon.
3. **(3) Dosing.** The loading dose for prasugrel is 60 mg followed by a maintenance dose of 10 mg/d.

c. Ticagrelor. Ticagrelor is a nonthienopyridine, reversible $P2Y_{12}$ receptor antagonist that was approved by the Food and Drug Administration in 2011. In the pivotal PLATelet inhibition and

patient Outcomes (PLATO) trial involving 18,624 patients presenting with ACS (59% of whom had NSTE-ACS), there was a significant 16% relative reduction in major adverse cardiac events and a 22% relative reduction in all-cause mortality in patients receiving ticagrelor versus clopidogrel. A significant benefit was noted across several subgroups including those treated medically and those who had previously received clopidogrel. On the basis of PLATO, ticagrelor is recommended in all patients with ACS, irrespective of the initial treatment strategy including those pretreated with clopidogrel.

1. **(1) Pharmacodynamics.** Ticagrelor is not a prodrug and does not require bioactivation. Ticagrelor has a faster onset of action (50% platelet inhibition at 30 minutes) and provides more potent platelet inhibition than clopidogrel. Although more potent, ticagrelor has a shorter half-life of 12 hours.
2. **(2) Side effects.** Ticagrelor is generally well tolerated. Dyspnea is the most common side effect experienced in as many as 20% of patients. This is often short-limited and does not require drug discontinuation in most patients.
3. **(3) Dosing.** The loading dose of ticagrelor is 180 mg followed by a maintenance dose of 90 mg twice daily. Subgroup analysis of the PLATO trial showed higher rates of bleeding in patients receiving ticagrelor and high aspirin dose (162 to 325 mg). The current guidelines therefore recommend only low-dose aspirin (81 mg) in patients receiving concomitant ticagrelor.

d. **Cangrelor.** This is an intravenous adenosine triphosphate analog that reversibly binds with high affinity to the $P2Y_{12}$ receptor and has an extremely short half-life of less than 10 minutes. It is given at a dose of 30 µg/kg/bolus followed by 4 µg/kg/min infusion. In the setting of NSTE-ACS, it is best utilized to ensure adequate platelet inhibition at the initiation of PCI in the setting of inadequate oral DAPT bioavailability.

To reduce the risk of GI bleeding, concomitant proton pump inhibitors should be utilized with DAPT, especially in high-risk patient. This includes patients aged >65 years and subjects with history of prior GI bleeding, dyspepsia, gastroesophageal reflux disease, significant alcohol use, and known *Helicobacter pylori* infection.

6. **Anticoagulant therapy.** In addition to DAPT, all patients with NSTE-ACS should be started on an anticoagulant. Several agents have been tested for this indication.

a. **Heparin.** UFH prevents coagulation by blocking thrombin and factor Xa. Because of a short half-life, UFH has to be administered as a continuous infusion in patients with ACS. A meta-analysis of six trials in patients with UA demonstrated that treatment with aspirin plus UFH reduced the incidence of death or nonfatal MI by 33% compared with treatment with aspirin alone.

1. **(1) Duration of therapy.** Current guidelines recommend that heparin (adjusted for activated plasma thromboplastin time) be continued for 48 hours or until PCI is performed.
2. **(2) Rebound ischemia.** Rebound ischemia is thought to result from the accumulation of thrombin during UFH administration and the ensuing platelet aggregation. Studies have shown that this rebound ischemia can be attenuated with the concomitant use of aspirin.
3. **(3) Recommendations.** Intravenous UFH can be used for anticoagulant therapy in patients with NSTE-ACS undergoing either an invasive or conservative treatment strategy unless contraindicated (e.g., active bleeding, known hypersensitivity, and history of heparin-associated thrombocytopenia).
4. **(4) Dosing.** Initially, heparin should be given as a weight-adjusted bolus (60 U/kg), followed with an infusion (12 U/kg/h). The activated partial thromboplastin time (aPTT) should be monitored every 6 hours until it stabilizes between 50 and 70 seconds and monitored subsequently every 12 to 24 hours thereafter. Standardized heparin nomograms have simplified and streamlined the initial orders for UFH and the subsequent adjustment of dosing based on aPTT levels.

b. Low-molecular-weight heparin (LMWH). LMWH is a more selective factor Xa inhibitor than heparin. The advantages of LMWH compared with UFH include increased bioavailability, a fixed dosing regimen, more effective thrombin inhibition, lower rates of heparin-induced thrombocytopenia (HIT), and more predictable and sustained anticoagulation.

1. **(1) Comparison with heparin.** Multiple trials have compared LMWH and UFH in patients with NSTE-ACS and shown similar or reduced rates of death or nonfatal MI, primarily a significant reduction in the latter. A meta-analysis of 12 trials involving 17,157 patients with NSTE-ACS that compared the use of different LMWHs with UFH found no significant benefit with LMWHs compared with UFH (odds ratio = 0.88, 95% confidence interval 0.69 to 1.12, $p = 0.34$).
2. **(2) Dosing. Enoxaparin** is administered as a 1-mg/kg dose given subcutaneously (SQ) every 12 hours. No routine laboratory values have to be followed. The dosing is reduced to once a day in patients with creatinine clearance (CrCl) <30 mL/min.
3. **(3) Recommendations.** In patients with NSTE-ACS who may undergo either a conservative or an early invasive therapy, enoxaparin is an acceptable agent for anticoagulation.

c. Direct thrombin inhibitors (DTIs). DTIs inhibit clot-bound thrombin more effectively than UFH and are not inactivated by plasma proteins or platelet factor 4, making them an ideal agent in patients with HIT. Hirudin is an older generation DTI that is no longer used clinically and has been supplanted by its synthetic derivative, bivalirudin. **Bivalirudin** reversibly inhibits thrombin and has a short half-life of 25 minutes. In the **ACUITY** trial of 13,819 patients with high-risk NSTE-ACS with planned invasive strategy, bivalirudin was noninferior to heparin plus GP IIb/IIIa inhibition, with 30-day rates of ischemia of 7.7% versus 7.3%, respectively, but there was a significantly lower rate of major bleeding with bivalirudin. Similar results were also noted in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4 (ISAR-REACT 4) trial. In the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox trial, the use of bivalirudin compared with heparin was not associated with any clinical benefit on the composite of death, MI, stroke, or major bleeding in 7,213 patients with ACS (3,203 with NSTE-ACS). Randomization to bivalirudin, however, did result in decreased rates of Bleeding Academic Research Consortium (BARC) bleeding (11% vs. 16%, $p = 0.001$) and major BARC 3–5 bleeding (1.4% vs. 2.5%, $p < 0.001$).

1. **(1) Recommendation.** Bivalirudin is now rarely utilized in the era of radial artery catheterization given its increased cost. Bivalirudin should be considered when NSTE-ACS patients who are at a high risk for bleeding undergo PCI.

d. Factor Xa inhibitors. Fondaparinux is a heparin pentasaccharide analog that selectively inhibits factor Xa. In comparison with UFH, fondaparinux has decreased binding to plasma proteins along with dose-independent clearance with a longer half-life. These properties translate into more predictable and sustained anticoagulation, which permits fixed-dose, once-daily administration.

1. **(1) Comparison with enoxaparin.** The **Organization to Assess Strategies in Acute Ischemic Syndromes 5 (OASIS-5)** trial evaluated the efficacy of fondaparinux versus enoxaparin in 20,078 patients with NSTE-ACS. Patients receiving fondaparinux (2.5 mg SQ once daily) had a similar rate of the combined end point of death, MI, or refractory ischemia at 9 days as those randomized to enoxaparin (1.0 mg/kg SQ twice daily). The use of fondaparinux was associated with a lower rate of major bleeding at 9 days as compared with enoxaparin (2.2% vs. 4.1%, $p < 0.001$). However, in this trial, there was an increased incidence of catheter-associated thrombus noted, and the trial protocol was modified to allow for use of open-label UFH, which initially was not allowed during PCI.
2. **(2) Dosing.** The dosing of fondaparinux for NSTE-ACS is 2.5 mg SQ once daily. Fondaparinux is renally cleared and its use is contraindicated in those patients with a CrCl <30 mL/min.

3. **(3) Recommendations.** Fondaparinux can be used for anticoagulant therapy in those patients selected to undergo a conservative medical approach. It is the preferred therapy in patients with increased risk of bleeding being managed with medical therapy. For patients who undergo angiography and PCI, an additional agent with anti-IIa activity (UFH or bivalirudin) should be administered given the increased rates of catheter-associated thrombus with fondaparinux alone.

e. Glycoprotein IIb/IIIa inhibitors

1. **(1) Background.** Platelet aggregation eventually requires the activation of GP IIb/IIIa receptors on the platelet surface. The GP IIb/IIIa receptors of adjacent platelets bind fibrinogen molecules that allow cross-linking of the platelets, which subsequently initiates thrombus formation. Blocking the GP IIb/IIIa receptor therefore inhibits platelet aggregation and reduces thrombus formation. With the availability of potent DAPT, use of these agents has significantly decreased over time. Currently, these agents are mainly utilized for bailout and thrombotic complications in the cath lab. When PCI is indicated in the absence of effective DAPT, tirofiban/integrilin may be administered to endure adequate and complete platelet inhibition while allowing the oral DAPT agents to be adequately absorbed and bioavailable. Three agents, namely, **abciximab** (a monoclonal antibody to the human GP IIb/IIIa receptor), **eptifibatide**, and **tirofiban**, with the latter two being small molecule, reversible inhibitors, were significantly utilized in the past. The trials that evaluated the benefit of GP IIb/IIIa inhibitors in patients with NSTE-ACS are now only of historical significance.
2. **(2) Recommendations: Based on current evidence**, GP IIb/IIIa inhibitors have a selective role, mainly as a bailout indication during the performance of PCI.

f. Fibrinolytic agents.

There is no role for fibrinolytic therapy in patients with NSTE-ACS because it is associated with worse outcomes. A meta-analysis of fibrinolytic therapy in the management of UA demonstrated an increase in death or nonfatal MI in patients receiving fibrinolytics (9.8% for fibrinolytics vs. 6.9% for placebo).

g. Protease-activated receptor-1 antagonist.

The novel, oral thrombin receptor (protease-activated receptor-1) antagonist, vorapaxar, has been evaluated in patients with ACS and peripheral arterial disease. The addition of vorapaxar to standard therapy did not significantly reduce major adverse cardiac events and was associated with increased risk of bleeding and intracranial hemorrhage. Although the drug is approved in patients with ACS, it is not given any recommendation by American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for this indication.

h. Oral anticoagulation.

Patients presenting with ACS continue to have significant residual risk even with optimal medical therapy and ~10% subjects suffer another cardiovascular event within 1 year of initial ACS presentation. Because of this residual risk, addition of oral anticoagulant to standard DAPT has also been tested in patients with ACS. Addition of low-dose rivaroxaban (2.5 and 5 mg twice daily) to predominantly DAPT with aspirin and clopidogrel was tested in patients with recent ACS. Although there was significant reduction in composite of MI, death, and stroke as well as stent thrombosis, it was at the cost of slightly higher risk of bleeding including intracranial hemorrhage. Although not currently approved in the United States, the European Society of Cardiology guidelines have given a class IIb indication for addition of low-dose rivaroxaban (2.5 mg twice daily) in high-risk patients with NSTE-ACS.

C. Ischemia guided versus early invasive strategy.

In the absence of contraindications, high-risk patients with NSTE-ACS should be managed by an early invasive strategy. This includes all patients with a confirmed NSTEMI. This strategy is guided by early angiographic

definition of coronary anatomy and subsequent revascularization by PCI or CABG based on the nature and extent of disease. When performed by experienced operators, radial access for performance of coronary angiography as well as PCI should be utilized. A meta-analysis of multiple randomized clinical trials has confirmed a reduction in death, MI, stroke, and bleeding with a radial compared to a femoral approach. An ischemia-guided strategy may be utilized in intermediate- and low-risk patients. In the absence of spontaneous ischemia during medical therapy, these patients usually undergo evaluation for inducible ischemia with a functional study. Select patients who meet criteria for high risk on stress testing are then referred for coronary angiography whereas the remainder are discharged on optimal medical therapy.

The evidence basis to support adoption of an invasive approach in high-risk patients is strong. Bavry et al. performed a contemporary meta-analysis of seven randomized trials evaluating an early invasive versus a conservative approach in the management of patients with NSTE-ACS. In this pooled analysis of 8,375 patients, there was a 25% relative reduction in all-cause mortality at 2 years with use of early invasive as compared with conservative therapy (4.9% vs. 6.5%, $p = 0.001$). Table 2.3 summarizes the approach to NSTE-ACS.

1. The 2014 ACC/AHA guidelines provide specific treatment strategies for the following patient populations:

a. Patients who have **refractory angina despite medical therapy, hemodynamic instability, or electrical instability** are recommended to undergo an **urgent/immediate invasive strategy**.

TABLE 2.3 Initial Management Strategy in NSTE-ACS: Early Invasive versus Ischemia-Guided Appr

Immediate invasive (within 2 h)	Refractory angina Signs/symptoms of HF with new or worsening mitral regu Hemodynamic instability Sustained VT or VF
Early invasive (within 24 h)	GRACE risk score >140 Troponin elevation New or presumable new ST-depression
Delayed invasive (within 25–72 h)	Prior PCI within 6 mo or prior CABG LV function < 40%
Ischemia-guided therapy	Low-risk score (TIMI 0 or 1 or GRACE < 109) Low-risk troponin-negative female patients Physician or patient preference in low- to intermediate-ris

CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LV, left ventricular; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

c. For patients who are **initially stabilized but are at high risk for adverse events**, it is reasonable to undergo an **early invasive strategy** (within 24 hours). This includes patients who are troponin positive, those with GRACE score >140, and those with new or presumably new ST-segment depressions.

d. A **delayed invasive strategy** (within 25 to 72 hours) is reasonable in patients with diabetes, renal insufficiency, reduced systolic function, and early postinfarct angina.

e. For patients with a low-risk score (TIMI 0 or 1 or GRACE < 109) or low-risk, troponin-negative female patients, it is reasonable to proceed with an ischemia-guided approach.

f. An early invasive strategy is not recommended in patients with extensive comorbidities (e.g., hepatic, renal, pulmonary failure; cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization and in those with acute chest pain and a low likelihood of ACS who are troponin negative, especially women.

g. Patients being treated with an initial ischemia-guided approach benefit from an early echocardiogram to evaluate LV function and should undergo risk stratification with a stress test before or shortly after discharge to identify patients who would benefit from revascularization.

2. **Randomized trials.** The following is a summary of the randomized trials that have compared an early invasive versus an early conservative approach in different patient populations.

a. Two earlier trials performed prior to the current era of antiplatelet therapy and coronary stenting were the **TIMI IIIB** and **Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH)** trials. Both of these trials showed similar long-term outcomes (death or MI) between early invasive and conservative treatment strategies; however, there was an increase in early mortality associated with invasive therapy in the VANQWISH study.

b. In the **Fast Revascularization during InStability in Coronary artery disease II (FRISC II)** trial, patients with NSTE-ACS were randomized in a factorial design to an early invasive or conservative strategy and to dalteparin or placebo. An early invasive strategy was associated with a reduction in the rate of death or MI at 6 months (9.4% vs. 12.1%, $p = 0.031$) and reduced symptoms of angina and rehospitalization, regardless of treatment with dalteparin.

c. In the **Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy - Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18)** trial, patients with NSTE-ACS treated with aspirin, heparin, and tirofiban were randomized to an early invasive or a conservative strategy. Patients assigned to an **early invasive approach underwent catheterization within 4 to 48 hours**, with revascularization as appropriate. Patients assigned to the conservative arm underwent cardiac catheterization only if there was objective evidence of recurrent ischemia or abnormal stress test. An early invasive strategy was associated with a reduction in the composite of death, nonfatal MI, or rehospitalization for ACS at 6 months (15.9% vs. 19.4%, $p= 0.025$), as well as a reduction in the incidence of death or nonfatal MI at 6 months (7.3% vs. 9.5%, $p < 0.05$).

d. In the **Randomised Intervention Treatment of Angina 3 (RITA 3)** trial, an early invasive strategy for moderate-risk patients with NSTE-ACS was associated with a decreased rate of all-cause mortality, MI, or refractory angina compared with conservative therapy at 5 years. However, the reduction in mortality dissipated at 10-year follow-up with no statistical differences between groups.

e. In the **Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-COOL)** trial, patients with NSTE-ACS treated with intensive medical therapy (aspirin, heparin, clopidogrel [600-mg loading dose], and tirofiban) were randomized to immediate invasive therapy (median time of 2.4 hours) versus delayed invasive therapy after a "cooling off" period (median

time of 86 hours). Those who had early intervention had a significant reduction in death or MI at 30 days compared with those who had a "cooling off" period (5.9% vs. 11.6%, $p = 0.04$).

f. In the **Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS)** trial, 1,200 patients with NSTE-ACS with elevated troponins were randomized to either early invasive therapy (angiography within 24 to 48 hours) or initial conservative strategy with selective invasive therapy. There was no difference in the primary composite end point of death, MI, or rehospitalization for ACS at 1 year between the two groups (22.7% vs. 21.2%, $p = 0.33$). The aggressive medical therapies and high rates of revascularization (47%) in the initial conservative strategy group are two among many potential explanations for the findings of this trial.

g. In the **The Timing of Intervention in Acute Coronary Syndromes (TIMACS)** trial, patients with NSTEMI presenting within 24 hours of onset of symptoms were randomized to undergo angiography as soon as possible (within 24 hours) or after a minimum delay of 36 hours. These patients received contemporary medical therapy including acetylsalicylic acid, clopidogrel (>80%), heparin or fondaparinux, and GP IIb/IIIa inhibitors (23%). Overall, there was a nonsignificant trend toward a reduction in death, new MI, or stroke at 6 months for patients who received an early invasive strategy (11.3% for delayed angiography vs. 9.6% in the early intervention, $p = 0.15$). However, there was a significant reduction in the secondary end point of death, MI, or refractory ischemia for patients randomized to an early invasive strategy (12.9% vs. 9.5%, $p = 0.003$) that was primarily driven by a decrease in refractory ischemia. Overall, this study supports an early invasive strategy for patients presenting with NSTE-ACS, particularly for those among the highest tertile of risk according to the GRACE scale.

h. The **The Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD)** trial assessed whether a very aggressive strategy of emergent intervention (analogous to primary PCI for STEMI) would benefit patients presenting with NSTE-ACS versus delayed angiography and intervention. Immediate angiography and intervention did not decrease the rate of the primary outcome of median troponin I release (2.1 ng/mL for the invasive strategy vs. 1.7 ng/mL for the delayed strategy) nor did it show a trend toward improved outcomes in the secondary end point of death, MI, or urgent revascularization at 1 month (13.7% for early invasive management vs. 10.2% for the conservative approach, $p = 0.31$).

VI. HOSPITAL DISCHARGE AND POSTDISCHARGE CARE.

The risk of recurrent MI or death is highest during the first 2 months after NSTE-ACS. Although patients with NSTE-ACS usually receive definitive therapy during hospitalization, close follow-up care after hospital discharge is imperative. Follow-up must include lifestyle alteration, risk factor modification, and secondary prevention. Referrals for cardiac rehabilitation in stable patients, smoking cessation efforts, and dietary changes have all been shown to improve outcomes. Hypertension, dyslipidemia, depression, and diabetes mellitus must be diagnosed and aggressively treated. Patients must be reassured and educated about their acceptable level of activity. Compliance with DAPT **β-blockers, statins/cholesterol-lowering regimens, and/or angiotensin-converting enzyme inhibitors should be emphasized**. Specific recommendations regarding a secondary prevention postdischarge medication regimen are discussed in the chapter on post-MI risk stratification.

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CHAPTER 3

Complications of Acute Myocardial Infarction

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I. **INTRODUCTION. In-hospital mortality after acute myocardial infarction (MI) is primarily caused by circulatory failure from severe left ventricular (LV) dysfunction and/or other acute complications of MI.** These complications can be broadly classified as **mechanical, arrhythmic, embolic, and inflammatory (e.g., pericarditis)**.

II. **MECHANICAL COMPLICATIONS.** Mechanical complications of acute MI include ventricular septal rupture (VSR), acute mitral regurgitation (MR), ventricular free wall rupture, ventricular pseudoaneurysm, and ventricular aneurysm.

A. Ventricular septal rupture

1. **Clinical presentation.** VSR occurred in 1% to 2% of patients after acute MI in the prethrombolytic era and accounted for 5% of the peri-infarction mortality. The incidence has dramatically decreased in the postthrombolytic era. In the substudy of the Assessment of Pexelizumab in Acute Myocardial Infarction of 5,745 patients with ST-elevation MI from 2004 to 2006, VSR occurred 0.17% of the time. VSR is more likely to occur in patients who are **older, are female, had prior stroke, have chronic kidney disease, and have congestive heart failure.** It commonly occurs in the setting of a **first MI, in the background of delayed or absent reperfusion therapy.** Early revascularization has been associated with lower risk of VSR and may account for the decreasing incidence.

a. **Signs and symptoms.** Patients with post-MI VSR may appear relatively stable early in the disease course. Recurrence of angina, pulmonary edema, hypotension, and shock may develop abruptly later in the course. Alternatively, precipitous onset of hemodynamic compromise characterized by hypotension, biventricular failure, and a new murmur may be the initial manifestation.

b. **Physical findings.** The diagnosis should be suspected when a new **harsh pansystolic murmur** develops, especially in the setting of worsening hemodynamic profile and biventricular failure. For this reason, it is important that **all patients with MI have a well-documented cardiac examination** at presentation and frequent evaluations thereafter.

1. **(1)** The murmur is usually best heard at the **lower left sternal border**; it is accompanied by a **thrill in 50% of the cases**. In patients with a large VSR and severe heart failure or cardiogenic shock, the murmur may be of low intensity or inaudible, but **the absence of a murmur does not rule out VSR**.

2. (2) Several features differentiate the murmur of VSR from that of acute MR (Table 3.1). The murmur may radiate to the base and the apex of the heart. A third heart sound (S_3), loud P_2, and signs of tricuspid regurgitation may be present.

2. **Histopathology.** The defect usually occurs at the myocardial infarct border zone, located in the **apical septum with anterior MI** and in the **basal posterior septum with inferior/lateral MI**, and with similar frequency. A VSR almost always occurs in the setting of a transmural MI. The defect can be one single large defect or a meshwork of serpiginous channels. Multiple fenestrations are especially common with inferior MIs.

TABLE 3.1 Differential Diagnosis of a New Systolic Murmur after Acute Myocardial Infarction

Differentiating Features	Ventricular Septal Rupture	Acute Mitr
Location of MI	Anterior = nonanterior	Inferoposte
Location of murmur	Lower left sternal border	Cardiac ap
Intensity	Loud	Variable; m
Thrill	50% of patients	Rare
RV failure	More likely	Less likely
Pulmonary edema	Less likely	More likely
V-waves in PCWP	Present or absent	Almost alw
V-waves in PA tracing	Absent	Present
O_2 step-up in PA	Almost always present	Absent

3.MI, myocardial infarction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RV, right ventricular.

4. **Diagnostic testing**

a. **An electrocardiogram** (ECG) may show atrioventricular (AV) node or infranodal conduction abnormalities in approximately 40% of patients.

b. **Echocardiography**

1. (1) **Transthoracic echocardiography is the test of choice** for the diagnosis of VSR. It is important for the clinician to interrogate the area of interest with color Doppler ultrasound. Lowering the Nyquist limit will enable definition and help define the size of the defect. The echocardiogram will also provide insight into the choice of management.
Basal VSR is best visualized in the parasternal long axis with medial angulation, the apical long axis, and the subcostal long axis. **Apical VSR** is best visualized in the apical four-chamber view.
2. (2) In some cases, **transesophageal echocardiography** may help in determining the extent of the defect and assessing suitability for potential percutaneous closure.
3. (3) Echocardiography may help determine the size of the defect and the magnitude of the left-to-right shunt by comparing flow across the pulmonary valve with flow across the aortic valve.
4. (4) An assessment of right ventricular (RV) and LV function is key to prognostication and management as they remain important determinants of mortality.

c. **Right heart catheterization.** Pulmonary artery (PA) catheterization with oximetry measurement can help diagnose the presence and size of a left-to-right shunt. Diagnosis involves fluoroscopically guided measurement of the oxygen saturation in the superior vena cava (SVC) and inferior vena cava (IVC); high, mid, and low right atrium (RA); base, mid, and apical levels of the RV; and the PA.

1. **(1)** Normal oxygen saturations for these chambers are 64% to 66% in the SVC, 69% to 71% in the IVC, 64% to 67% in the RA, 64% to 67% in the RV, and 64% to 67% in the PA.
2. An oxygen step-up at the level of the RV is characteristically seen with VSR. A left-to-right shunt across the ventricular septum typically results in a **5% or greater** increase in oxygen saturation between the RA and the RV or PA.

Shunt fraction is calculated as follows:

$$Q_p/Q_s = (SaO_2 - MVO_2)/(PVO_2 - PaO_2)$$

In this equation, Q_p is pulmonary flow; Q_s is systemic flow; SaO_2 is peripheral arterial oxygen saturation; MVO_2 is mixed venous oxygen saturation; PVO_2 is pulmonary venous oxygen saturation; and PaO_2 is pulmonary arterial oxygen saturation. $MVO_2$is calculated by multiplying the SVC oxygen saturation by three, adding the IVC oxygen saturation, and then dividing the sum by four. PVO_2 is generally assumed to be equal to the peripheral oxygen saturation. **$Q_p/Q_s \geq 2$ suggests the presence of a considerable shunt.**

3. **(2)** For a patient with an intracardiac shunt, **cardiac output measured by means of the thermodilution technique is inaccurate; the Fick method should be used**. The key to measurement of accurate systemic flow in the presence of a shunt is that the oxygen content measured in the PA will be abnormally elevated and must be measured in the chamber immediately **proximal** to the shunt (i.e., the RA or the SVC and IVC in the case of VSR). The Fick equation is normally calculated as follows:

$$\text{Cardiac output} = O_2 \text{ consumption}/([SaO_2 - PaO_2] \times \text{hemoglobin [Hgb]} \times 1.34 \times 10)$$

d. **Left heart catheterization.** Ventriculography performed after angiography or percutaneous coronary intervention (PCI) may reveal VSR if the suspicion is high. Visualization is best in the left anterior oblique projection with cranial angulation.

e. **Cardiac magnetic resonance imaging (MRI) and computed tomography (CT)** are additional imaging modalities that can be utilized. However, the studies are more difficult to perform in hemodynamically unstable patients and do not play a significant role in this setting.

5. Therapy

a. **Priority of therapy.** Surgical closure is the treatment of choice (American Heart Association [AHA]/American College of Cardiology [ACC] class I recommendation), although the timing of surgical repair is controversial. Data from the Society of Thoracic Surgeons (STS) database suggests lower mortality in those undergoing delayed repair allowing for evolution of the infarct and stability of the friable myocardium; however, this may simply be a result of survival bias. The mortality rate for patients with VSR treated medically is extremely poor and many do not survive to a delayed surgery. Ultimately the timing of closure must take into account the patient's stability, the risk of clinical deterioration, surgical comorbidities, and the VSR anatomy.

b. **Vasodilators** can decrease left-to-right shunt and increase systemic flow by means of reducing systemic vascular resistance (SVR); however, a greater decrease in pulmonary vascular resistance may actually increase shunting. The vasodilator of choice is **intravenous nitroprusside**, which is titrated to a mean arterial pressure (MAP) of 70 to 80 mm Hg.

c. **Mechanical support** as a bridge to recovery and closure in patients with VSR is currently given a IIa (level of evidence C) recommendation by the European Society of Cardiology (ESC).

1. **(1)** An **intra-aortic balloon pump (IABP)** may be inserted as a bridge to a surgical procedure, unless there is marked aortic regurgitation. IABP counterpulsation decreases SVR, decreases shunt fraction, increases coronary perfusion, and maintains blood pressure. After insertion of an IABP, vasodilators can be tailored with hemodynamic monitoring.
2. **(2)** Case reports/series document other mechanical support devices as a bridge to surgery. These agents should be considered in the setting of cardiogenic shock and include both venoarterial **extracorporeal membrane oxygenation (ECMO)** and **percutaneous ventricular assist devices (pVAD), specifically** Tandemheart. Impella use has been reported but there is concern for harm in this setting.

d. **Surgical therapy**

1. **(1) Cardiogenic shock and multisystem failure** are associated with high surgical mortality, further supporting earlier operations on these patients before complications develop. Mortality in patients with cardiogenic shock and VSR was 81% in the SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK? (SHOCK) trial registry. When surgical repair is considered unlikely or futile, appropriate patients may be considered for surgical mechanical support including Total Artificial Heart with a goal to cardiac transplantation.
2. **(2) Surgical mortality is high** among patients with **basal septal rupture associated with inferior MI** (70% compared with 30% in patients with anterior infarcts) because of the greater technical difficulty and the need for concomitant mitral valve repair in these patients, who often have coexisting MR. RV dysfunction because of infarction and/or pressure and volume overload further increases the risk profile of these subjects.

e. **Percutaneous therapy.** Although surgical closure remains the treatment of choice for VSR, emerging data suggest that **percutaneous closure** may be a viable treatment for high-risk surgical patients and patients in whom surgical closure has failed. In a 2013 series of 30 patients treated with percutaneous VSR closure (12 as primary closure and 18 for residual VSR after surgery), mortality at 30 days was 42% and 11% in the respective groups. In our institution, a percutaneous approach is utilized for temporary palliation and as a bridge to surgical repair only in patients considered too high risk to undergo surgery.

B. **Acute severe MR.** Severe MR caused by papillary muscle rupture is a life-threatening complication of acute MI occurring in 0.25% of patients following an MI with a median time to presentation of 13 hours. Acute severe MR accounted for 7% of the cases of cardiogenic shock and 5% of the mortality observed after cardiogenic shock complicating acute MI in the SHOCK registry.

1. **Clinical presentation**

a. **Signs and symptoms.** These are variable and depend on the anatomy of the papillary muscle involved and its impact on the integrity of the mitral valve. Patients with partial or complete rupture of one or more heads of the papillary muscle lose significant leaflet support. The resultant torrential MR can result in pulmonary edema and severe respiratory distress along with cardiogenic shock.

In the setting of rupture of a minor papillary head or a chordae tendinae, MR may occasionally be better tolerated.

b. **Physical findings.** A new **pansystolic murmur that is audible at the cardiac apex with radiation to the axilla or the base of the heart suggests acute MR**. In posterior papillary muscle rupture, the murmur radiates to the left sternal border and may be confused with the murmur of VSR or aortic stenosis. The intensity of the murmur does not predict the severity of the MR. The **murmur may often be quiet, soft, or absent** in patients with poor cardiac output or in persons with elevated left atrial pressure because of the rapid equilibration of pressures. Resting tachycardia and mechanical ventilation can also make murmur recognition challenging.

2. Pathophysiology. Papillary muscle rupture is **more common with an inferior MI** because the posteromedial papillary muscle receives blood supply from the posterior descending artery, whereas the anterolateral papillary muscle has dual blood supply from the left anterior descending and circumflex arteries. Papillary muscle rupture is more likely to occur in patients with a **first MI**, and in many patients the **infarct size may be relatively small. The discordance between the degree of hemodynamic instability and the extent of myocardium in jeopardy is often a clue to this diagnosis.**

3. Diagnostic testing

a. An **ECG** usually shows evidence of recent inferior or posterior MI.

b. A **chest radiograph** may demonstrate pulmonary edema. In some patients, focal pulmonary edema may be seen in the right upper lobe because of flow directed at the right pulmonary veins.

c. **Transthoracic echocardiography** with Doppler and color flow imaging is the diagnostic modality of choice.

1. **(1)** The **mitral valve leaflet is usually flail** with severe MR.

2. **(2)** Color Doppler imaging is useful in differentiating papillary muscle rupture with severe MR from VSR after MI.

d. **Transesophageal echocardiography. Transthoracic echo may underestimate the degree of acute MR.** Rapid equalization of pressure, resting tachycardia, and poor acoustic windows may contribute to this finding. An eccentric jet in this setting should lead to the performance of **transesophageal echocardiography** to quantify the severity and elucidate the mechanism of MR.

e. **PA catheterization.** Hemodynamic monitoring with a PA catheter may reveal **large V-waves in the pulmonary capillary wedge pressure (PCWP) tracing**. However, patients with VSR may also have large V-waves because of increased pulmonary venous return in a normal-sized and normally compliant left atrium. Among patients with severe MR and reflected V-waves in the PA tracing, oxygen saturation in the PA may be higher than that in the RA, complicating differentiation from VSR. There are two methods for differentiating MR from VSR with a right heart catheter:

1. **(1)** Prominent V-waves in the PA tracing before the incisura are almost always associated with acute severe MR (FIG. 3.1).

2. **(2)** Blood for oximetry is obtained with fluoroscopy to ensure sampling from the main PA rather than distal branches.

4. Therapy

a. **Priority of therapy.** Papillary muscle rupture should be identified early. Patients should receive **aggressive medical therapy** and consideration for **emergent surgical repair**.

b. **Vasodilator therapy** is beneficial in the treatment of patients with acute MR. **Intravenous nitroprusside** decreases SVR, reduces regurgitant fraction, and increases stroke volume and cardiac output. Nitroprusside can be titrated to a MAP of 70 to 80 mm Hg.

c. **Mechanical support**

1. **(1) Intra-aortic balloon pump.** Vasodilator therapy is contraindicated in patients with significant **hypotension** and an IABP should be inserted promptly. An IABP decreases LV afterload, improves coronary perfusion, and increases forward cardiac output. Patients with hypotension can often be given vasodilators after insertion of an IABP to improve hemodynamic values.
2. **(2) ECMO, left ventricular assist device, and pVAD** are also potential mechanical support devices that can be used as a bridge to surgical intervention.

d. **Percutaneous therapy.** Improvement in hemodynamic values and reduction in MR has been reported after PCI in patients with severe MR caused by papillary muscle dysfunction from ischemia but is unlikely to affect severity when mechanical integrity of the valve is compromised. **PCI of the infarct-related artery has no role in this setting.**

1. **(1) Surgical therapy with concomitant revascularization should be considered immediately for patients with papillary muscle rupture.**
2. **(2)** The prognosis is very poor among patients treated medically. Even though perioperative mortality (20% to 25%) is higher than that for elective surgical treatment, surgical therapy should be considered for every patient. Long-term survival in those with successful surgical correction is similar to those with an uncomplicated MI.

FIGURE 3.1 Giant V-waves on the pulmonary capillary wedge (PCW) tracing can be transmitted to the pulmonary artery (PA) pressure, producing a notch (*asterisk*) on the PA downslope. (Adapted from Kern M. *The Cardiac Catheterization Handbook*. 2nd ed. St. Louis, MO: Mosby-Year Book; 1991. Copyright © 1991 Elsevier. With permission.)

e. **Coronary angiography** should be performed before surgical correction, because concomitant revascularization is associated with improved short- and long-term mortality.

C. Ventricular free wall rupture

1. **Clinical presentation.** The incidence of ventricular free wall rupture after MI in the reperfusion era is <1%. However, ventricular free wall rupture accounts for approximately **10% of mortality after MI**. In the SHOCK registry, in-hospital mortality associated with ventricular rupture was >60%. Rupture occurs in the first 5 days in 50% of patients and within 2 weeks in 90% of patients. Ventricular free wall rupture occurs in the setting of a transmural MI. Risk factors include advanced age, female sex, first MI, and poor coronary collateral vessels. The incidence of ventricular free wall rupture is lower in patients treated with primary PCI compared with thrombolytics.

a. **Signs and symptoms**

1. **(1) Acute course.** With acute rupture, patients develop tamponade, electromechanical dissociation, and sudden death. Sudden onset of chest pain with straining or coughing may suggest the onset of myocardial rupture.

2. **(2) Subacute course.** Some patients may have a contained rupture and present subacutely with pain suggestive of pericarditis, nausea, and hypotension. In a large retrospective analysis of post-MI patients, 2.6% of patients were found to have sustained subacute ventricular free wall rupture. Bedside echocardiography may reveal localized pericardial effusion or pseudoaneurysm.

b. **Physical findings.** Jugular venous distention, pulsus paradoxus, diminished heart sounds, and a pericardial rub suggest subacute rupture. New to-and-fro murmurs may be heard in patients with subacute rupture or pseudoaneurysm.

2. **Pathophysiology**

a. Rupture most commonly occurs at the anterior or lateral wall, although any wall may be involved.

b. There are **three distinct types of ventricular free wall rupture** (Fig. 3.2):

1. **(1) Type I** generally occurs within the first 24 hours and is a slit-like full-thickness rupture characterized by abrupt onset of symptoms (this rupture type increases with thrombolytics).
2. **(2) Type II** occurs as a result of erosion of the myocardium at the site of infarction. The rupture progresses more slowly and symptoms may be subacute.
3. **(3) Type III** occurs late and is characterized by expansion of the infarct zone with marked wall thinning and then rupture through the subsequent aneurysmal segment.

3. **Diagnostic testing.** There may not be time for diagnostic testing in the treatment of patients with acute ventricular free wall rupture.

a. In addition to evidence for new MI, an **ECG** may show junctional or idioventricular rhythm, low-voltage complexes, and tall precordial T-waves. A large proportion of patients have transient bradycardia immediately preceding rupture.

b. **Transthoracic echocardiography** reveals findings of **cardiac tamponade** in patients with a subacute course. Visualization of ventricular free wall rupture may be improved with echocardiographic contrast agents.

c. **Cardiac catheterization.** Hemodynamic evaluation with a PA catheter may reveal **equalization of the RA pressure, RV diastolic pressure, PA diastolic pressure, and PCWP** consistent with tamponade. During left heart catheterization, analysis of the arterial waveform may reveal significant **respiratory variations in the systolic blood pressure (pulsus paradoxus)**. Ventriculography performed in the right anterior or left anterior oblique orientation may allow visualization of the rupture.

d. **Cardiac MRI and CT** can be utilized in hemodynamically stable patients but are usually not available for critical decision making.

4. **Therapy.** Reperfusion therapy has reduced the overall incidence of cardiac rupture.

a. **Priority of therapy.** The goal is to rapidly identify the problem and perform emergency surgical treatment.

b. **Medical therapy** has little role in the treatment of these patients, except for aggressive supportive care in anticipation of surgical correction. **FIGURE 3.2** Morphologic classification of ventricular free wall rupture. (Reprinted from Becker AE, van Mantgem JP. Cardiac tamponade. A study of 50 hearts. *Eur J Cardiol*. 1975;3:349–358. Copyright © 1975 Elsevier. With permission.)

c. **Percutaneous therapy**

1. **(1) In the setting of hemodynamic extremis, immediate pericardiocentesis** should be performed in patients with tamponade as soon as the diagnosis is made and while arrangements are being made for transport to the operating room.
2. **(2)** An indwelling catheter should be clamped and left in the pericardial cavity and connected to a drainage bag during transfer to the operating room so that continued decompression of the pericardial cavity with recurrent hemodynamic compromise can be achieved.

d. **Surgical therapy.** Emergency thoracotomy with surgical repair is the definitive therapy and is the **only chance for survival among patients with acute ventricular free wall rupture**.

D. Ventricular pseudoaneurysm (i.e., contained rupture)

1. **Clinical presentation.** Ventricular pseudoaneurysm is **more likely to occur with inferior MI than with anterior MI**.

a. **Signs and symptoms.** Pseudoaneurysms may remain clinically silent and be discovered during routine investigation; however, patients may present with chest pain, dyspnea, recurrent tachyarrhythmia, and sudden cardiac death.

b. **Physical findings.** Systolic, diastolic, or to-and-fro murmurs related to flow of blood across the narrow neck of the pseudoaneurysm during systole and diastole may be appreciated.

2. **Pathophysiology.** Ventricular pseudoaneurysm is caused by contained rupture of the LV free wall.

a. The **outer walls of a true ventricular aneurysm are formed by infarcted myocardium and scar**, whereas the **outer walls of a pseudoaneurysm are formed by the pericardium and mural thrombus**. A pseudoaneurysm may remain small or undergo progressive enlargement.

b. Ventricular pseudoaneurysms communicate with the body of the ventricle through a **narrow neck, the diameter of which is typically <50% of the diameter of the fundus**.

3. **Diagnostic testing**

a. A **chest radiograph** may show cardiomegaly with an abnormal bulge on the cardiac border.

b. An **ECG** may demonstrate persistent ST-segment elevation, as with true aneurysms.

c. **Ventriculography is a reliable method of diagnosis**.

d. **Echocardiography, cardiac MRI, and cardiac CT** may be utilized in evaluation as well. Echocardiographic contrast agents may increase the diagnostic accuracy.

4. **Therapy.** Spontaneous rupture may occur without warning in approximately one-third of patients with a pseudoaneurysm. **Surgical resection is recommended for patients with or without symptoms, regardless of the size of the pseudoaneurysm, to minimize the risk of death.**

E. Ventricular aneurysm

1. **Clinical presentation.** The incidence of ventricular aneurysm after MI in the reperfusion era is approximately <5% and occurs **more commonly with anterior MI than with inferior or posterior MI**.

a. **Signs and symptoms**

1. **(1) Acute aneurysm.** Acute development of a large ventricular aneurysm can result in severe LV dysfunction and cardiogenic shock. Patients with an acute MI that involves the apex of the LV, particularly those with transmural anteroapical infarcts, are at greatest risk. Acute aneurysms expand during systole. This expansion wastes contractile energy generated by normal myocardium and puts the entire ventricle at a mechanical disadvantage.
2. **(2) Chronic aneurysms** persist >6 weeks after MI, are less compliant than acute aneurysms, and rarely expand during systole. Patients with chronic aneurysms may experience heart failure, ventricular arrhythmias, mural thrombus, and systemic embolism, but frequently are asymptomatic.

b. Physical findings. A dyskinetic segment of the ventricle may be apparent during inspection or may be felt during palpation. The apical impulse may be displaced to the left of the mid-clavicular line because of cardiac enlargement. An S_3 or S_4 gallop may be appreciated due to LV dilation and stiffening. A systolic murmur of MR may occur due to changes in LV geometry.

2. **Pathophysiology.** Infarct expansion and progressive LV dilation are consequences of absent or ineffective coronary reperfusion. The aneurysmal segment initially consists of necrotic tissue and is later replaced by fibrous scar tissue.

3. **Diagnostic testing**

a. ECG

1. **(1) Acute aneurysm.** The ECG reveals evidence of ST-segment elevation MI, which may persist despite evidence of reperfusion.
2. **(2) Chronic aneurysm.** ST-segment elevation that persists >6 weeks occurs in patients with chronic ventricular aneurysms.

b. Chest radiography may reveal a localized bulge in the cardiac silhouette.

c. Transthoracic echocardiography is the diagnostic **test of choice** and accurately depicts the aneurysmal segment. It may also reveal the presence of a mural thrombus. Echocardiography is useful in differentiating a true aneurysm from a pseudoaneurysm. Typically, true aneurysms have a wide neck, whereas pseudoaneurysms have a narrow neck in relation to the diameter of the aneurysm.

d. Cardiac **MRI and CT** may also be utilized to characterize ventricular aneurysm and better detect thrombus.

4. **Therapy**

a. Medical therapy

1. **(1) Acute aneurysm.** LV failure caused by acute aneurysm is managed with **intravenous vasodilators** and **IABP** therapy. **Angiotensin-converting enzyme (ACE) inhibitors** have been shown to reduce infarct expansion and progressive LV remodeling. Because infarct expansion starts early, ACE inhibitors should be initiated within the first 24 hours of the onset of acute MI if blood pressure allows.
2. **(2) Chronic aneurysm.** Heart failure associated with chronic aneurysm formation is managed with afterload reduction, namely with ACE inhibitors.
3. **(3) Anticoagulation.** Anticoagulation with **warfarin** should be prescribed (AHA/ACC class I indication) to patients found to have a LV mural thrombus or embolic phenomenon. See below for discussion.

b. **Surgical therapy.** Patients with refractory heart failure and/or refractory ventricular arrhythmias should be considered for aneurysmectomy. Surgical resection may be followed by conventional closure or newer techniques (e.g., inverted T-closure and endocardial patch) to maintain LV geometry.

TABLE 3.2 Causes of Hypotension in Patients Presenting with Inferior Myocardial Infarction

Right ventricular infarction
Left ventricular failure
Bradyarrhythmia
Acute severe mitral regurgitation
Ventricular septal rupture
Bezold–Jarisch reflex

F. **LV failure and cardiogenic shock.** Please refer to Chapter 4 addressing this condition.

G. **RV failure.** Mild RV dysfunction is common after **MI of the inferior or inferoposterior wall**; however, hemodynamically significant RV impairment occurs in only 10% of patients. The **proximal right coronary artery** (RCA) is commonly involved. Extensive, irreversible RV damage is unusual because the RV has lower oxygen requirements because of its smaller muscle mass, is perfused during systole and diastole, and often receives extensive left-to-right collateral blood flow. Restoring patency of the infarct-related artery usually results in restoration of RV function within 48 to 72 hours.

1. Clinical presentation

a. **Signs and symptoms.** The triad of **hypotension, jugular venous distention, and clear lung fields** is highly specific (but has poor sensitivity) for RV infarction. Patients with severe RV failure have symptoms of a low cardiac output state, including diaphoresis; cool, clammy extremities; and altered mental status. Patients often are hypotensive and oliguric. The use of **nitrates or β-blockers during routine MI treatment may precipitate profound hypotension** and provides the first clue of RV involvement. Table 3.2 lists causes of hypotension among patients with inferior wall MI.

b. **Physical findings.** Patients with RV failure without concomitant LV failure may have elevated jugular venous pressure (JVP) and an RV S_3 with clear lungs. The combination of JVP >8 cm H_2O and **Kussmaul sign** (i.e., failure of JVP to decrease with inspiration) is sensitive and specific for severe RV failure. Elevated right-sided pressures can occasionally result in **right-to-left shunting** through a patent foramen ovale and manifest as desaturation. This should be considered in patients with RV infarction and hypoxia. Table 3.3lists the clinical findings associated with an RV infarction.

2. Pathophysiology.

RV involvement depends on the location of the RCA occlusion. Marked dysfunction occurs only if occlusion is proximal to the acute marginal branch. The degree of RV involvement also depends on the presence of left-to-right collateralization and the extent of diastolic reverse perfusion through the Thebesian veins.

3. Diagnostic testing

a. An **ECG** usually shows **inferior ST-segment elevation**. ST-segment elevation in **V_4R** in the setting of suspected RV infarction has a positive predictive value of 80%. RV infarction is also suggested by ST-segment elevation that is greater in lead III than lead II. ST-segment elevation exceeding 1 mm may be seen in V_1 and occasionally in V_2 and V_3 (Fig. 3.3).

TABLE 3.3 Clinical Findings Associated with Right Ventricular Infarction

Hypotension
Elevated jugular venous pressure
Kussmaul sign
Abnormal jugular venous pressure pattern (y ≥ x descent)
Tricuspid regurgitation
Right-sided S_3 and S_4
Pulsus paradoxus
High-grade atrioventricular block

b. A **chest radiograph** is usually normal and there is no evidence of pulmonary congestion.

c. **Transthoracic echocardiography** is the diagnostic **study of choice** for RV infarction. It may demonstrate RV dilation and severe RV dysfunction and usually shows LV inferior wall dysfunction. It is also useful in differentiating RV infarction from other syndromes that can mimic it, such as cardiac tamponade.

d. **PA catheterization.** Hemodynamic monitoring with a PA catheter usually reveals **high RA pressures with low PCWP**. Acute RV failure results in underfilling of the LV and a low cardiac output state. The PCWP is usually low unless concomitant, severe LV dysfunction is present. In some patients, RV dilation can cause decreased LV performance resulting from ventricular interdependence. As the RV dilates, the septum flattens or bows into the LV and restricts ventricular filling. RA pressure >10 mm Hg with an RA pressure to PCWP ratio ≥0.8 strongly suggests RV infarction.

4. Therapy

a. Medical therapy

1. **(1) Fluid administration.** Management of RV infarction involves volume loading to increase preload and cardiac output. Fluid boluses up to a liter may be considered with monitoring of hemodynamic status. Overzealous fluid administration in a patient may result in marked RV dilation with a shift in the interventricular septum that can impede LV filling and further decrease LV preload. A central venous pressure of approximately 15 mm Hg may serve as a target.
2. **(2) Inotropes.** When volume loading fails to increase cardiac output, the use of inotropes is indicated. Administration of **dobutamine**will augment RV contractility and increases cardiac output.

b. Percutaneous therapy

1. **(1)** Patients who undergo successful **reperfusion** of the infarct-related artery have improved RV function and decreased 30-day mortality rates. This is ideally achieved by performing immediate primary PCI.

2. **(2) AV sequential pacing** may markedly improve hemodynamics in a patient with RV infarction and bradyarrhythmia or loss of sinus rhythm. **A longer AV delay of approximately 200 ms and a heart rate of 80 to 90 beats/min are usually optimal for these patients.**

FIGURE 3.3 Electrocardiogram demonstrating acute inferior myocardial infarction with right ventricular involvement.

3. **(3)** In a patient with refractory shock, an IABP may be considered. When available, support with a temporary RV support device like an RP Impella or a Protek Duo should be considered.

H. Dynamic left ventricular outflow tract (LVOT) obstruction. Dynamic LVOT obstruction is an **uncommon complication** of acute anterior MI. Although this complication has been cited only in case reports, it may be an underappreciated and underreported complication.

1. **Clinical presentation**

a. **Signs and symptoms.** Patients may have respiratory distress, diaphoresis, and cool, clammy extremities in addition to the typical signs and symptoms of acute MI. Patients with severe obstruction may appear to be in cardiogenic shock, with severe orthopnea, dyspnea, and oliguria in addition to altered mental status from cerebral hypoperfusion.

b. **Physical findings** frequently include a new systolic ejection murmur heard best at the left upper sternal border with radiation to the neck. A new systolic murmur can be heard at the apex with radiation to the axilla, as a result of systolic anterior motion (SAM) of the mitral leaflet. An S_3 gallop, pulmonary rales, hypotension, and tachycardia may also occur.

2. **Pathophysiology.** The dynamic LVOT obstruction that may occur as a complication of acute anterior MI is related to compensatory hyperkinesis of the basal and mid segments of the LV. The increased contractile force of these regions decreases the cross-sectional area of the LVOT. The resultant increase in velocity of blood through the outflow tract can produce decreased pressure below the mitral valve and cause anterior mitral valve leaflet displacement toward the septum (i.e., Venturi effect). This results in further outflow tract obstruction and MR. It has been postulated that this complication can play a role in ventricular free wall rupture. LVOT obstruction leads to increased end-systolic intraventricular pressure, which leads to increased stress of the weakened, necrotic infarcted zone.

3. **Diagnostic testing. Transthoracic echocardiography** is the diagnostic test of choice and helps evaluate the hyperkinetic segments, the LVOT obstruction, and the presence of systolic SAM of the mitral leaflet.

4. **Medical therapy** is focused on decreasing myocardial contractility and heart rate while expanding intravascular volume and increasing afterload modestly.

a. **β-Blockers** should be added judiciously and with careful monitoring of the heart rate, blood pressure, and cardiac output.

b. **Intravenous hydration** should be initiated with several small (250 mL) boluses of normal saline to increase preload and decrease LVOT obstruction and SAM. The patient's hemodynamic and respiratory status should be monitored closely during this therapeutic intervention.

III. ARRHYTHMIC COMPLICATIONS. Arrhythmias are a common complication after acute MI and are associated with significant mortality. Please refer to the dedicated chapters for further discussion.

IV. EMBOLIC COMPLICATIONS.

The contemporary incidence of LV mural thrombus after acute MI is approximately 1% to 2%. The incidence of mural thrombus in patients with a **large anterior wall MI** may increase to approximately 10%, especially in the absence of timely reperfusion. Other factors associated with LV mural thrombus include **decreased LV ejection fraction, wall motion abnormalities, and LV aneurysm**.

a. Clinical presentation

1. **Signs and symptoms.** The most common clinical presentation of an embolic complication is stroke, although patients may have limb ischemia, renal infarction, and intestinal ischemia. Most episodes of systemic embolization occur in the first 2 weeks after acute MI.
2. **Physical findings.** The physical findings depend on the site of embolism.

a. Patients with stroke present with neurologic deficits.

b. Embolism to the peripheral circulation results in limb ischemia and cold, pulseless, and painful extremities.

c. Renal infarctions may cause hematuria and flank pain.

d. Mesenteric ischemia causes abdominal pain and bloody diarrhea.

3. **Diagnostic testing**

a. **Transthoracic echocardiography** is the initial diagnostic test of choice to evaluate for LV mural thrombus. Echocardiographic contrast agents may increase the diagnostic accuracy.

b. **Cardiac MRI** has similar specificity but is more sensitive than echocardiography in the detection of an LV mural thrombus.

b. Therapy

with anticoagulation is recommended in the early setting of a ventricular thrombus associated with an acute MI and is a class IIa recommendation by the ACC/AHA.

1. **Vitamin K antagonists** reduce the rate of embolization. Intravenous heparin or low molecular weight heparin can be used in the acute setting until therapeutic on warfarin. Goal international normalized ratio is 2 to 3. Anticoagulation does not necessarily resolve the thrombus and it may become calcified and laminated over time. Controversy exists on the duration of anticoagulation necessary if there is persistence of the thrombus beyond 3 to 6 months.
2. **Novel anticoagulants** such as dabigatran, rivaroxaban, and apixaban have not been studied in this population and **not currently approved** for this indication.
3. For those requiring dual antiplatelet, care must be taken when initiating **"triple therapy." Bleeding risks must be considered** in each individual patient. Newer strategies, such as early discontinuation of aspirin, are being studied in those requiring triple therapy.

V. INFLAMMATORY COMPLICATIONS

. **Early pericarditis.** The incidence of pericarditis has decreased in the reperfusion era. Cardiac MRI studies, however, suggest that it is underdiagnosed as it may be asymptomatic, or masked by the ECG changes and symptoms that accompany acute MI.

1. **Clinical presentation.** Early pericarditis occurs in patients with transmural MI. A transient pericardial friction rub may be audible in some patients before symptoms become prominent.

a. **Signs and symptoms**

1. **(1)** Patients report progressive, severe chest pain that lasts for hours. The **pain is postural**: worse when the patient is supine and alleviated if the patient sits up and leans forward. The pain is usually pleuritic in nature and is worsened with deep inspiration, coughing, and swallowing.
2. **(2) Radiation of pain to the trapezius ridge** is nearly pathognomonic for acute pericarditis and does not occur in patients with ischemic pain. The pain may also radiate to the neck and less frequently to the arm or back.

b. Physical findings. The presence of a pericardial friction rub is pathognomonic for acute pericarditis; however, it can be evanescent.

1. **(1)** The rub is best heard at the left lower sternal edge with the diaphragm of the stethoscope.
2. **(2)** The rub has three components: one component each in atrial systole, ventricular systole, and ventricular diastole. In about 30% of patients, the rub is biphasic, and in 10% it is uniphasic.
3. **(3)** The development of pericardial effusion may cause fluctuations in the intensity of the rub, although the rub may still be heard despite substantial pericardial effusion.

2. Etiology and pathophysiology. Pericarditis typically results from an area of localized pericardial inflammation overlying the infarcted myocardium. The inflammation is fibrinous in nature. The development of an evanescent pericardial rub correlates with a larger infarct and hemodynamic derangements.

3. Diagnostic testing

a. An **ECG** is important in the diagnosis of pericarditis; however, evolving electrocardiographic changes may make the diagnosis difficult for patients who have had MI. Unlike ischemia, in which the changes are limited to a particular territory, pericarditis produces generalized electrocardiographic changes.

1. **(1)** The ST-segment elevation seen with pericarditis is a concave upward or saddle-shaped curve.

TABLE 3.4 Electrocardiographic Changes of Pericarditis

Stage I	ST-elevation, upright T-waves
Stage II	ST-elevation resolves, upright to flat T-waves
Stage III	ST-isoelectric, inverted T-waves
Stage IV	ST-isoelectric, upright T-waves

2. **(2)** In pericarditis, T-waves become inverted after the ST-segment becomes isoelectric, whereas in acute MI, T-waves may become inverted when the ST-segment is still elevated.
3. **(3)** Four phases of electrocardiographic abnormality have been described in association with pericarditis (Table 3.4).

b. Echocardiography may reveal pericardial effusion, which strongly suggests pericarditis, although the absence of effusion does not rule out the diagnosis. When suspected, an MRI may be confirmatory with enhancement of the involved pericardium noted on gadolinium imaging.

4. Therapy

a. Aspirin is used to manage post-MI pericarditis and doses as high as 650 mg every 4 to 6 hours may be needed (class I recommendation).

b. **Nonsteroidal anti-inflammatory agents and corticosteroids should not be used to treat these patients** (class III recommendation). These agents may interfere with myocardial healing and contribute to infarct expansion.

c. **Colchicine** may be beneficial in those when aspirin is not effective. Colchicine 0.6 mg every 12 hours plus conventional therapy with aspirin decreases symptom recurrence in patients with idiopathic pericarditis.

a. **Late pericarditis (i.e., Dressler syndrome).** This is rarely seen and occurs 1 to 8 weeks after MI. The pathogenesis is unknown, but an autoimmune mechanism has been suggested.

1. **Clinical presentation.** Patients may present with chest discomfort that suggests pericarditis, pleuritic pain, arthralgia, malaise, fever, pericardial friction rub, elevated leukocyte count, and an elevated sedimentation rate. Echocardiography may reveal a pericardial effusion.

2. **Therapy** is similar to that for early post-MI pericarditis: aspirin, colchicine, and avoidance of nonsteroidal anti-inflammatory drugs and corticosteroids. However, if >4 weeks have elapsed since the MI, nonsteroidal anti-inflammatory agents may be indicated for severe symptoms.

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CHAPTER 4

Cardiogenic Shock Complicating Acute Myocardial Infarction

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I. INTRODUCTION. Hypotension with resultant inadequate end-organ perfusion can be due to a number of different mechanisms following acute myocardial infarction (MI; e.g., distributive, obstructive, hypovolemic, and cardiogenic). **To treat the patient effectively, the correct inciting mechanism(s) must be identified.** In pure cardiogenic shock, there is **evidence of ineffective tissue perfusion** because of primary failure of the left ventricular (LV) and/or right ventricular (RV) myocardium to meet the demand. Clinically, this usually manifests as hypotension and may be accompanied by signs of hypoperfusion that may include the presence of cold and clammy peripheries, oliguria, and confusion. Right heart catheterization in the setting of LV dominant shock reveals a low cardiac index <1.8 to 2.2 L/min/m^2, adequate or elevated LV and/or RV filling pressures, and significant heterogeneity in systemic vascular resistance that depends on the degree of vasodilatory inflammatory response. Cardiac tamponade, mechanical, and arrhythmogenic complications should be excluded in this setting because these merit special consideration (see Chapter 3).

II. CLINICAL PRESENTATION. Cardiogenic shock complicates 5% to 8% of ST-elevation myocardial infarction (STEMI) and 2.5% of non–ST-elevation myocardial infarction (NSTEMI) cases in the current era of early reperfusion. Onset is typically within the first 24 hours of admission and it is not unusual for patients to present with mild symptoms and a borderline low blood pressure with tachycardia.

A. Symptoms

1. Patients in cardiogenic shock from LV failure typically present with **respiratory distress**. **Confusion, lethargy, nausea, diaphoresis, or anxiety** may occur because of inadequate tissue perfusion.
2. Those with predominant RV failure usually present with no respiratory symptoms.

B. Physical findings

1. **Hypotension, tachycardia, diminished urine output (<30 mL/h), and cool, mottled, and cyanotic extremities** typically characterize the clinical presentation of cardiogenic shock. Peripheral pulses are often diminished in cardiogenic shock because of decreased pulse pressure **(pulsus parvus)**. In a failing left ventricle, the strength of every other beat may alternate, a phenomenon known as **pulsus alternans**. A **dyskinetic segment of the**

ventricle may be apparent during inspection or may be felt during palpation. An **S_3 gallop** is often noted in this setting.

2. Patients with acute mechanical complications of MI such as ventricular septal rupture, acute mitral regurgitation, ventricular free wall rupture, ventricular pseudoaneurysm, ventricular aneurysm, RV failure, and dynamic outflow tract obstruction may present with additional physical findings as discussed in Chapter 3 dedicated to MI complications. These findings can alter the strategy of revascularization as discussed later in this chapter.
3. Cardiogenic shock because of LV failure may cause pulmonary congestion and inspiratory rales. However, **a significant proportion of patients in the SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK?) registry had no pulmonary congestion**. Neither auscultation nor chest radiograph detected pulmonary edema in 28% of the patients.
4. A select group of patients may exhibit **preshock**. This clinical entity is characterized by signs of hypoperfusion with resting tachycardia but without frank hypotension because of a compensatory increase in systemic vascular resistance. On right heart catheterization, these patients have an ineffective cardiac index and are at high risk for in-hospital mortality.

III. PROGNOSIS.

Despite advancements in coronary reperfusion, **contemporary mortality associated with MI complicated by cardiogenic shock remains high at 40% to 70%**. **Prior infarct, older age, female sex, diabetes, and anterior infarction** are risk factors for the development of cardiogenic shock after MI. Mortality with cardiogenic shock has decreased significantly in younger patients undergoing primary percutaneous coronary intervention (PCI; 30% to 40%), but remains high (60% to 70%) among the elderly (age > 75 years) regardless of revascularization. Patients may present anywhere along a spectrum of severity, and mortality exponentially increases with worsening clinical presentation, hemodynamic derangement, and prolonged time to reperfusion from symptom onset. The only proven intervention to definitively reduce mortality in this setting is **early revascularization.**

A. Patients with left main or saphenous vein graft culprit lesions tended to have the highest mortality in the SHOCK trial, whereas those with right coronary artery lesions fared the best.
B. Increasing age, shock on admission, clinical evidence of end-organ hypoperfusion, anoxic brain damage, systolic blood pressure, prior coronary artery bypass grafting, anterior MI location, and creatinine >1.9 mg/dL are predictors of a poor outcome.
C. Timing from symptom onset to revascularization and thrombolysis in myocardial infarction flow grade in the culprit vessel may also predict mortality.

IV. ETIOLOGY AND PATHOGENESIS

A. **Etiology.** A number of complications following acute MI can result in cardiogenic shock. Table 4.1 outlines the various etiologies of *cardiogenic* shock complicating acute MI that need to be considered. **In the SHOCK registry, LV failure (79%), severe mitral regurgitation (7%), ventricular septal rupture (4%), RV failure (3%), and ventricular free wall rupture (1%) were the leading causes of cardiogenic shock in this clinical setting.** Isolated RV failure was observed to cause shock in up to 5% of cases. **Bradyarrhythmias, tachyarrhythmias, and ventricular stunning following an electrical storm** can also precipitate cardiogenic shock. **Medications** administered for acute MI such as β-blockers, intravenous antiarrhythmics with negative inotropic properties, angiotensin-converting enzyme inhibitors, and morphine can cause iatrogenic shock by

precipitating hypotension. In the Clopidogrel and Metoprolol in Myocardial Infarction Trial, early β-blocker use was associated with an increased risk of developing cardiogenic shock. **Occult bleeding**resulting from antiplatelet and anticoagulation therapies as well as access site bleeding may result in hypotension and circulatory collapse and should be excluded.

TABLE 4.1 Causes of Cardiogenic Shock Complicating Acute Myocardial Infarction

Left ventricular failure
Right ventricular failure
Ventricular septal rupture
Acute mitral regurgitation
Ventricular aneurysm
Ventricular free wall rupture
Cardiac tamponade
Dynamic left ventricular outflow tract obstruction
Arrhythmia
Iatrogenic (e.g., β-blocker related)

B. **FIGURE 4.1** Expansion of the pathophysiologic paradigm of cardiogenic shock to include the potential contribution of inflammatory mediators. iNOS, inducible nitric oxide synthase; LVEDP, left ventricular end-diastolic pressure; NO, nitric oxide; $ONOO^-$, peroxynitrite; SVR, systemic vascular resistance. (From Hollenberg SM. Pathophysiology. In: Hochman JS, Ohman EM, eds. *Cardiogenic Shock*. Oxford, England: Wiley-Blackwell; 2009. Copyright © 2009 American Heart Association. Reprinted by permission of John Wiley & Sons, Inc.)

C. Cardiogenic shock because of LV failure usually occurs in the setting of an extensive MI. Autopsy studies have revealed that at least 40% of the LV is usually and up to 40% of patients have a history of prior MI. Patients typically have significant **left main** or **severe three-vessel coronary artery disease** (16% and 53%, respectively, in the SHOCK trial) and the majority have proximal involvement of the **left anterior descending artery**. Occasionally, in the setting of an ischemic cardiomyopathy, a small acute MI in a nonanterior location may precipitate shock. **It is critical to evaluate and eliminate other etiologies of shock when the degree of hemodynamic instability is disproportionate to the size of the presenting infarction.**

D. **Pathophysiology.** Ineffective LV stroke volume results in hypotension with compensatory tachycardia. In the setting of extensive coronary artery disease, hypotension and rising LV end-diastolic pressures compromise coronary perfusion and precipitate ischemia both in the infarct and in the noninfarcted myocardium. As a result, a vicious cycle ensues, culminating in circulatory collapse, irreversible end-organ injury, and death. Revascularization may halt this process by salvaging ischemic heart muscle and restoring hemodynamic stability.

Although vasopressor use can temporarily improve hemodynamics, these agents increase oxygen demand, induce coronary vasospasm, and can precipitate ischemia and electrical instability. Hypotension typically leads to compensatory peripheral vasoconstriction and an increase in systemic vascular resistance. However, observations from the SHOCK registry refuted this classic paradigm. Many patients with cardiogenic shock were noted to have a low systemic resistance, similar to patients with septic shock. This vasodilatory response is likely a result of significant myocardial injury which in turn induces a systemic inflammatory response–like syndrome that is responsible for this finding. Up to one-fifth of patients in cardiogenic shock may present in this manner. Figure 4.1 provides an overview of the pathophysiology of cardiogenic shock caused by acute MI and the expansion of the paradigm to include the contribution of inflammatory mediators.

V.DIAGNOSTIC STUDIES

A. **Laboratory studies** may reveal metabolic acidosis with elevated lactic acid, acute renal failure, transaminitis, electrolyte abnormalities (sodium, potassium), and reactive leukocytosis.

B. **Electrocardiogram.** Patients with cardiogenic shock resulting from LV failure usually have extensive electrocardiographic abnormalities consistent with massive infarction, severe diffuse ischemia, or evidence of a large, prior MI. Extensive ST-segment deviations are common. Both STEMI and NSTEMI can manifest as cardiogenic shock.

C. **Chest radiography** may reveal pulmonary congestion.

D. **We strongly advocate for hemodynamic monitoring** with an **arterial line** and **pulmonary artery (PA) catheter in this setting.** Invasive monitoring can help establish the diagnosis in unclear cases, identify the etiology, guide management, and measure treatment response. Swan-Ganz may also identify complications of acute MI, including RV infarction, acute mitral regurgitation, ventricular septal rupture, and presence of cardiac tamponade. Right heart catheterization enables the clinician to accurately measure cardiac output and index in this setting as well as estimate systemic and pulmonary vascular resistance. Estimation of cardiac power in this setting is highly prognostic, and measures like the Pulmonary Artery Pulsatility index help assess adequate RV response. Accurate assessment of serial hemodynamic parameters of LV, RV, and peripheral status are vital to evaluate treatment response and to assess when and which mechanical circulatory devices to support the circulation are indicated.

E. **Comprehensive transthoracic echocardiography in all patients with cardiogenic shock is warranted.** Echo enables the clinician to determine the dominant etiology of shock as well as the extent of myocardial injury. It can identify mechanical complications of acute MI that contribute to cardiogenic shock. It may also draw attention to additional causes of cardiogenic shock such as aortic dissection, cardiac tamponade, or pulmonary embolism.

VI.MANAGEMENT

A. **Successful early revascularization** limits infarct size and translates into improved mortality. Thus, every effort should be made to facilitate prompt angiography to define coronary anatomy in the patient with acute MI and cardiogenic shock. In the SHOCK trial, early revascularization saved **13 lives per 100 treated at 1 year** compared with a strategy of medical stabilization and delayed revascularization. This strategy should be strongly considered in all patients aged <75 years in the absence of contraindications; select older patients with good premorbid functional status also derived a similar benefit from this

approach. PCI is the dominant and preferred modality of revascularization, but surgery should be considered in select situations guided mainly by the extent and location of disease and concomitant valvular function.

1. **Fibrinolysis** should be administered to patients who present initially with STEMI and cardiogenic shock (preferably within 3 hours from symptom onset, but acceptable up to 12 hours) to a facility ***without PCI capability or unable to transfer to a PCI-capable facility in <120 minutes***. A reduction in mortality was observed in several studies including a post hoc analysis from the SHOCK trial.
2. **Primary PCI** remains the preferred method of revascularization in shock because it is more likely to offer timely and successful revascularization. A strategy of **multivessel PCI was recommended in this setting** with a goal of achieving complete revascularization and decreasing remote ischemia**.** This clinical dogma has **now been disproven** by the results of the CULPRIT SHOCK trial; a strategy of multivessel PCI in this study was associated with increased mortality compared with a culprit vessel–alone approach.
3. Emergent **coronary artery bypass grafting as the revascularization strategy should be considered in select patients in this setting.**

B. Percutaneous mechanical circulatory support. The availability of temporary devices that provide mechanical circulatory support has revolutionized the management of cardiogenic shock. Although these devices have not proven to decrease mortality in this setting, their adoption enables a strategy of **a bridge to decision to be adopted in patients with refractory shock despite revascularization.** Circulatory support prevents or enables recovery of end-organ injury while providing the clinician time to gauge the impact of revascularization and also assess candidacy for advanced support with a durable ventricular assist device (VAD) or transplantation. Patients who improve can then be weaned off support whereas eligible patients in refractory shock may be considered for VAD or transplantation. In patients with refractory shock without further treatment options, withdrawal of care in a controlled fashion may be considered when appropriate. Experimental studies suggest that early ventricular unloading may enhance myocardial salvage following revascularization. Studies are currently evaluating the utility of this strategy in clinical practice by adopting early LV unloading with mechanical support (Impella) while performing adjunctive revascularization.

1. **Intra-aortic balloon counterpulsation (IABP).** This is the most available and traditional supportive device. IABP counterpulsation reduces afterload, improves coronary and peripheral perfusion, and decreases the myocardial oxygen requirement via reduction in wall stress. Contraindications to placement include the presence of significant peripheral vascular disease, aortic dissection, and more than moderate aortic insufficiency. The largest sized balloon appropriate for the patient's height should be selected. At 30 days and 1 year, the Intraaortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) trial failed to show a significant difference in rates of all-cause mortality or secondary end points (e.g., length of stay, renal function) in patients receiving IABP support compared with those who did not. Current guidelines recommend against routine use of IABP support in cardiogenic shock complicating acute MI. Nevertheless, we feel that early rapid IABP insertion can stabilize hemodynamics enough to permit angiography and revascularization and should be considered in select patients. Current American College of Cardiology/American Heart Association guidelines give a class

IIa recommendation for the use of IABP support for patients who do not stabilize with pharmacologic therapies.

2. Percutaneous LV assist devices such as the **Impella** (LP or CP) can provide 2.5 to 4.0 L/min support, directly unload the left ventricle, and be placed before or after revascularization. Robust circulatory support can be provided by the Impella 5.0 device, but currently necessitates a surgical cut-down for insertion. The prospective Impella LP2.5 vs. IABP in Cardiogenic Shock (ISAR-SHOCK) trial randomized patients with cardiogenic shock from MI to IABP (n = 13 patients) versus Impella 2.5 support (n = 12 patients) and demonstrated that Impella provided significantly more support (change in cardiac index 0.5 vs. 0.1 L/min/m^2) with a low rate of major complications. A firm conclusion regarding mortality differences cannot be drawn from this trial because of the small sample size. In cases of severe RV failure, the Impella-RP right-sided percutaneous support device can be considered and has been shown to improve hemodynamics. The **TandemHeart** (Fig. 4.2) device provides percutaneous left atrial to femoral artery bypass flow at rates of up to 5.0 L/min with percutaneous access and can serve as a bridge to recovery or more definitive therapy. Limited case series from high-volume centers suggest that the TandemHeart device is able to rapidly reverse the terminal hemodynamic compromise seen in patients with severe cardiogenic shock refractory to IABP and/or high-dose vasopressor support. The device unloads the LV by decompressing the left atrium and may be especially useful when considering support in the setting of a ventricular septal rupture. Placement is, however, challenging because it requires technical expertise to cross the interatrial septum, especially in the setting of hemodynamic instability. **Extracorporeal membrane oxygenation (ECMO)** is an established therapy that can be implemented expeditiously in a percutaneous (or surgical) fashion in experienced hands. When utilized in a venoarterial configuration, ECMO provides full hemodynamic support and, as an additional advantage, can support oxygenation if lung function is compromised. Peripheral ECMO can markedly increase LV afterload and strategies should be adopted to avoid LV distension when indicated.

C. **Transvenous pacing.** Patients with inadequate heart rate because of bradyarrhythmia or chronotropic incompetence may require temporary pacing to increase the heart rate and augment cardiac output. **Atrial pacing** maintains atrioventricular synchrony and normal LV contraction and is preferable to ventricular pacing if atrioventricular conduction is intact. Pacemaker-dependent patients may need their rates increased to augment cardiac output.

D. **Medical therapy.** In the setting of circulatory collapse, pharmacologic agents are initially utilized to maintain hemodynamics while supportive mechanical devices are being considered.

1. **Vasopressors.** In general, our initial pressor of choice is **norepinephrine** started at 2 to 5 µg/min and titrated to a maximal dose of 30 µg/min. If there is chronotropic incompetence, **dopamine** can be helpful and is started at 3 µg/kg/min and titrated to a maximal dose of 20 µg/kg/min. Dopamine may be associated with higher mortality in cardiogenic shock than norepinephrine when titrated to maintain an effective mean arterial pressure.

FIGURE 4.2 The TandemHeart percutaneous left ventricular assist device. (Reprinted with permission from CardiacAssist, Inc.)

2. **Inotropic agents** generally increase myocardial work and theoretically worsen ischemia and provoke arrhythmias. These agents should be avoided if possible. Similar to vasopressors, they are used temporarily to maintain perfusion pressure until insertion of mechanical support.

a. **Dobutamine** has a positive inotropic action comparable to that of dopamine and may decrease afterload. Dobutamine is started at a dose of 2.5 µg/kg/min and increased to a maximal dose of 40 µg/kg/min.

b. **Milrinone**, a phosphodiesterase inhibitor with inotropic and vasodilator action, may be beneficial in some patients, especially those with RV dysfunction. Milrinone is given as a 50-µg/kg bolus over 10 minutes, followed by an infusion of 0.375 to 0.75 µg/kg/min. The bolus may be omitted in the care of patients with low blood pressure. Patients without adequate blood pressure may not tolerate milrinone. This agent should be used with caution in patients with hemodynamic instability because of the long half-life and renal clearance of this agent.

TABLE 4.2 Hemodynamic Effects of Medications Used to Manage Cardiogenic Shock

Medication	Preload	Afterload	Inotropy
Dopamine (3–10 µg/kg/min)	0	−	++++
Dopamine (>10 µg/kg/min)	0	+++	+++
Norepinephrine (2–300 µg/min)	0	++++	+
Epinephrine (0.05–1 µg/kg/min)	0	+++	+++
Phenylephrine (0.5–15 µg/kg/min)	0	++++	0
Dobutamine (2.5–25 µg/kg/min)	−	−	++++
Milrinone (0.375–0.75 µg/kg/min)	− −	− −	+++
Nitroglycerin (2.5–300 µg/min)	− − −	−	0
Nitroprusside (0.3–10 µg/kg/min)	− − −	− − −	0

0, no effect; −, decrease; +, increase.

3. **Vasodilators** such as **nitroglycerin** and **sodium nitroprusside** can play an important role in the management of post-MI LV failure by means of preload and afterload reduction. These agents can be particularly helpful in weaning percutaneous mechanical circulatory support. However, in the acute setting of cardiogenic shock, their use may be limited by refractory hypotension.

4. Table 4.2 summarizes the hemodynamic effects of vasoactive medications used in the management of cardiogenic shock.

5. **Antiplatelet and anticoagulation.** Aspirin and therapeutic heparin should be administered to all patients at the time of diagnosis of STEMI barring any contraindication. Given the prevalence of left main or severe multivessel disease in patients who present with shock, it is prudent to withhold upstream administration of an oral $P2Y_{12}$ inhibitor such as clopidogrel, ticagrelor, or prasugrel. In lieu of oral $P2Y_{12}$ inhibitors, administration of intravenous cangrelor or a glycoprotein IIb/IIIa inhibitor should be strongly considered adjunctive to PCI. Crushed oral $P2Y_{12}$ inhibitor can be administered to facilitate absorption when indicated.

6. **β-Blockers and calcium channel blockers** should be avoided given their negative inotropic properties.

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CHAPTER 5

Post–Myocardial Infarction Risk Stratification and Management

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I. **INTRODUCTION.** Although patient outcomes following myocardial have improved, beneficial evidence-based therapies remain underutilized. Following initial management of myocardial infarction (MI), the goals of the physician must be to successfully stratify patients according to risk, implement medical interventions, and initiate risk factor modification during the initial hospitalization and follow-up visits.

II. **RISK STRATIFICATION.** Initial risk stratification and management for both ST-elevation myocardial infarction (STEMI) and non–ST-elevation acute coronary syndrome (NSTEACS) has been detailed in prior chapters. Following initial management, additional risk stratification should be applied to help identify patients at risk for early and late complications as well as to guide evidence-based secondary prevention therapies.

A. **Age** is the ***most important predictor of mortality*** after MI. The average age of patients with first MI is approximately 65 years. Although older patients are at greatest risk and may benefit most, they receive less aggressive treatment compared with younger patients, who have the lowest overall mortality.

B. **Assessment of left ventricular (LV) function**

1. **LV function** is the second most important predictor of mortality after MI. An inverse relation exists between left ventricular ejection fraction (LVEF) and mortality. Mortality is greatest for patients with an LVEF <40%.

   a. Assessment of LV function is indicated for all patients diagnosed with MI.

   b. Echocardiography is often utilized to assess LV function because it is readily available, is relatively inexpensive, and can assess extent of infarction, status of the remote myocardium, concomitant valvular function, as well as mechanical complications of MI. Echo during follow-up can evaluate for adverse ventricular remodeling over time that may result in LV dilatation and drop in LVEF.

   c. Left ventriculography performed during diagnostic catheterization can also be a convenient way to estimate LV function, but involves exposure to additional contrast and can exacerbate hemodynamic instability in the setting of ongoing ischemia or LV dysfunction.

d. Cardiac magnetic resonance imaging (MRI) has emerged as the gold standard for assessing LV function and is useful when other methods are inconclusive or contradictory. With cardiac MRI utilizing gadolinium, LVEF and LV volumes, transmurality and extent of scar, and viability as well as integrity of the microvasculature can be accurately assessed.

C. Other indicators. Biomarkers are useful in further risk-stratifying patients after MI.

1. **Cardiac troponin** elevation identifies high-risk patients and incremental increases in troponin levels, indicating a larger territory of infarction and higher risk.
2. Elevated serum levels of high-sensitivity **C-reactive protein** and **B-type natriuretic peptide may also provide prognostic information**.
3. New **ST-segment changes**, both elevation and depression, portend higher risk of death, heart failure, recurrent ischemia, and severe coronary artery disease (CAD). This is particularly true of persistent ST-elevations after revascularization which can indicate distal embolization or persistent microvascular dysfunction.
4. **Electrical instability**, such as ventricular arrhythmias and atrial fibrillation, are associated with increased risk.
5. Anterior MI, renal insufficiency, poor glycemic control, and anemia are also associated with worse outcomes.

D. Risk models. Various models utilize a combination of the aforementioned risk factors to quantitate a predictive score of patient risk for subsequent cardiac events and mortality. Examples include thrombolysis in myocardial infarction (TIMI) and the Global Registry of Acute Coronary Events.

E. Assessment of residual ischemia

1. The ***extent of CAD*** and ***presence of residual ischemia*** are two strong predictors of mortality among patients who have had an MI.
2. Patients with severe anatomical stenosis, or proven functional ischemia (fractional flow reserve guided) in the noninfarct zone, should undergo additional revascularization of these arteries. Whereas the optimal timing of revascularization is uncertain, anatomical and patient characteristics may lead the operator to perform percutaneous coronary intervention (PCI) of the noninfarct artery at the same sitting, later in the index hospitalization, or following discharge.
3. Occasionally, patients with residual disease will undergo a stress test following discharge to guide the need for additional revascularization. Select patients with extensive anatomical disease suitable for percutaneous revascularization will undergo coronary artery bypass graft (CABG) later in the hospital stay or electively following discharge.
4. Whereas the overwhelming majority of STEMI patients are treated with primary PCI or a pharmaco-invasive strategy, those stable STEMI patients who do not undergo coronary angiography should undergo a submaximal stress test 2 to 3 days after presentation. For the minority of post-MI patients who have not undergone angiography (i.e., those who were treated with a conservative strategy), stress testing ideally before hospital discharge or shortly thereafter (preferably within 3 to 7 days of initial presentation) should be performed, if the results will alter treatment. Submaximal stress testing is safe for those with non–ST-elevation MI (NSTEMI) who do not have signs of ongoing ischemia or heart failure for the preceding 12 to 24 hours.

a. **Submaximal exercise stress testing is optimal for noninvasive risk stratification.** This test provides considerable prognostic information, assesses functional capacity and efficacy of medical therapy, and can guide cardiac rehabilitation after discharge. Patients who achieve at least 3 metabolic equivalents (METs) of the task have a good prognosis. Inability to achieve 3 METs, hypotension during exercise, or marked ST-segment depression or elevation is an indication for coronary angiography.

b. **Stress imaging with echocardiography** or **radionuclide imaging is** recommended in patients who have uninterpretable electrocardiograms (ECG; e.g., baseline ST-T changes, LV hypertrophy, intraventricular conduction delays, paced rhythm, or digoxin-related effects). Addition of either imaging modality increases both the sensitivity and specificity of detecting CAD. Patients with severe resting or exercise-induced LV dysfunction or evidence of extensive ischemia (large perfusion defect, multiple moderate perfusion defects, wall motion abnormalities at low-dose dobutamine or low heart rate, and stress-induced LV dilation) are considered high risk and should undergo coronary angiography. **Adenosine and dipyridamole** are pharmacologic agents used safely in conjunction with imaging for post-MI stress testing if a patient cannot exercise.

c. **Cardiac MRI** has several advantages in this population as well. It has the capability of quantifying the degree of infarcted territory and accurate assessment of LV function. Using various protocols, cardiac MRI can also identify viable ischemic tissue and microvascular dysfunction and evaluate for complications of MI (valvular disease, pericarditis, etc.).

III. **MEDICAL THERAPY AFTER MI.** Initial acute therapy for MI has been previously discussed. After initial evaluation and stabilization, which in the current era usually involves coronary angiography and revascularization of the culprit artery (if one is identified), the next step in therapy is to initiate proper secondary prevention.

A. **Smoking cessation is mandatory.** ***Smoking doubles the rate of reinfarction and death*** after MI, causes coronary artery spasm, and reduces the effectiveness of β-blocker therapy. The risk reduction attributed to smoking cessation is rapid and nearly equals that of post-MI patients who never smoked in only 3 years. Half of all patients who stop smoking after MI will begin smoking again within 6 to 12 months. Many approaches to smoking cessation have been attempted, including pharmacologic therapy, formal smoking cessation programs, hypnosis, and abstinence.

1. **Nicotine substitutes** can be delivered by a variety of vehicles, including transdermal patches, chewing gum, nasal spray, and inhalers. These systems can deliver 30% to 60% of the nicotine of cigarettes. Although nicotine substitutes are not recommended for the acute phase of MI, use of these agents is safe in later phases. Patients who start smoking again should discontinue the use of nicotine substitutes.

2. **Pharmacotherapy. Bupropion** appears to be an effective aid in smoking cessation. The dose is doubled after 3 days and it is then taken twice daily for 7 to 12 weeks. Patients set a goal to stop smoking 1 to 2 weeks into therapy. **Varenicline**, a partial agonist of nicotine receptors, provides nicotine stimulation while blocking cigarette nicotine effects. In a head-to-head trial, varenicline was more effective than bupropion at the 12-week time period, but data suggest no significant difference in rates of abstinence at 1 year. In addition, the Food and Drug Administration issued a communication in 2011 warning that varenicline may increase the risk of cardiovascular (CV) events.
3. **Recommendations.** Physicians can aid patients in their effort to stop smoking by using a stepped approach with education and a firm recommendation to quit smoking, devising a plan, and reinforcing the need to quit. Patients who are likely to relapse are older, less educated, or heavy smokers. Formal smoking cessation programs have been shown to have high rates of patient abstinence. Coinhabitants should also stop smoking to increase the likelihood of success.

B. Lipid management

1. **Low-density lipoprotein (LDL).** Most patients with acute MI have abnormal lipid profiles. Several large, secondary prevention trials have demonstrated that lowering of lipids can reduce the incidence of future mortality, reinfarction, and stroke.
    a. **Diagnostic testing.** All patients who have had an MI should have a complete lipid panel (e.g., total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG)) measured during hospitalization.
    b. **Diet.** Current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend that all patients should start the AHA step II diet (<7% of total calories as saturated fat and <200 mg/d cholesterol). However, adherence to step II diet is low.
    c. **Therapy.** The goals for therapy have been previously discussed. In the absence of contraindications, all patients should be treated with high-dose statin therapy. Statin-intolerant patients should be considered for treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or ezetimibe. Recent data confirms that further lowering LDL levels to 30 mg/dL is associated with clinical benefit and no additional harm. When target LDL levels on maximally tolerated statin therapy are >70 mg/dL, the addition of these agents may also be considered, especially in high-risk subjects. Besides having long-term benefits in reducing cardiac events (which are thought to be the result of more than just lipid lowering), multiple studies including the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering and Pravastatin or Atorvastatin Evaluation and Infection Therapy trials have demonstrated that early initiation of high-intensity statin therapy during an acute coronary syndrome (ACS) is associated with a reduction in major adverse cardiac events.
2. **HDL.** Low HDL cholesterol levels are an independent risk factor for MI. Traditionally, HDL cholesterol can be modestly raised nonpharmacologically through exercise. The cholesteryl

ester transfer protein (CETP) inhibitors result in early sustained and marked increases in HDL with significant reduction in LDL levels, also noted with evacetrapib and anacetrapib. Randomized clinical trials, however, showed no CV benefit with CETP-inhibitor mediated HDL elevation. Multiple clinical studies continue to evaluate the role of HDL modification in this setting.

3. **Triglycerides.** Hypertriglyceridemia may be an independent risk factor for CAD, commonly accompanied by low HDL levels or diabetes. However, as with HDL, treatment to lower TG levels has not been shown to reduce cardiac events. Notably, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial showed that whereas extended release niacin was effective in lowering TG levels significantly, cardiac events were not reduced. Modest TG reduction is usually seen with statin therapy and lifestyle modification. Short of very high TG levels (generally >500 mg/dL) where hypertriglyceridemia can lead to pancreatitis, targeted therapy to reduce TG levels is generally not recommended.

C. **Diabetes management.** The American Diabetes Association recommends treating glucose levels with the goal of lowering the hemoglobin A1c to below or around 7%. The concept of "intensive" glucose control has been challenged by trials demonstrating adverse events associated with this strategy. The Action to Control Cardiovascular Risk in Diabetes trial, a large randomized study of over 10,000 outpatients, was stopped early because of excess mortality in the intensive therapy group assigned to achieve a hemoglobin A1c <6% compared with the standard therapy group whose target A1c was between 7% and 7.9%. Large CV outcome trials with newer classes of agents in diabetes like sodium glucose cotransporter 2 inhibitors and glucagon-like peptide receptor 1 agonists have shown a CV benefit with these agents. As a result, these newer agents should be preferentially utilized in this population and this is detailed in Chapter 44 on diabetes and cardiovascular disease.

D. **Antiplatelet therapy**

1. All patients who have had an MI should take **aspirin** upon presentation and continue indefinitely unless there are absolute contraindications. Aspirin therapy after MI results in a mortality reduction of 25 lives per 1,000 patients treated. Aspirin reduces the rates of vascular mortality, nonfatal stroke, and nonfatal MI. Doses of at least 75 to 162 mg daily are recommended for all patients presenting with ACS. Patients receiving dual antiplatelet therapy (DAPT; e.g., aspirin plus thienopyridines) have fewer side effects, such as bleeding, at lower aspirin doses.

2. **Oral $P2Y_{12}$ inhibitors** (i.e., clopidogrel, prasugrel, ticagrelor) inhibit platelets via adenosine diphosphate antagonism. Clopidogrel remains the most widely used antiplatelet medication, and 1 year of therapy was shown to reduce major adverse cardiac events in patients after unstable angina and NSTEMI (including those who were not revascularized) in the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial. The benefit was also observed in STEMI with the Clopidogrel as Adjunctive Reperfusion Therapy trial and Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT). **Prasugrel and ticagrelor are more potent $P2Y_{12}$inhibitors that also have a faster onset of action.** Prasugrel was superior to clopidogrel for patients undergoing PCI for ACS in the Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis In Myocardial Infarction 38(TRITON-TIMI 38), and ticagrelor was proven superior to clopidogrel in ACS patients (including those not undergoing PCI) in the Platelet Inhibition and Patient Outcomes

trial. Notably, when compared with clopidogrel in patients presenting with ACS who did not undergo PCI in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes trial, prasugrel was not superior to clopidogrel. Because of their higher potency, both prasugrel and ticagrelor are associated with increased bleeding when compared with clopidogrel. Importantly, **prasugrel is absolutely contraindicated in patients with prior stroke and relatively contraindicated in patients over age 75 or <60 kg. Ticagrelor should only be used with low-dose (81 mg) aspirin.**

3. **Adding other medications,** such as sulfinpyrazone and dipyridamole, has not been shown to be more efficacious than aspirin alone and is not recommended for patients who have had an MI.

E. Warfarin sodium

1. Patients with a **large anterior MI and LV thrombus** treated with warfarin are at decreased risk for embolic stroke. Randomized trials do not exist, but most physicians recommend 6 weeks of warfarin therapy for this group of patients. This may assist in stabilization and endothelialization of the thrombus.
2. Data for the routine use of warfarin in conjunction with aspirin for secondary prevention of reinfarction are conflicting. The Combination Hemotherapy and Mortality Prevention study and the Coumadin Aspirin Reinfarction Study trial found no benefit from the addition of warfarin to standard aspirin therapy. However, recurrent events in the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis 2 trial were reduced following fibrinolysis with the addition of warfarin to aspirin for 3 months post-MI. The routine use of warfarin after MI is currently not recommended except for other established indications for anticoagulation, such as atrial fibrillation, deep venous thrombosis, LV thrombus, or prosthetic heart valves. Patients with concomitant use of dual antiplatelet agents for coronary disease are at significant risk for bleeding and hence this therapy should be used judiciously in these patients.

F. Newer oral anticoagulants

1. Rivaroxaban at a dosage of 2.5 and 5 mg twice daily was evaluated against placebo in 15,526 patients with a recent ACS (93% on DAPT with aspirin + clopidogrel) over a mean 13 months of follow-up. The use of rivaroxaban resulted in a significant reduction in the composite end point of CV death, MI, and stroke (8.9% vs. 10.7%, $p = 0.008$) but was associated with higher rates of bleeding (2.1% vs. 0.6%, $p < 0.001$). A mortality benefit was noted with the lower dose of rivaroxaban compared with placebo, and less fatal bleeding compared with the higher dose of rivaroxaban was noted (0.1% vs. 0.4%, $p = 0.04$).
2. The need for triple therapy in patients with an ACS is associated with an unacceptably high bleeding risk. A number of trials utilizing novel strategies involving novel oral anticoagulant agents are being evaluated in this setting.

G. β-Blockers

1. **Indications.** β-Blockers are anti-ischemic, antihypertensive, and antiarrhythmic and they reduce LV wall stress. Mortality reduction results from decreased risk of sudden death, non–sudden cardiac death (SCD), and nonfatal infarction. Overall, the use of β-blockers reduces post-MI events by approximately 20%.
    a. **The beneficial effects of β-blockers are greatest among patients who are at high risk,** such as patients with anterior infarction, complex ventricular ectopy, advanced age, and LV dysfunction. In the COMMIT trial, metoprolol given at presentation significantly

reduced reinfarction and ventricular fibrillation in patients with acute MI who were hemodynamically stable; mortality benefit was not significant, although this was probably the result of a net hazard during days 0 to 1 for patients presenting with New York Heart Association (NYHA) class III or IV heart failure. Several studies have found that only 50% of patients who sustain an MI actually receive β-blockers. **β-Blockers should be started as soon as possible in hemodynamically stable patients with MI** and should be continued indefinitely. Moderate LV dysfunction and compensated congested heart failure are not contraindications to β-blocker treatment.

b. **β-Blockers** without intrinsic sympathomimetic activity, such as carvedilol, metoprolol, propranolol, timolol, and atenolol, appear to have the greatest benefit. Reduction in heart rate seems to be important in achieving a mortality benefit.

2. **Contraindications.** Relative contraindications include second- or third-degree heart block, severe asthma, severe chronic obstructive pulmonary disease, severe or decompensated congestive heart failure, heart rate <60 beats/min, hypotension with systolic blood pressure <120 mm Hg, or other signs of a low-output state. In patients with heart rate >100 beats/min, cardiogenic shock should be ruled out by history and examination before administering β-blockers. Diabetes is not a contraindication; however, the dose of the β-blocker may have to be reduced or discontinued if hypoglycemic episodes are frequent or severe.

H. Angiotensin-converting enzyme (ACE) inhibitors

1. **Indications.** Ventricular remodeling can be attenuated by ACE inhibitors, reducing ventricular dilation and development of congestive heart failure. During infarction, the expression of ACE increases within the myocardium. Several large randomized clinical trials have demonstrated that ACE inhibitors reduce mortality. These trials include Survival and Ventricular Enlargement, Acute Infarction Ramipril Efficacy, and Trandolapril Cardiac Evaluation. The greatest benefit was found among patients with large areas of infarction, anterior infarction, and infarction that impaired LV function. **ACE inhibitor therapy should be considered in all patients after an acute MI** in the absence of contraindications. The ACC/AHA guidelines give a class I recommendation to ACE inhibitors for patients with an LVEF <40%, or with hypertension, diabetes, or chronic kidney disease and a class IIb recommendation for all patients with cardiac or vascular disease. Angiotensin receptor blockers (ARBs) may be substituted if ACE inhibitors are not tolerated. The Valsartan in Acute Myocardial Infarction (VALIANT) trial evaluated post-MI patients with clinical signs of heart failure and low ejection fraction (EF) (<35% by echo or angiography or <40% by radionuclide ventriculography). Even though this study did not support superiority of valsartan therapy, it demonstrated noninferior mortality outcomes between groups treated with valsartan, captopril, or the two combined. However, adverse events including hypotension and medication dose reductions because of renal causes were more frequent in the valsartan and valsartan plus captopril groups. Cough, rash, and taste disturbances were more commonly reported in the captopril group.

2. **Side effects** include cough, worsening renal function, hypotension, and angioedema. ACE inhibitors and ARBs should generally not be used concomitantly because of increased adverse

events, especially renal impairment and hypotension, as was shown in the Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial and VALIANT trials.

I. Aldosterone antagonists

1. **Indications.** The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study trial demonstrated that eplerenone, when added to optimal medical therapy in post-MI patients with an EF of 40% or less, reduced the risk of death from any cause as well as the risk for a combination of death from CV causes and hospitalization for CV events. Optimal medical therapy included ACE inhibitors, ARBs, β-blockers, and coronary reperfusion.
2. **Contraindications.** Because of its diuretic property and effect on the renin–angiotensin–aldosterone neurohormonal system, eplerenone should not be used in patients with renal dysfunction (creatinine > 2.5 mg/dL) or hyperkalemia (serum potassium > 5.0 mmol/L).

J. Calcium channel blockers.

The preferred agent after ACS is a β-blocker unless truly contraindicated. Calcium channel blockers are reserved for patients with **refractory angina** and not recommended for routine use after MI. Longer acting preparations should be used if necessary, whereas short-acting dihydropyridine antagonists should be avoided.

1. **Indications.** The use of calcium channel blockers should be limited to patients with refractory angina or rapid atrial arrhythmias or to patients with clear contraindications to the use of β-blockers.
2. **Contraindications.** Calcium channel blockers should be avoided in patients with congestive heart failure or high-degree atrioventricular block after an MI. Short-acting dihydropyridine antagonists, such as nifedipine, may increase the risk of death or infarction after MI. Short-acting nifedipine may be especially harmful to patients with hypotension or tachycardia and can induce coronary steal or reflex sympathetic activation, which increases myocardial oxygen demand. Verapamil and diltiazem are contraindicated in the care of patients with LV dysfunction or congestive heart failure after MI. These agents may be useful in patients with contraindications to β-blockers who do not have LV dysfunction or congestive heart failure. Few data are available for the effect of the second-generation agents, amlodipine and felodipine, on survival after MI.

K. Estrogen replacement therapy.

The Heart and Estrogen/Progestin Replacement Study found no benefit from hormone replacement therapy as secondary prevention for coronary disease, because the therapy was associated with an early increase in death and MI. The Women's Health Initiative also observed an increased risk of CV events and breast cancer with hormone replacement therapy. Initiation of estrogen for primary and secondary prevention of CV disease is not recommended and should be discontinued at the time of MI.

L. Antioxidants.

Previous epidemiologic studies suggested that vitamin E, vitamin C, and β-carotene were associated with a lower incidence of CAD, but more recent studies failed to corroborate these findings. The heart protection study (HPS) did not demonstrate a mortality or CV benefit from antioxidant therapy. Several other large randomized trials have failed to show either primary or secondary benefit for other similar vitamin supplementation strategies. The ACC/AHA guidelines, therefore, do not support the use of vitamin C or vitamin E, β-carotene, or folate with or without B_6 and B_{12}, for primary or secondary prevention.

IV. PREVENTION OF SCD AFTER MI

A. Risk stratification for SCD

1. **All patients are at risk** for SCD after MI, with the greatest risk encountered during the first year (3% to 5%), most commonly because of ventricular arrhythmias.

2. **Reduced LV function (<40%)** remains the best predictor of mortality. Measurement of LV function soon after MI may reflect myocardial stunning, so echocardiography should be remeasured at the time of possible implantable cardioverter defibrillator (ICD) implantation, usually 40 days after MI for primary prevention or 3 months if reperfused after MI, via either PCI or CABG.
3. Many studies have found that patients who have more than six premature ventricular contractions per hour have a 60% relative increased risk for SCD. Patients with ventricular fibrillation or sustained ventricular tachycardia more than 48 hours after MI are also at increased risk. Monomorphic ventricular tachycardia is a manifestation of scar-related reentrant ventricular tachycardia.
4. Various techniques have been tested to identify patients at increased risk for SCD, but none is sensitive enough to be recommended for routine use. Signal-averaged ECG, heart rate variability, QT-interval dispersion, and baroreflex sensitivity are noninvasive tests, with each test having a low (<30%) positive predictive value. Repolarization alternans (T-wave alternans) appears to have a higher sensitivity and specificity for inducible ventricular arrhythmia during electrophysiologic (EP) testing. Still invasive EP testing has a low predictive value for future cardiac events. Consequently, **these modalities are not recommended for routine post-MI risk stratification.**

B. Therapy

1. The only medications proven to reduce risk for SCD are **β-blockers.** All patients should receive β-blockers after an MI unless absolutely contraindicated.
2. **Amiodarone** has multiple antiarrhythmic effects, but is primarily classified as a class III agent. Trials of amiodarone in the care of patients who have had an MI with LVEF <40% have shown conflicting results, although a significant reduction in mortality has not been demonstrated. Amiodarone is still the preferred antiarrhythmic therapy for symptomatic or sustained ventricular arrhythmias in post-MI patients. **Lidocaine** is sometimes used as an alternative to amiodarone and may be used as an adjunctive medication when ventricular tachycardia is refractory to amiodarone alone. The use of type Class 1c antiarrhythmic agents (i.e., encainide, flecainide, and propafenone) after MI is contraindicated because of increased mortality observed with these medications.
3. **Early implantation of an ICD after MI has not been shown to be beneficial.** The Defibrillator in Acute Myocardial Infarction Trial found no mortality benefit despite a reduction in arrhythmogenic death when ICDs were implanted within 40 days after MI despite LVEF <35%. The Immediate Risk-Stratification Improves Survival (IRIS) trial enrolled patients at increased risk for sudden death within 31 days of an MI. Such patients were those with an EF = 40% and a heart rate > 90 beats/min or those with evidence of nonsustained ventricular tachycardia on ECG or Holter monitor, or both. Overall mortality was not reduced in those in whom an ICD was implanted compared with the group treated with medical therapy. In contrast, the Multicenter Automatic Defibrillator Implantation Trial II investigators and others demonstrated a survival benefit in patients with LV dysfunction and previous MI receiving a prophylactic ICD. The Multicenter Unsustained Tachycardia trial noted improved survival with ICD implantation in patients who had inducible ventricular arrhythmias with EP study. Therefore, class I indications for ICD therapy post-MI include patients with ischemic cardiomyopathy EF < 35% with NYHA class II or III symptoms at least 40 days post-MI, ischemic cardiomyopathy EF < 30% with NYHA class I symptoms at least 40 days post-MI,

and ischemic cardiomyopathy EF < 40% with inducible ventricular fibrillation or sustained ventricular tachycardia on EP study. Patients who undergo either percutaneous or surgical revascularization after MI should have an assessment of LV function after 3 months to help determine the appropriateness of ICD implantation.

4. **Wearable cardiac defibrillator.** Wearable cardiac defibrillators (WCDs) such as the Zoll LifeVest are externally worn devices that detect and treat ventricular arrhythmias. No consensus guideline exists for their appropriate use post-MI, although in general they can be considered for patients with an LVEF <35% who would be expected to qualify for an ICD after 40 days. The VEST Prevention of Early Sudden Death trial evaluated the role of the WCD in reducing SCD in post-MI patients with an LVEF <35% and did not show a reduction of this primary end point at 90 days.

V. THERAPY AND PREVENTION AFTER HOSPITAL TREATMENT

A. Cardiac rehabilitation programs seek to improve the biopsychosocial aspects of patients after MI by addressing the benefits of exercise, weight loss, proper diet, smoking cessation, and good mental health. Both randomized data and meta-analyses have demonstrated a mortality benefit associated with cardiac rehab in patients after MI.

1. Formal rehabilitation programs use **exercise and patient education** to help patients modify their lifestyles. The benefits of cardiac rehabilitation include improvement in a patient's commitment to treatment, increased functional capacity, and reduced likelihood of readmission for recurrent ischemia. The **social support** offered is associated with a 25% reduction in both cardiac and all-cause mortality. Depression after MI is common, and patients must be screened during follow-up. Depression is also an independent risk factor for mortality, possibly by decreasing commitment to therapy and exercise. There are limited data regarding the safety and efficacy of antidepressant medications in the post-MI setting. In a small study, sertraline was found to be safe and efficacious for the treatment of major depressive disorder after ACS.
2. **Home programs and family care.** Although cardiac rehabilitation has been shown to have many benefits, less than one-half of patients who have had an MI participate in formal programs. Home programs may be helpful, but they do not provide the social network found in group rehabilitation programs. Because most cardiac arrests after MI occur within 18 months after discharge, family members should be encouraged to learn basic cardiopulmonary resuscitation.

B. Soon after receiving the diagnosis of MI, patients should be counseled regarding **lifestyle modification** to improve weight control, diet, exercise, lipid control, blood pressure, and smoking cessation.

1. Optimal control of hypertension and diabetes should be achieved.
2. **Weight reduction.** Among adults in the United States, approximately two-thirds of the population, or nearly 130 million persons, are overweight (i.e., body mass index > 25 kg/m^2). Patients should be encouraged to achieve (or maintain) an ideal body weight. All patients should begin an AHA step II diet to achieve lipid goals. Fewer than 50% of patients comply with step II diet, and many patients will need additional pharmacologic therapy to manage hyperlipidemia.
3. **Resumption of daily activities**
    a. At discharge, all patients who have had an MI should receive information regarding resumption of sexual activity, driving, work, and exercise.

b. **Sexual activity** can be resumed within a week for most patients. Oral phosphodiesterase inhibitors **are absolutely contraindicated in patients on concomitant nitrate therapy. Nitrates should not be used** within 24 hours of sildenafil and 48 hours of tadalafil. Vardenafil has a similar half-life as sildenafil and thus similar precautions should be taken. **Driving** can also be resumed within a week. Most patients who have had an MI who do not have symptoms can **return to work** within 2 weeks.

c. A patient's performance on an **exercise test** can be used to generate an activity prescription. Patients who can perform at least 5 METs on a submaximal exercise test without marked ST-segment depression or development of angina have a good long-term prognosis.

d. Because of the lowered oxygen tension in most commercial aircraft (pressurized to 7,500 to 8,000 feet), only patients in stable condition should **travel by plane** within the first 2 weeks after MI. They should carry sublingual nitroglycerin and request a wheelchair for transportation.

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CHAPTER 6

Stable Angina

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I. INTRODUCTION. Angina pectoris, derived from the Greek "ankhon" (strangling) and the Latin "pectus" (chest), is the term used to describe the syndrome of chest discomfort resulting from myocardial ischemia. Angina pectoris (often abbreviated to angina) is characterized as stable or unstable based on symptom pattern.

A. Anginal symptoms are defined as stable if there is no substantial change in symptoms over several weeks. Symptoms of stable angina can fluctuate from time to time, depending on myocardial oxygen consumption, emotional stress, or change in ambient temperature. In general, the clinical definition of stable angina pectoris closely correlates with the stability or quiescence of an atherosclerotic plaque and decreased clinical risk.

B. Angina is said to be unstable when the symptom pattern worsens abruptly (increase in frequency and duration) without an obvious cause of increased myocardial oxygen consumption. Similarly, the onset of rest angina in a patient for whom angina was previously provoked by some degree of exertion may signal an unstable syndrome.

C. For some patients with new-onset angina that has been stable over a few weeks, clear distinction between stable and unstable angina is not possible. These patients can be considered to be in an intermediate stage between unstable and stable angina.

II. CLINICAL PRESENTATION. For most patients with chest pain, the diagnosis of angina pectoris can be made with careful history taking. The presence of risk factors for coronary artery disease (CAD), such as hypertension, diabetes mellitus, smoking, family history, hyperlipidemia, claudication, and advanced age, increases the likelihood that the chest pain is being caused by myocardial ischemia.

A. Symptoms. The constellation of symptoms characteristic of angina pectoris includes the following four cardinal features.

1. Location. Discomfort is commonly located in the retrosternal area with radiation to the neck, shoulders, arms, jaws, epigastrium, or back. In some instances, it involves these areas without affecting the retrosternal area.

2. Relation to a trigger. Symptoms are typically triggered by physical activity, emotional stress, exposure to cold, consumption of a heavy meal, or smoking.

a. Some patients will experience the resolution of angina despite continued exertion, which is known as the "walk-through phenomenon." Others may experience the "warm-up phenomenon," in which an initial exertion produces angina but a similar second exertion does not reproduce anginal

symptoms. These circumstances probably result from the recruitment of collateral coronary flow during the initial episode of ischemia.

b. "Decubitus angina," which is a less common manifestation, occurs with a change in posture believed to be caused by a shift in blood volume. Nocturnal angina, which occurs at night, is frequently associated with nightmares and tachyarrhythmias.

3. Character. Most patients describe angina as a vague chest discomfort. They describe it as a squeezing, burning, tight, choking, heavy, and occasionally hot or cold sensation. Many patients do not perceive angina as pain, per se. Some patients may experience dyspnea, profound fatigue, weakness, lightheadedness, nausea, diaphoresis, altered mental status, or syncope in the absence of any chest discomfort. These symptoms are often referred to as "anginal equivalents." Noncardiac causes of chest pain (gastrointestinal [GI], respiratory, musculoskeletal, etc.) may be indicated by fleeting chest pain, unrelenting chest pain not affected by activity, antecedent chest trauma, association with food intake, location inferior to the umbilicus, pleurisy, and so on.

4. Duration. The chest pain associated with ischemia typically lasts 3 to 5 minutes. Ischemic pain usually does not last more than 30 minutes without causing myocardial infarction (MI). Chest pain triggered by emotional distress tends to last longer than that triggered by exercise. Chest pain that lasts <1 minute is unlikely to be of cardiac origin, especially when it is not associated with other typical symptoms or findings.

Women may present with symptom constellations that may be different in location or quality in comparison to the symptoms described by men or may have ischemia manifest as anginal equivalents, such as nausea or dyspnea.

Chest pain is defined as "typical angina" if it consists of characteristic substernal discomfort, is provoked by stress, and is relieved by rest or nitroglycerin. It is considered "atypical" if it involves two or fewer of the previously mentioned criteria.

5. Classification. Various classifications are available to assess the severity and to predict the outcome among patients with angina. The Canadian Cardiovascular Society classification is the most popular (Table 6.1). Other classification systems include the Specific Activity Scale, the Duke Activity Status Index, and the Braunwald classification.

B. Physical findings. For patients with a history of chest pain, physical examination helps identify risk factors for CAD and occult cardiac abnormalities.

1. The signs associated with a high risk for CAD include elevated blood pressure or manifestations of hypertensive vascular disease such as retinal arteriopathy, signs of hyperlipidemic conditions including corneal arcus or xanthelasma, and evidence of carotid or other peripheral vascular disease.

2. Physical examination performed during an episode of chest pain may reveal rales, tachycardia, hypertension, an S_3 or S_4 gallop, or a systolic murmur from ischemic mitral regurgitation, all of which generally disappear with resolution of symptoms.

C. Baseline electrocardiogram (ECG)

1. A baseline ECG is **useful for the initial screening** of CAD, although the majority of patients with chest pain have a normal ECG. Presence of pathologic Q-waves or persistent ST-depression is associated with an unfavorable outcome. The ECG can also demonstrate other abnormalities, such as left ventricular (LV) hypertrophy, bundle branch block, and preexcitation syndromes.

TABLE 6.1 Classification of Angina

CCS Class	Definition	Comment
I	Ordinary physical activity does not cause angina	Angina only with extraordinary exertion at work or re
II	Slight limitation of ordinary activity	Angina with walking more than two blocks on a level flight of stairs at a normal pace
III	Marked limitation of ordinary physical activity	Walking one to two blocks on a level surface or clim pace
IV	Inability to carry on any activity without discomfort	Angina at rest or with minimal activity or stress

2.CCS, Canadian Cardiovascular Society.

3. Information obtained from the ECG is **useful in the assessment of chest pain** and helps to stratify patients who are at risk for an adverse event.

4. ECG at the time of chest pain can also **help identify the cause of the chest pain**. Transient changes in the T-wave, ST-segment, or conduction patterns point toward a cardiac source of the chest pain; however, a normal ECG does not exclude ischemia as being the etiology of chest pain.

III. DIAGNOSTIC TESTING. For a patient with stable symptomatic CAD, investigations are aimed at risk stratification and management of symptoms and unfavorable outcomes.

A. Stress testing. The basic principle of stress testing is to provoke ischemia or produce coronary vasodilation, followed by functional assessment with different modalities to detect ischemia. Stress tests can be categorized according to the methods used to provoke and detect myocardial ischemia. The sensitivity and specificity of each test to identify coronary stenosis vary according to the study population, definition of disease, definition of a positive test result, protocol used for the stress testing, and experience of the interpreter. The following is a brief overview of noninvasive cardiac testing. **For a thorough discussion on noninvasive imaging and stress modalities, please refer to the dedicated chapters 46, 47.**

1. **Methods to induce ischemia.** Exercise is the most physiologically sound and useful method for inducing ischemia. An exercise test is considered adequate if 85% or more of age-predicted maximum heart rate (220 minus age) is achieved. Exercise testing provides an objective assessment of functional capacity, which provides useful prognostic information. Pharmacologic testing, with dobutamine or adenosine/adenosine derivatives (i.e., dipyridamole), can be used for patients who cannot exercise to an adequate heart rate.

2. **Methods to assess ischemia**

a. **Stress ECG.** Exercise ECG provides useful diagnostic information about the patients with normal baseline ECGs who are at intermediate risk for CAD. Stress ECG is also used to create an exercise prescription in patients with stable angina. The sensitivity and specificity of stress ECG are poor among patients with an abnormal baseline ECG, LV hypertrophy, ventricular pacing, left bundle branch block (LBBB), or intraventricular conduction disturbance and among patients taking digitalis or other medications that affect conduction and depolarization. Ischemic

electrocardiographic changes during vasodilator testing have high specificity but poor sensitivity. Electrocardiographic changes during dobutamine infusion have sensitivity and specificity similar to those of exercise ECG.

b. **Echocardiographic imaging.** Stress echocardiography is an economical test with good specificity for identifying the location and extent of ischemic territories. This is assessed by the induction of regional wall motion abnormalities with stress or dilation of the LV cavity with stress (which may indicate global ischemia). Exercise is preferred in patients with intermediate or high pretest probability who are able to exercise. If the patient is unable to exercise, a dobutamine stress test can be performed. A biphasic response with dobutamine, in which contractility initially increases with lower doses of dobutamine and then decreases with higher doses, is diagnostic of ischemia. Augmentation of contractility in hypokinetic segments may indicate the presence of hibernating myocardium in a specific coronary distribution. At some medical centers, dipyridamole and adenosine stress tests are performed with echocardiographic imaging. This method is less sensitive in detecting underlying CAD. Results of stress echocardiography are difficult to interpret in some patients with a hypertensive response to exercise and in some patients with severe mitral or aortic regurgitation. Preexisting wall motion abnormalities may further complicate image interpretation.

c. **Radionuclide imaging.** Single-positron emission computed tomography (SPECT) can be performed after injection with thallium 201 or technetium (Tc) 99m–labeled radiopharmaceuticals. Positron emission tomography (PET) can be performed utilizing rubidium 82 or 13N ammonia tracers. PET imaging provides greater spatial resolution and diagnostic accuracy in comparison with SPECT imaging. In addition, PET enables quantification of coronary blood flow and assessment of coronary flow reserve. Injection of fluorine 18–labeled deoxyglucose allows assessment of myocardial viability in patients with resting perfusion defects. The sensitivity and specificity of SPECT nuclear testing are decreased among patients with severe obesity, balanced three-vessel disease, and LBBB.

B. Resting echocardiography provides useful information in the overall assessment of suspected stable angina.

1. Regional wall motion abnormalities involving the left ventricle are commonly caused by CAD and may represent resting ischemia or prior MI. Any impairment in LV systolic function, LV hypertrophy, and/or presence of substantial mitral regurgitation are associated with heightened clinical risk and poorer outcome. LV systolic function may guide the choice of medical therapy versus revascularization.
2. Echocardiography is the test of choice to quantify aortic stenosis or the presence of hypertrophic cardiomyopathy.

C. Magnetic resonance imaging (MRI)

1. Ischemic evaluation using pharmacologic stress (dobutamine or adenosine) and cardiovascular magnetic resonance can be used to evaluate myocardium in jeopardy. MRI uses gadolinium as a contrast medium to evaluate regional wall motion abnormalities and ejection fraction as well as segmental myocardial perfusion (when using adenosine). MRI can also provide direct visualization of the coronary arteries, although computed tomography angiography is much better for this application.
2. Delayed-phase gadolinium imaging also provides information on the location and transmurality of myocardial scar.
3. The weaknesses of MRI include high cost, lack of portability, and unsuitability for use in many patients with pacemakers and defibrillators.

D. Electron beam computed tomography (EBCT)

1. EBCT is a noninvasive method that allows quantification of coronary artery calcification. The test is rapid and provides a "calcium score." This test does not provide sufficient detail to accurately quantify and grade stenosis because of atherosclerotic lesions. An increasing calcium score correlates strongly with heightened risk of cardiovascular events, and abnormal findings should lead to further risk factor modification and cardiovascular risk assessment.

E. Multidetector computed tomography

1. Coronary computed tomography angiography (CCTA) allows for the evaluation of the epicardial coronary tree using a noninvasive approach. The sensitivity of CCTA for assessing coronary stenosis approaches 97% with a specificity of 86% when using 64-slice technology. Importantly, the negative predictive value of CCTA is 99%, with an optimal study and appropriate patient selection. Severe coronary artery calcification or previous coronary stent placement may significantly detract from image quality, rendering the specific coronary segments uninterpretable. Larger stents may be grossly evaluated for patency but accurate quantification for in-stent restenosis in anatomical locations distal to the left main coronary artery (LMCA) is not always feasible.

F. Coronary angiography

1. **Strengths.** Coronary angiography is the standard for anatomic assessment of coronary arterial stenosis and provides important prognostic information.

a. Patients with >75% stenosis involving at least one coronary artery have a lower survival rate than patients with 25% to 50% or <25% stenosis. Even for mild stenosis, risk for MI is markedly higher than for no stenosis.

b. The severity of lesions demonstrated with angiography is not predictive of plaque stability; two-thirds of patients with acute MI have stenosis of >50% diameter at the site of plaque rupture before MI. It is possible, however, to assess plaque instability on the basis of angiographic characteristics or morphologic features of the lesion.

1. (1) Eccentric lesions with narrow necks, overhanging edges, or scalloped borders (type II plaques) are more unstable than concentric lesions with smooth borders (type I plaques).
2. (2) Lesion roughness (i.e., irregular borders) is predictive of plaque instability and heightens the risk of future infarction.
3. (3) The morphologic characteristics of the plaque help in judging the feasibility and risk of percutaneous or surgical intervention.

c. Ventriculography performed at the time of selective coronary angiography adds an important dimension to risk stratification by providing an index of LV systolic function and regional wall motion characteristics as well as the presence and degree of mitral regurgitation.

2. **Indications.** In the management of stable angina, use of angiography is variable. An American College of Cardiology and American Heart Association (ACC/AHA) task force classified the indications for coronary angiography into three categories. The relevant indications in the context of stable angina are presented in Table 6.2.

3. **Limitations.** Coronary angiography underestimates plaque burden, possibly because of vascular remodeling and the diffuse nature of the disease. Coronary angiography is insensitive to intraluminal plaque burden and does not show coronary flow reserve. Adjunctive imaging and functional testing facilitates the investigation of hazy areas on coronary angiograms, which may be caused by calcium, thrombus, severe eccentric lesion, or dissection.

G. Intravascular ultrasound allows visualization of the cross-sectional image of coronary arteries. This modality helps to quantitate plaque area, artery size, and luminal stenosis; assess hazy areas on coronary angiograms, questionable areas of stenosis, and extent of stenosis; and sometimes determine the calcium content and morphology of a plaque. Hypodense areas in a plaque may correlate with high lipid content, which may indicate fast-growing or potentially unstable plaque. This information can help assess the need for and options of therapy. This modality does not, however, have a defined role in routine evaluation of patients with stable angina, because of the invasive nature of the test.

H. Optical coherence tomography (OCT) is an intracoronary imaging modality that has better resolution than intravascular ultrasound (IVUS) but provides less depth. Benefits of OCT include visualization of thrombus and thin-cap atheroma, better understanding of stent characteristics (degree of apposition and stent endothelialization, etc.), and arterial remodeling. This technique requires injection of contrast medium during imaging (usually totaling 8 to 15 cc per run) and is relatively contraindicated in patients with chronic kidney disease.

TABLE 6.2 Indications for Coronary Angiography in Stable Angina

Class I (general agreement among cardiologists)
Severe anginal symptoms (CCS class III or IV) with OMT (LOE C)
Noninvasive testing indicates high risk of coronary disease (LOE C)
Survivors of sudden cardiac death or potentially fatal ventricular tachyarrhythmia (LOE B)
Symptoms of congestive heart failure with angina (LOE B)
Class II (frequently used but controversial)
Symptoms of angina and an LV ejection fraction <50% with intermediate risk/demonstrable ischemia
Symptoms of angina and positive stress test (IIa, LOE C)
Inadequate information from noninvasive testing (IIa, LOE C)
Severe angina with preserved ventricular function and intermediate risk noninvasive testing (IIa, LOE
Patients who are unable to be evaluated noninvasively (IIa, LOE C)
Patients who cannot undergo stress testing with a high pretest probability of coronary disease (IIa, LC
Suspicion of left main or three-vessel coronary disease (IIa, LOE C)
Class III (unjustified use of angiography)
Low-risk patients who have not had noninvasive testing (LOE C)
Patients with a preserved LV ejection fraction (>50%) and low risk (LOE B)
Mild symptoms that resolve with medical therapy (LOE C)
Patients who would not or cannot undergo revascularization (LOE B)

I.CCS, Canadian Cardiovascular Society; LOE, level of evidence; LV, left ventricular; OMT, optimal medical therapy.

J.Invasive functional assessment. Invasive assessment of the functional significance of an intermediate stenosis can be made by means of coronary blood flow measurement with intracoronary Doppler ultrasound and direct measurement of a pressure gradient across a stenosis.

1.With the help of a small transducer mounted on a guidewire, coronary blood flow can be measured by means of a fixed sample volume and pulsed Doppler.

a.In the left coronary artery, most coronary flow occurs during diastole. In normal arteries, a ratio of proximal-to-distal flow velocity approaching 1 is considered normal. In the presence of coronary stenosis, coronary blood flow becomes mainly systolic because the diastolic component of the flow is jeopardized first.

b.Three indices can help identify physiologically important stenosis:

1. **(1)** Diastolic-to-systolic average peak coronary flow velocity ratio of <1.8 distal to the obstruction
2. **(2)** A proximal-to-distal average peak coronary flow velocity ratio of >1.7
3. **(3)** Coronary flow reserve (i.e., increase in coronary flow with adenosine, which is administered after intracoronary nitroglycerin) with a less than twofold increase in peak velocity

2.Direct measurement of pressure gradients can be accomplished with a transducer mounted on a catheter. Ratio of mean pressure distal and proximal to the lesion after maximum vasodilation (fraction flow reserve [FFR]) of <0.75 to 0.80 indicates a hemodynamically significant lesion. These techniques supplement angiography in determining the functional significance of an intermediate (30% to 70%) angiographic stenosis. In a group of patients with angiographically intermediate stenosis, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) investigators were able to demonstrate lower rates of mortality and MI (8.4% vs. 23.9%, $p = 0.02$) with less stent placement when a strategy of FFR-guided (vs. angiography-guided alone) percutaneous coronary intervention (PCI) was pursued.

K.Holter monitoring

1.After MI, increased ventricular ectopy is predictive of increased cardiovascular morbidity and mortality. This association is less important among patients with stable angina without prior MI, and routine Holter testing for risk stratification is not indicated. No medical treatment aimed at suppressing ventricular ectopy has been shown to improve outcomes.

IV.THERAPY.

The goals of therapy in stable CAD are to prevent cardiovascular morbidity and mortality and to improve quality of life.

A.Therapeutic options. Medical therapy, PCI, and coronary artery bypass grafting (CABG) have all been shown to control symptoms and improve exercise time to ischemia. In an era of rudimentary medical therapy, CABG had been proven to decrease cardiovascular mortality in specific patient subsets. Although PCI has been shown to improve stable anginal symptoms and improve quality of life, a decrease in mortality has not been proven in randomized controlled trials (RCTs).

B.Pharmacologic therapy

1.Platelet inhibitors

a.The Antiplatelet Trialists' Collaboration was a meta-analysis that included approximately 100,000 patients from 174 trials involving antiplatelet therapy. This data set showed that aspirin (acetylsalicylic acid [ASA]) reduced the rate of stroke, MI, and death among high-risk patients,

including those with stable angina without previous MI. There is general support in the literature for limiting the dose of ASA to 75 to 81 mg daily, and the most recent ACC/AHA guidelines assign a class I, level of evidence (LOE) A, recommendation to aspirin therapy.

b. Among patients with true allergy or intolerance to aspirin, clopidogrel has been shown to decrease the frequency of fatal and nonfatal vascular events in peripheral, cerebral, and coronary vessel diseases.

c. In the initial analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, performed on a large group of patients included with either prior cardiovascular events or multiple cardiovascular risk factors, there was no benefit from the use of dual antiplatelet therapy (DAPT) over aspirin alone in preventing MI or death. A prespecified analysis of higher risk patients only (such as those with prior MI) did show a decrease in cardiovascular events for the group receiving clopidogrel in addition to aspirin. This suggests that an appropriate group of patients may benefit from prolonged DAPT.

d. The benefits of prolonged DAPT in secondary prevention observed in CHARISMA were confirmed in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction (TIMI) 54 trial. In patients who had an MI 1 to 3 years prior, both ticagrelor dosages at 90 and 60 mg twice daily with aspirin reduced the risk of death, MI, and stroke by approximately 15% compared with low-dose aspirin alone. This strategy came with a significantly increased risk ($p < 0.001$) of TIMI major bleeding (2.6% and 2.3% with ticagrelor 90 and 60 mg, respectively, compared with 1.06% with aspirin alone).

e. Patients with stable CAD who undergo stenting with a bare-metal stent (BMS) should receive DAPT (aspirin + clopidogrel) for at least 1 month; when a drug-eluting stent (DES) is utilized, the treatment should be extended for at least 6 months. Patients who tolerate DAPT without significant bleeding concerns should be considered for longer duration DAPT treatment. This is best achieved on a patient-by-patient basis by reviewing the potential bleeding risk of the patient against the anticipated ischemic risk. A number of clinical and procedural variables need to be considered in this decision and risk scores like the DAPT score are useful in making this decision.

2. **Antithrombotic therapy:** Historically only stable CAD patients with a primary indication for long-term anticoagulation like atrial fibrillation or mechanical prosthetic valve have been treated with this class of agents. The Cardiovascular Outcomes for People Using Anticoagulation Strategies trial evaluated the of role rivaroxaban (2.5 mg twice) with low-dose aspirin, compared to rivaroxaban 5 mg twice daily and aspirin alone in 27,936 subjects with stable atherosclerotic disease. Over 23 months of follow-up, the combination of low-dose rivaroxaban and aspirin was associated with a 24% risk reduction in the composite cardiovascular death, stroke, and MI (4.1% vs. 5.4%, $p < 0.001$), but was associated with increased major bleeding events (3.1% vs. 1.9%, $p < 0.01$). Consequently, these agents will have a role in stable CAD patients at high ischemic risk who are felt to have a low or acceptable risk of bleeding.

3. **Lipid-lowering agents.** Secondary prevention with lipid-lowering therapy, specifically statins, has demonstrated marked reduction in risk for subsequent cardiovascular events. Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme reductase. They are the most effective medical therapy for lowering levels of low-density lipoprotein (LDL) and have also been shown to upregulate nitric oxide (NO) synthase, decrease expression of endothelin-1

messenger ribonucleic acid, improve platelet function, and decrease production of detrimental free radicals; all of these promote normal endothelial function.

a. **Indications.** The Scandinavian Simvastatin Survival Study, Cholesterol and Recurrent Events, Long-term Intervention with Pravastatin in Ischemic Disease, and Heart Protection Study trials have provided convincing evidence that in patients with evidence of cardiovascular disease with normal or elevated cholesterol levels, statins decrease mortality, the rate of MI and stroke, and the need for CABG.

b. **Effectiveness.** Studies have shown that in patients with stable CAD (treating to new targets trial) or post-acute coronary syndrome (ACS) evaluation and infection therapy–thrombolysis in myocardial infarction 22 (PROVE IT-TIMI-22), aggressive lipid lowering to an LDL goal of 70 mg/dL decreases the risks of cardiovascular death, MI, and stroke compared with patients treated to an LDL goal of 100 mg/dL. There is also a suggestion that aggressive statin therapy retards and even results in a mild degree of plaque regression as measured by IVUS. Recent trials with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and ezetimibe have confirmed further reduction in cardiovascular events when LDL is reduced to 30 mg/dL. Achieving very low LDL levels <25 mg/dL in this population has not been associated with any noted side effects.

c. **Choice of agents.** Statins should be the first line of therapy in patients with established CAD. Provision of statin therapy in this population carries a class I, LOE A, recommendation in the absence of contraindications. Ezetimibe may be added to statins to further reduce LDL levels. PCSK9 inhibitors have been shown to reduce LDL dramatically in those intolerant to statins and in others unable to reach target LDL levels on maximum tolerated statin therapy. Fibric acid derivatives and ω-3 fatty acids may be considered to treat residual hypertriglyceridemia following maximal statin treatment. Although low high-density lipoprotein (HDL) levels are associated with increased cardiovascular risk, it is not a target for intervention because agents that increase HDL have **not** been shown to improve outcome.

d. **Guidelines.** Current guidelines support aggressive lowering of LDL cholesterol levels in patients with established coronary disease with moderate- (if over age 75) or high-intensity (if under 75 years old) statin therapy with a goal of ≥50% LDL cholesterol reduction. Recent evidence, however, supports intensive LDL reduction to achieve LDL levels <70 mg/dL in this population because trails that achieved lower LDL levels are associated with additional clinical benefit. As a result, addition of nonstatin agents (PCSK9 inhibitors or ezetimibe) to further drive down LDL levels may be considered. This decision can be guided by additional LDL cholesterol reduction desired, patient choice, cost, and drug tolerability. Patients at highest risk to develop clinical events include older individuals aged 65 years, patients with prior MI or nonhemorrhagic stroke, active smokers, presence of symptomatic peripheral artery disease with prior MI or stroke, history of non-MI–related coronary revascularization, presence of residual CAD with >40% stenosis in two major epicardial vessels, HDL cholesterol <40 mg/dL for men and <50 mg/dL for women, high-sensitivity C-reactive protein >2 mg/L, or presence of metabolic syndrome.

4. Nitrates (Table 6.3)

a. **Mechanism of action.** Nitrates decrease cardiac workload and oxygen demand by means of reducing preload and afterload of the left ventricle. They also redistribute blood flow to the ischemic subendocardium by means of decreasing LV end-diastolic pressure, vasodilation of epicardial vessels, and improvement of collateral blood flow to ischemic tissue. Nitrates may also be weak inhibitors of platelet aggregation, although the clinical relevance of this is unclear.

TABLE 6.3 Nitrates

Medication	Route of Administration	Each
Nitroglycerin (glyceryl trinitrate, Nitro-Bid, Nitrostat, and Nitro-Dur)	Sublingual tablet	0.15
	Sublingual spray	0.4 r
	Sustained-release capsule	2.5–
	Ointment (topical)	0.5″-
	Disk (patch)	1 dis
	Intravenous	5–40
	Buccal tablet	1 mg
Isosorbide dinitrate (Isordil, Sorbitrate, and Dilatrate SR)	Sublingual tablet	2.5–
	Chewable tablet	5–10
	Oral tablet	10–4
	Sustained-release tablet	40–8
Isosorbide-5-mononitrate (Imdur and Ismo)	Sublingual tablet	10–4
	Sustained release	60 m
Erythrityl tetranitrate (Cardilate)	Sublingual tablet	5–10
		10 m

b. Evidence for effectiveness. Nitrates can decrease exercise-induced myocardial ischemia, alleviate symptoms, and increase exercise tolerance in patients with stable angina.

1. **(1)** Adding nitrates to an optimal β-blocker regimen does not improve frequency of anginal episodes, glyceryl trinitrate consumption, exercise duration, or duration of silent ischemia.
2. **(2)** In some small studies, the efficacy of nitrates in reducing anginal episodes was increased with concomitant use of angiotensin-converting enzyme (ACE) inhibitors.
3. **(3)** No study has shown survival benefit with the use of nitrates to treat patients with chronic stable angina.

c. Selection of preparations. Because nitrates have a fast onset of action, a sublingual tablet or oral spray offers immediate relief of an anginal episode. For short-term prophylaxis (up to 30 minutes), nitroglycerin tablets can be used when activities known to precipitate angina are anticipated. Timing and frequency of the doses can be individualized according to the diurnal rhythm of anginal episodes. A nitrate-free interval of about 8 hours is adequate for preventing tolerance. Use of long-acting medications and transcutaneous delivery systems improves compliance but still necessitates a nitrate-free interval.

d. Side effects. Oral nitrates should be taken with meals to prevent heartburn.

1. **(1)** Headache is common and can be severe. Severity usually decreases with continued use and often can be controlled by decreasing the dose.
2. **(2)** Transient episodes of flushing, dizziness, weakness, and postural hypotension can occur, but these effects are usually abrogated by positioning and by other procedures that facilitate venous return.

e. Drug interactions. Hypotension can occur with the use of other vasodilators, such as ACE inhibitors, hydralazine, or calcium channel blockers. **Concurrent use of phosphodiesterase type 5 (PDE5) inhibitors like sildenafil (Viagra) and nitrates can lead to severe hypotension and, therefore, is *absolutely contraindicated*.**

f. Controversies

1. **(1) Tolerance.** Sustained therapy attenuates the vascular and antiplatelet effects of nitrates. Although the basis for this phenomenon of nitrate tolerance is not completely understood, sulfhydryl depletion, neurohormonal activation, and increased plasma volume are likely involved. Administration of *N*-acetylcysteine, folic acid, hydralazine, ACE inhibitors, or diuretics does not consistently prevent nitrate tolerance. Intermittent nitrate therapy is the only way to avoid nitrate tolerance.
2. **(2) Rebound angina.** Intermittent use of nitrates is not associated with serious rebound of angina among patients taking maintenance therapy with β-blockers. Dosing to allow for a longer nitrate-free interval is also not associated with rebound.

5. β-Blockers (Table 6.4)

a. Mechanism of action.

Blocking the β_1-adrenergic receptors in the heart decreases the rate–pressure product and myocardial oxygen demand. Decreased tension in the LV wall allows favorable redistribution of blood flow from the epicardium to the endocardium.

1. **(1)** Coronary vasospasm is rare from the β_2-receptor blocking effect, but use of nonselective β-blockers should be avoided among patients with known, active vasospasm.
2. **(2)** β-Blockers have a variable degree of membrane-stabilizing effect.

b. Evidence for effectiveness.

β-Blockers decrease mortality after MI. The mortality benefit is not proven among patients with stable angina without prior MI or heart failure, although symptomatic improvement is well documented with multiple agents. Initiation of β-blockers carries a class I, LOE B, recommendation as the initial therapy for relief of symptoms in patients with stable angina.

TABLE 6.4 β-Blockers

Compound	Daily Dose (mg)	Frequency	Excretion	Lipid Solubility	Intrinsic Activity	Sympathom
Selective β-Blockers						
Metoprolol						
Short acting	50–400	Every 12 h	Liver	Moderate		
Long acting		Every 24 h			None	
Atenolol	25–200	Every 24 h	Kidney	None	None	
Acebutolol	200–600	Every 12 h	Kidney	Moderate	Low	
Nebivolol	5–40	Every 24 h	Kidney	High	None	
Betaxolol	20–40	Every 24 h	Kidney		Low	
Nonselective β (β_1 + β_2)-Blockers						
Propranolol	80–320	Every 4–6 h	Liver			
Long acting		Every 12 h		High	None	
Nadolol	80–240	Every 24 h	Kidney	Low	None	
Timolol	15–45	Every 12 h	Liver	Moderate	None	

TABLE 6.4 β-Blockers					
Pindolol	15–45	Every 8–12 h	Kidney	Moderate	Moderate
Labetalol[a]	600–2,400	Every 6–8 h	Liver	None	None
Carvedilol[a]					
Short acting	25–50	Every 12 h	Liver	Moderate	None
Long acting	10–80	Every 24 h			

c. [a]Also a potent α_1-antagonist.

d. Side effects. The most important side effects are related to blockade of β_2-receptors. However, data show that some of the side effects may occur less frequently than previously believed, and potentially lifesaving therapy should be offered to those at greatest risk for adverse events.

1. **(1)** Bronchoconstriction, masking of symptoms caused by hypoglycemic reaction among patients with diabetes, exacerbation of symptoms of peripheral vascular disease, and central nervous system (CNS) side effects such as somnolence, lethargy, depression, and vivid dreaming are well documented. The CNS side effects are thought to be related to the lipid solubility of these compounds.
2. **(2)** Symptomatic bradycardia and precipitation of heart failure are concerns for patients with a diseased conduction system and preexisting heart failure, respectively.
3. **(3)** Decreased libido, impotence, and reversible alopecia can be a problem for some patients.
4. **(4)** β-Blockers adversely alter lipid profile by increasing LDL cholesterol and decreasing HDL cholesterol.

e. Drug interactions. Severe bradycardia and hypotension can occur with concomitant use of some calcium channel blockers.

f. Selection of preparations. Cardioselectivity, lipid solubility, mode of excretion, and frequency of dosing are the main considerations when selecting a particular agent. The major cardiospecific agents (i.e., β_1-blockade) include metoprolol, atenolol, bisoprolol, and nebivolol. Of note, nebivolol also induces the endothelial NO pathway and contributes to vasodilation. Intrinsic sympathomimetic activity (ISA) is not a clinically important factor in the choice of a medication, although benefits in patients with CAD have been decreased with agents having ISA, such as pindolol and acebutolol.

g. Effect on lipids. The clinical significance of lipid abnormalities associated with β-blockers is unclear. β-Blockers have been associated with a decline in HDL level and a rise in triglycerides level. β-Blockers can improve survival among patients in New York Heart Association (NYHA) class I or II heart failure and angina. The condition of a patient with NYHA class III or IV disease should be stabilized before β-blocker therapy is instituted.

6. Calcium channel blockers (Table 6.5)

a. Mechanism of action. These agents block calcium entry into vascular smooth muscle cells and cardiac cells by inhibiting calcium channels, but they do not affect the regulation of intracellular calcium release. The result is decreased contraction of muscle cells.

1. **(1)** The four types of calcium channels are L, T, N, and P.
2. **(2)** The T-type calcium channels are located in the atria and sinoatrial node and affect the phase I of depolarization.

3. **(3)** The L-type channels contribute to entrance of calcium into the cell during phase III of the action potential.
4. **(4)** The N and P types of channels are present mainly in the nervous system.
5. **(5)** The three main groups of calcium channel blockers are dihydropyridines (e.g., nifedipine), benzothiazepines (e.g., diltiazem), and phenylalkylamines (e.g., verapamil).

TABLE 6.5 Calcium Channel Blockers

Compound	Each Dose (mg)	Frequency	Vasodilation	Sinoatrial Node Inhibition	Atrioventricu Inhibition
Nifedipine	30–120	Every 8 h	5	1	0
Nifedipine (Procardia XL)	30–180	Every 24 h			
Diltiazem	30–90	Every 6–8 h	3	5	4
Diltiazem (Cardizem CD)	120–300	Every 24 h			
Verapamil	40–120	Every 6–8 h	4	5	5
Verapamil (Calan SR and Isoptin SR)	120–240	Every 12 h			
Amlodipine (Norvasc)	2.5–10	Every 24 h	4	1	0
Felodipine (Plendil)	5–20	Every 24 h	5	1	0
Bepridil (Vascor)	200–400	Every 24 h	4	4	4
Isradipine (DynaCirc)	2.5–10	Every 24 h	4	4	0
Nicardipine (Cardene)	10–20	Every 8 h	5	1	0

activity; 5, most potent effect. Intermediate numbers suggest intermediate potency of effects.

7. The dihydropyridines bind to the extracellular portion of the L channels at a specific site. They do not bind to the T channels and do not have a negative chronotropic effect. Because of their extracellular site of action, dihydropyridines do not inhibit receptor-induced intracellular calcium release.
8. Verapamil binds to the intracellular part of the L channel and inhibits the T channel. Intracellular calcium release is inhibited by verapamil because of its intracellular binding site and reflex sympathetic activation is less effective. Use dependence occurs with verapamil because open channels are needed for transport of the drug into the intracellular binding site. In stable angina, verapamil helps by improving rate–pressure product and by increasing oxygen delivery from coronary vasodilation.

b. Evidence of effectiveness. Numerous placebo-controlled, double-blind trials have shown that calcium channel blockers decrease the number of anginal attacks and attenuate exercise-induced depression of ST-segments. Calcium channel blockers are either started in patients who are β-blocker intolerant (class I, LOE B) or as an adjunct in those for whom β-blockers have not provided symptomatic relief (class I, LOE B).

1. **(1)** Studies comparing the efficacy of β-blockers and calcium channel blockers in the management of stable angina in which death, infarction, and unstable angina were used as end points showed calcium channel blockers to be as effective as β-blockers.
2. **(2)** Increased mortality caused by short-acting nifedipine among patients with CAD has been demonstrated. If the use of nifedipine is contemplated, a long-acting preparation in conjunction with β-blocker therapy is the safer approach. The mechanism of increased mortality is unclear, but reflex tachycardia and coronary steal phenomenon are potential explanations.

c. **Side effects.** The most common side effects are hypotension, flushing, dizziness, and headache. Because a negative inotropic effect can precipitate heart failure, the use of calcium channel blockers to treat patients with impaired LV function is relatively contraindicated. Conduction disturbances and symptomatic bradycardia occur with the use of compounds that have a marked inhibitory effect on the sinoatrial and atrioventricular nodes. Bepridil is known to prolong QTc, and QT monitoring is necessary when this medication is used. Lower extremity edema is often seen with the use of dihydropyridine calcium channel blockers, which may necessitate lowering the dose or discontinuing the medication. The non–dihydropyridine calcium channel blockers are known to cause constipation.

d. **Drug interactions.** Digitalis levels are increased by the non–dihydropyridine calcium channel blockers verapamil and diltiazem. The use of these drugs is contraindicated in the presence of digitalis toxicity.

e. **Selection of preparations.** Calcium channel blockers have a variable negative inotropic effect.

1. **(1)** Amlodipine is most likely to be tolerated by patients with compensated heart failure. In decompensated heart failure, all calcium channel blockers should be avoided.
2. **(2)** Amlodipine, diltiazem, nifedipine, and verapamil are the only calcium channel blockers approved for angina by the US Food and Drug Administration.
3. **(3)** Patients with conduction disturbances should take agents with minimal effects on the conduction system. Longer acting preparations minimize the risk for precipitation of angina caused by reflex tachycardia.

7. **ACE inhibitors.** The rationale for using ACE inhibitors to manage chronic stable angina comes from post-MI and heart failure trials that demonstrated a significant reduction in ischemic events with the use of ACE inhibitors.

a. It is possible that ACE inhibitors, by decreasing mainly the preload and, to some extent, afterload, decrease myocardial oxygen demand and help in the management of chronic stable angina. The Heart Outcomes Prevention Evaluation trial in high-risk patients with CAD, stroke, diabetes, and peripheral vascular disease showed that ramipril was associated with a significant reduction in death, MI, and stroke in this population. A recent meta-analysis found that ACE inhibitors reduce the risk of these outcomes even in patients with atherosclerosis who do not have evidence of systolic dysfunction. It is notable that the randomized Prevention of Events with Angiotensin-Converting Enzyme Inhibition study evaluating the use of trandolapril in patients with preserved LV function did not find a benefit with respect to death, MI, angina, revascularization, or stroke. Numerous hypotheses to explain these divergent results, including dose effects, difference in medication effects, and the risk level of enrolled patients, have been postulated. Nevertheless, the use of ACE inhibitors is recommended (class I) for patients with hypertension, diabetes, chronic kidney disease, or an LV ejection fraction of less than 40% and is considered reasonable (class IIa, LOE B) for patients without class I indications but who have both stable angina and other vascular disease.

b. Serious **side effects** of ACE inhibitors include cough, hyperkalemia, and decreased glomerular filtration rate. They are contraindicated in the care of patients with hereditary angioedema or bilateral renal artery stenosis. Angiotensin receptor blockers may be substituted in this population.

8. Hormone replacement therapy (HRT). The lipid profiles of women change unfavorably after menopause. LDL, total cholesterol, and triglyceride levels increase and HDL level decreases. All these changes have an adverse effect on cardiovascular morbidity and mortality. Several large case-controlled and prospective cohort studies suggested that the postmenopausal use of estrogen alone or in combination with medroxyprogesterone acetate has a favorable effect on lipid profile and cardiovascular events. However, both the Women's Health Initiative study on primary prevention and the Heart and Estrogen/progestin Replacement Study on secondary prevention showed an increased risk of cardiovascular and cerebrovascular events in postmenopausal women receiving HRT. Another randomized trial quantifying coronary atherosclerosis angiographically showed negative results with respect to estrogen use. As a result, it has been postulated that the previously shown benefits might have been caused by the "healthy user" effect, and the use of HRT for primary prophylaxis against cardiovascular events is not recommended, as the most recent ACC/AHA guidelines assign HRT a class III, LOE A, recommendation.

a. **Benefits of use.** Although the use of estrogen has shown an increase in cardiovascular events, it is associated with some specific favorable findings. The positive effects of estrogen use include maintenance of normal endothelial function, reduction in levels of oxidized LDL, alteration in vascular tone, maintenance of normal hemostatic profile, a favorable effect on plasma glucose levels, reduction of osteoporotic fractures, and a reduction in menopausal symptoms.

b. **Side effects** include bleeding, nausea, and water retention. Because doses of estrogen are small, these side effects are uncommon. For patients with an intact uterus, routine gynecologic examination is mandatory for cancer surveillance. The risk of breast cancer is also increased with the use of HRT, and routine screening is beneficial.

9. Antioxidants. The role of vitamins A, C, and E is unclear in patients with CAD. All carry a **class III recommendation** from the ACC/AHA (LOE A). The initial observational studies on the role of daily vitamin E supplementation in reducing the risk of cardiovascular events among patients with proven atherosclerotic heart disease appeared promising. However, when vitamin E was tested in a randomized fashion, no benefit in its use was proved. There are also data suggesting that vitamin E may attenuate the effect of statins. Data are lacking about vitamins A and C. Most of the available information suggests no benefit in taking supranormal doses of these vitamins. Vitamin A does not prevent LDL oxidation, even though it binds to LDL molecules. Because it is water soluble, vitamin C does not bind to the LDL molecule. These two vitamins are not recommended for the prevention of progression of atherosclerosis.

10. Ranolazine

a. **Mechanism.** Ranolazine has been shown to work by inhibiting the late sodium channel in myocytes, which can otherwise remain open in pathologic states such as ischemia and heart failure. By reducing the late sodium entry into myocytes, ranolazine causes reduced sodium-dependent calcium entry into the cytosol. This downstream reduction in intracellular calcium levels is thought to reduce diastolic stiffness, thereby improving diastolic blood flow and reducing ischemia and angina. Earlier studies had suggested that effects of ranolazine were primarily through its impact on fatty acid metabolism; however, the weight of evidence now suggests that late sodium channel inhibition is its primary mechanism.

b. **Efficacy.** Numerous randomized studies of ranolazine, with or without background antianginal therapy, have shown a benefit in patients with stable angina with respect to frequency of anginal attacks, exercise duration, time to ST-segment depression on treadmill testing, and use of sublingual nitroglycerin. The most recent ACC/AHA guidelines suggest that ranolazine can be used either in combination with β-blockers when symptoms are uncontrolled (class IIa, LOE B) or in place of β-blockers if the patient does not tolerate β-blockers or if β-blockers are ineffective (class IIa, LOE B).

c. **Side effects.** Dizziness, headache, and GI intolerance are the most common side effects noted. Prolongation of the QT interval has been reported, especially in patients with hepatic or liver dysfunction because of decreased metabolism. **Prolonged QT interval** at baseline or during treatment follow-up **is a contraindication** to its use.

d. **Drug interactions.** Inhibitors of CYP3A4, such as azole antifungals, non–dihydropyridine calcium channel blockers, macrolide antibiotics, protease inhibitors, and grapefruit juice, should not be used concomitantly because of inhibition of ranolazine metabolism.

C. **Growth factors.** Therapy with direct infusion of vascular endothelial growth factor and basic fibroblast growth factor proteins has been shown to increase collateral blood flow in animal models. Thus far, no clinical benefit has been shown for these agents in several trials.

D. **Enhanced external counterpulsation (EECP)** has become a treatment option for patients with stable angina.

1. EECP involves the intermittent compression of the lower extremities in an effort to increase diastolic pressure and augment coronary blood flow. Three sets of balloons are wrapped around the lower legs, lower thighs, and upper thighs, with precise cuff inflation and deflation gated with the ECG. The lower cuffs are inflated at the start of diastole, as represented by the beginning of the T-wave, and simultaneous deflation of all three chambers is triggered just before systole at the onset of the P-wave.

2. In patients with refractory angina, clinical trials have demonstrated improvements in exercise tolerance, reduction in anginal symptoms, decreased use of nitroglycerin, and improvements in objective measures of ischemia as measured by thallium scintigraphy. These benefits are maintained at 2 years of follow-up. EECP carries a class IIb, LOE B, recommendation at present.

E. **Coronary sinus obstruction.** Coronary sinus occluder devices obstruct coronary sinus flow, increasing coronary sinus pressure. This theoretically increases perfusion of ischemic areas by decreasing the myocardial pressure gradient. Small, non-blinded trials have demonstrated some benefit in patients with Canadian Cardiovascular Society class III or IV angina on maximal medical therapies. Larger trials are underway to confirm this observation. At present, these devices are not being clinically used in the United States.

F. **Percutaneous coronary intervention.** The effectiveness of PCI to control symptoms in chronic stable angina and to prevent death or MI has been compared with medical management and CABG.

1. **Compared with medical treatment**

a. The Angioplasty Compared with Medicine trial compared PCI with medical therapy in approximately 200 patients with single-vessel and multivessel CAD. Patients with single-vessel CAD showed better symptomatic relief at 6 months with PCI but no difference in mortality or MI. Patients with multivessel CAD had no significant differences in symptoms, mortality, or MI.

b. The Medicine, Angioplasty, or Surgery Study randomized approximately 200 patients with proximal left anterior descending (LAD) artery disease to medical therapy, PCI, or CABG. This

study demonstrated no difference in the primary end point (i.e., death, MI, or refractory angina necessitating revascularization). Patients randomized to CABG had a lower incidence of events compared with the other two groups, driven by a decrease in repeat revascularization procedures.

c. The Randomized Intervention Treatment of Angina-2 trial randomized more than 1,000 patients with stable angina to medical therapy or PCI. After 2.7 years of follow-up, the primary end point (i.e., death or MI) was lower in the medically treated group. There was also a higher incidence of revascularization in the medically treated group. There was an improvement in angina, exercise capacity, and perceived quality of life in patients who underwent PCI.

d. The study on Optimal Medical Therapy (OMT) with or without PCI for Stable Coronary Disease (by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] Trial Research group) evaluated patients with severe angiographic disease of one or more vessels, and either classic symptoms or documented ischemia on provocative testing. Compared with aggressive medical therapy, an initial strategy of PCI with BMS did not reduce the primary end point of death or major adverse cardiovascular events including symptom relief. Notable limitations to the interpretation of this study include the fact that the OMT group had stringent follow-up to achieve the high rates of medical adherence, one-third of patients in the medical therapy group crossed over to PCI (but were included in the OMT group as intention-to-treat analysis), and almost 80% of patients had no or minimal angina. Furthermore, it should be stressed that all patients were enrolled after angiography had been performed.

e. In a substudy of patients enrolled in COURAGE on the basis of positive stress imaging, investigators found that PCI in addition to OMT was superior in reducing ischemia than OMT alone. Furthermore, the degree of residual ischemia was related to future risk of death or MI. The adequately powered International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial has been funded by the National Heart, Lung, and Blood Institute to address this issue.

f. The Occluded Artery Trial tested the hypothesis that routine PCI of totally occluded arteries 3 to 28 days after MI in high risk but asymptomatic patients would improve outcomes. In the 2,166 patients studied, there was no statistically significant difference in long-term cardiac events between the PCI and the medical therapy groups, although the PCI group had more rapid relief of angina.

g. The use of fourth-generation DES in comparison with BMS has significantly decreased the risk of in-stent restenosis and the need for target vessel revascularization, thereby improving quality of life, providing freedom from angina, and reducing the risk of repeat procedures. The FAME-2 trial randomized 888 patients with functionally significant stenosis, defined by a fractional flow reserve of less than 0.8, to either stenting with a DES or OMT. At 12 months, stented patients had a lower need for future urgent revascularization but no difference in all-cause mortality or MI.

2.Compared with CABG

a. The Emory Angioplasty versus Surgery Trial randomized approximately 400 patients with multivessel disease to PCI or CABG. After 8 years of follow-up, there was no difference in the combined end point of mortality, Q-wave MI, and large thallium perfusion defect. In patients with proximal LAD artery disease or diabetes, there was a nonsignificant trend toward improved survival with CABG.

b. The Bypass Angioplasty Revascularization Investigators (BARI) compared PCI with CABG in the management of multivessel disease. In this trial, there was no difference in survival between

patients randomized to PCI or CABG at 7 years of follow-up, although the subgroup of patients with diabetes had a better survival rate with CABG than with PCI (76.4% vs. 55.7%).

c. The Arterial Revascularization Therapies Study (ARTS) randomized 1,200 patients with multivessel disease to CABG or BMS placement. After 1 and 5 years of follow-up, there was no difference in mortality, MI, or stroke. Outcomes were similar for patients with stable and unstable angina. Among diabetic patients, however, mortality was greater for those who received PCI. There was a greater incidence of repeat revascularization in the PCI group, although the use of DES in ARTS 2 (compared with the historic CABG group from ARTS 1) shows a similar 1-year rate of revascularization between PCI and CABG groups.

d. The Surgery or Stenting study compared almost 1,000 patients with multivessel disease in the setting of ACS or non-ACS presentation. There was increased mortality and need for repeat revascularization in the PCI group, which could not be attributed to a diabetic population.

e. In the BARI 2 Diabetes (BARI 2D) trial, investigators compared prompt revascularization (PCI or CABG as deemed appropriate) and OMT in a group of patients with type 2 diabetes mellitus and CAD. The primary outcome of death was not significantly different in the two groups, nor was the rate of major cardiovascular events (the major secondary end point including death, MI, and stroke). When stratified by revascularization strategy, patients in the CABG group had greater freedom from major cardiovascular events (77.6% vs. 69.5%, $p = 0.01$); this finding was not significant in patients undergoing PCI. Notably, however, this trial was not designed to compare CABG and PCI as revascularization strategies.

f. The SYNergy between PCI with TAXus and cardiac surgery (SYNTAX) was a pivotal trial randomizing patients with three-vessel disease or left main trunk (LMT) stenosis to multivessel PCI versus CABG. The primary end point of death, stroke, MI, and repeat revascularization favored CABG (12.3% vs. 17.6%, $p = 0.002$). The secondary end point which included death, stroke, and MI was not different between the two groups (7.7% vs. 7.6%, $p = 0.98$). The primary end point favoring CABG was therefore driven primarily by increased rates of repeat revascularization in the PCI group (13.5% vs. 5.9%, $p < 0.001$), although, notably, the rate of stroke was also significantly lower in the PCI group (2.2% vs. 0.6%, $p = 0.003$).

g. The other major take-home point of the SYNTAX trial was the formulation of the SYNTAX score, which received a class I indication for evaluation of LMT or multivessel disease in the ACC/AHA PCI guidelines. The SYNTAX score grades coronary anatomy on the basis of lesion location, complexity, and functional impact and is a helpful tool for assessing patients at the individual level when discussing CABG versus PCI. In the trial, outcomes were assessed by SYNTAX score tertile: Patients with a low (0 to 22) or intermediate (23 to 32) score had no difference between the two modes of revascularization for the primary outcome. In patients with a score >32, however, CABG was favored for the primary outcome (10.9% vs. 23.4%, $p < 0.001$).

h. The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial enrolled 1,900 patients with stenoses of greater than 70% in two or more epicardial vessels, randomizing them to DES placement or CABG. At 1 year, the risk of MI (5.8% vs. 3.4%, $p = 0.02$) and the combined outcome of death, MI, or stroke (16.8% vs. 11.8%, $p = 0.004$) were significantly higher for patients in the PCI arm of the trial. The risk of stroke was higher with CABG than with PCI (1.9% vs. 0.9%, $p = 0.06$), and there was no difference in death (4.2% vs. 3.4%, $p = 0.35$) between the two groups. The benefit of CABG over PCI was maintained for patients of all SYNTAX scores.

i. In patients with LMT stenosis, guidelines had long recommended CABG as the treatment of choice. However, in the modern era of stent placement, PCI of "unprotected" LMT stenosis has gained favor. The most recent ACC/AHA guidelines assign a class IIa, LOE B, recommendation to left main stenting in patients with a low SYNTAX score and a high operative risk. In patients who are good candidates for surgery, CABG carries a class I, LOE B, recommendation in patients with LMT stenosis.

1. **(1)** In the prespecified subgroup of patients undergoing unprotected LMT PCI versus CABG in the SYNTAX trial, the primary outcome was similar between the two groups. As in the main study population, stroke was higher in the CABG group (2.7% vs. 0.3%, $p = 0.009$) and repeat revascularization was higher in the PCI group (11.8% vs. 6.5%, $p = 0.02$).
2. **(2)** The Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial randomized 1,905 patients with LMT stenosis and a SYNTAX score <32. At 3 years, PCI was noninferior to CABG for the primary composite end point of death, stroke, or MI (15.4% vs. 14.7%).
3. **(3)** In the Nordic-Baltic-British left main revascularization study trial, 1,201 patients were randomized to left main intervention with PCI (biolimus stent) versus CABG. In this study, PCI did not meet the set boundaries of noninferiority compared with CABG. The event rate for the composite of death, MI, repeat revascularization, and stroke with PCI was 28% compared with 18% for CABG making the latter the superior strategy ($p = 0.004$).

j. At present, strong consideration is given to CABG in the group of patients with multivessel disease and diabetes, LV dysfunction, or LMT disease who are able to undergo open heart surgery. In the general population with multivessel or LMT disease, however, there is a paucity of evidence showing a survival advantage to CABG over PCI, and recent trials with modern treatment practices (including DES implantation, aggressive antiplatelet therapy, off-pump coronary artery bypass procedures, and use of arterial grafts) have shown favorable comparisons between the two treatment strategies. The ACC/AHA guidelines indicate that in patients with three-vessel CAD or with severe stenosis of the proximal LAD and another vessel, CABG should be pursued (class I, LOE B). For patients who are able to undergo either of the treatments, an educated decision should be made by the patient, the cardiologist, and a cardiac surgeon using a heart team approach.

3. **Revascularization methods.** For details of PCI strategy and equipment, please see Chapter 63.

G. Coronary artery bypass grafting

1. **Compared with medical treatment.** Compared with medical treatment, CABG improves the survival rate among patients with high-risk stable angina. The benefit is most profound in patients with three-vessel CAD, impaired LV function, or substantial LMCA stenosis.

a. This information is derived from the Coronary Artery Surgery Study, European Coronary Surgery Study, and Veterans Administration Cooperative Study. These trials were completed before generalized awareness grew regarding the benefits of medical management with β-blockers, ACE inhibitors, antiplatelet agents, or lipid-lowering medications.

b. Surgical techniques have also changed significantly, with greater use of arterial conduits including internal mammary artery (IMA) grafts, minimally invasive surgery, and improved techniques of cardiac tissue preservation and anesthesia.

2. **Venous or arterial grafts.** There are different techniques of CABG. The use of minimally invasive bypass surgery involving the left internal mammary artery (LIMA) in patients with isolated LAD artery stenosis has not shown any difference in the rate of mortality, MI, or stroke in comparison to PCI but has shown a decrease in the need for repeat revascularization. With

open sternotomy, in which the use of LIMA is well studied, mammary arterial grafting has better long-term outcome compared with vein graft conduits. Given the success of the (LIMA) graft, other arterial conduits have been used, such as the right internal mammary artery (RIMA), the radial artery, and the right gastroepiploic artery.

a. Twenty percent of venous grafts are nonfunctional at 5 years and only 60% to 70% are functional after 10 years. In contrast, >90% of LIMA to LAD artery grafts are patent 20 years after the operation.

b. **IMA** grafts have a better patency rate at 10 years when used for LAD lesions (95%) than for circumflex (88%) or right coronary artery (76%) lesions. The patency rates are higher for LIMA compared with RIMA and for in situ grafts compared with free grafts.

c. Patient survival is better with an IMA graft than when only saphenous venous grafts are used. This survival benefit persists for up to 20 years.

d. The radial artery graft was introduced into clinical practice around the year 1970 and initially had mixed results. However, at approximately 1 year, 92% of the grafts are patent, and at 5 years, 80% to 85% of grafts are open. The 5-year angiographic patency rates of 92% have been reported for right gastroepiploic arterial grafts.

3. **Previous CABG.** Little information is available on the treatment of patients who have already undergone bypass surgery and have stable angina. Although another bypass operation may be offered to these patients, direct comparison with medical treatment in this patient population has not been made. The use of multiple arterial grafts at the time of first CABG reduces the need for reoperation. The most recent ACC/AHA guidelines recommend PCI in patients with prior CABG who have one or more significant (greater than 70%) stenoses who have angina despite OMT.

4. **Compared with PCI.** This is discussed in Section IV.C.E.2.

H. Hybrid coronary revascularization: In some patients, in whom the aorta is calcified or who possess poor targets for full surgical revascularization, hybrid revascularization is an option. In this procedure, a combination of bypasses (almost always including the LIMA anastomosed to the LAD) and PCI (to lesions unable to be bypassed) is performed. The procedure may be performed simultaneously, in a hybrid operating room, or sequentially, with PCI occurring hours to days after CABG. Although no published randomized trials have assessed the efficacy and outcomes of this in comparison to traditional PCI or CABG, this procedure carries a class IIa, LOE B, recommendation in the most recent ACC/AHA guidelines.

I. Lifestyle modification

1. **Exercise**

a. **Rationale.** Exercise conditions the skeletal muscles, which decreases total body oxygen consumption for the same amount of workload. Exercise training also lowers heart rate for any level of exertion, which decreases the oxygen demand on the myocardium for any workload. Some evidence shows that higher physical activity and exercise can decrease cardiovascular morbidity and mortality.

b. **Recommendation.** For secondary prevention, aerobic and isotonic exercises with a goal of achieving a sustained heart rate of approximately 70% to 85% of the maximum predicted heart rate for at least 30 to 60 minutes at least 5 times per week has been shown to improve survival and carries a class I, LOE B, recommendation. For beginners, a supervised exercise or rehabilitative program, in which 50% to 70% of maximal predicted heart rate is achieved, is also helpful.

Isometric exercises are not recommended because they increase myocardial oxygen demand substantially.

2. **Diet.** A low-fat diet that includes cereals and grains, skimmed dairy products, fruits and vegetables, fish, and lean meats should be recommended and this is effective in providing cardiovascular risk reduction in patients with CAD. These are integral components of the "Mediterranean Diet," which has been shown to reduce cardiovascular risk. Consumption of one (for nonpregnant women) or one to two (for men) standard alcoholic beverages per day is reasonable if not contraindicated (i.e., because of liver disease or alcoholism). This is a class IIb, LOE C, recommendation. A multidisciplinary approach to the care of patients with CAD that includes a nutritionist/dietician can be quite helpful in personalizing patients' eating habits.

3. **Smoking cessation.** Cigarette smoking is associated with progression of atherosclerosis, increased myocardial demand because of an α-adrenergic increase in coronary tone, and adverse effects on hemostatic values, all of which can lead to worsening of stable angina. Smoking cessation decreases cardiovascular risk among patients with established CAD, including patients who have undergone CABG. Physician counseling is the best approach to achieve this goal and adjunctive therapies include nicotine replacement patches, gum, or sprays, or medications such as bupropion and varenicline.

4. **Psychological factors.** Anger, hostility, depression, and stress are shown to adversely affect CAD. Results of small, nonrandomized trials show that biofeedback and various relaxation techniques can help modify these factors.

V. RECOMMENDED APPROACH TO STABLE ANGINA

A. The following approach is suggested for the treatment of patients with stable angina.

1. It is reasonable to risk-stratify patients with stable angina using stress testing with imaging, such as nuclear isotope imaging or echocardiography.

a. LV systolic function should be assessed with echocardiography to guide therapy and to identify patients with LV systolic dysfunction.

b. Patients with small perfusion defects or small wall motion abnormalities, high threshold for ischemia, normal LV systolic function, and clear symptoms should be treated with medication.

2. If symptoms continue after medical therapy is maximized, angiography should be planned. Coronary angiography should also be performed for patients with evidence of impaired perfusion involving multiple territories, a low threshold for ischemia, and LV systolic dysfunction.

3. **Single-vessel disease.** If a patient has single-vessel CAD that does not involve the LMT or supply a large myocardial territory, medical management with risk factor modification is the appropriate first step.

a. If patients cannot tolerate medical treatment or have symptoms despite maximum medical therapy, revascularization should be offered.

4. Among patients with **multivessel CAD**, medical treatment remains an alternative for patients who have normal LV systolic function, mild symptoms, and relatively smaller areas of myocardium at risk.

a. The decision for multivessel PCI versus CABG in this group of patients should be made on an individual basis, taking into consideration the angiographic anatomy, LV function, patient comorbidities (especially diabetes), surgical risk, and patient preference.

b. Any doubt regarding viability of the myocardium at risk should be addressed with appropriate diagnostic studies before revascularization.

5. In patients with "unprotected" LMT stenosis, the previous recommendations of CABG in all patients who are able to undergo surgery have been revised. PCI for severe LMT disease may be appropriate in select patients.
6. Regardless of treatment strategy, aggressive risk factor modification, including use of lipid-lowering agents, lifestyle modification, and aspirin therapy, is an essential component of management.

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CHAPTER 7

Other Ischemic Syndromes: Silent Ischemia, Microvascular Angina, and Stress Cardiomyopathy

Chetan P. Huded

I. SILENT ISCHEMIA

A. Introduction. Patients with objective evidence of myocardial ischemia in the absence of symptoms are said to have silent ischemia. **Silent ischemia may occur in patients with and without established coronary artery disease (CAD).** A significant proportion of patients (>40%) with stable angina and those following acute coronary syndromes (ACSs) manifest this condition. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial, 13% of the patients enrolled in that study with stable CAD had evidence of silent ischemia. In patients with stable CAD, the presence of silent ischemia is even more common than symptomatic ischemia. Silent target vessel ischemia is also common after successful percutaneous coronary intervention (PCI). Silent ischemia has been associated with the presence of high-risk coronary anatomy by angiography, and the presence of silent ischemia during daily life has been shown to be a strong predictor of mortality. Silent ischemia may be documented by a variety of diagnostic modalities, including resting electrocardiogram (ECG), ambulatory ECG (AECG), nuclear myocardial perfusion imaging (MPI), and echocardiography. In high-risk patients without established CAD (patients with diabetes, strong family history of CAD, or a high-risk coronary artery calcium score by external beam computed tomography), silent ischemia is often discovered by stress testing obtained for primary screening.

B. Presentation. Patients with silent ischemia may be loosely categorized into three groups.

1. **Type I** have **asymptomatic** ischemia with no known CAD history with **asymptomatic** myocardial infarction (MI) patterns on noninvasive imaging such as ECG or stress testing. In the Framingham study, 12.5% of patients with MI had an unrecognized "silent" infarction. Patients may also present with arrhythmias or sudden death from scar because of prior MI. These patients are considered to have an ineffective "anginal warning system." A subset of this group includes patients with **asymptomatic** ischemia without prior infarction.
2. **Type II** have **symptomatic** MIs but subsequent **asymptomatic** ischemic syndromes. Patients in this category are most often encountered after a positive stress test or the rarely ordered AECG. Type II patients may have an abnormal **pain threshold.**

3. **Type III** encompasses the largest patient population with silent ischemia. These patients with known CAD have both **symptomatic** and **asymptomatic** ischemia. Between 20% and 40% of patients with chronic anginal symptoms also have silent ischemic episodes. About 75% of ischemic episodes are silent and 25% are symptomatic.

C. Mechanisms

1. The exact explanation for a lack of symptoms in the face of unequivocal ischemia remains unknown, but likely represents **abnormal modulation of cardiac pain perception at different levels in the afferent pathway of the heart**. Results of one study implicated gating of afferent signals at the thalamic level as a potential mechanism for silent ischemia. Symptomatic patients had activation of basal frontal, anterior, and ventral cingulate cortices and the left temporal pole, whereas asymptomatic patients had **cortical activation limited to the right frontal region.**
2. **The association between diabetes and silent ischemia and painless infarction** has been attributed to **autonomic neuropathy**. Additionally, higher threshold for pain has been related to increased baseline plasma β-endorphin levels and increased age. A potential connection also exists between baroreceptor function and pain perception. This may explain the relationships among increased systolic blood pressure, reduced sensitivity to ischemic pain, and the demonstration of anginal relief with carotid sinus stimulation.
3. It also has been proposed that, among type III patients, asymptomatic ischemia may represent **shorter and less severe episodes**compared with symptomatic episodes.

D. Diagnosis. Testing to detect ischemia in asymptomatic patients is controversial.

The 2014 European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization give a class III recommendation against screening asymptomatic individuals for silent ischemia by any imaging modality, although the guidelines state that screening for silent ischemia may be considered in certain high-risk patients such as those with diabetes mellitus. However, in patients with known CAD and a prior history of silent ischemia and high risk for future cardiac events, the 2014 American College of Cardiology and American Heart Association guidelines on stable ischemic heart disease give a class IIa recommendation for nuclear MPI, echo, or cardiac magnetic resonance imaging (MRI) stress testing at 2 year or longer intervals to detect recurrent ischemia.

E. Therapy

1. **Medications** effective in treating symptomatic CAD (i.e., nitrates, calcium channel antagonists, β-blockers, and angiotensin-converting enzyme [ACE] inhibitors) are also effective in reducing the burden of silent ischemia. In one randomized study, metoprolol was found to be better than diltiazem in reducing the mean number and duration of ischemic episodes. However, **the combination of calcium channel antagonists and β-blockers was more effective than either agent alone.** Lipid-lowering therapy has also shown a reduction of ischemia on AECG. Ranolazine was proven ineffective in reducing ischemia on AECG monitoring after non–ST-segment elevation ACSs in one large randomized controlled trial.
2. **The goal of therapy remains controversial.** The clinical value of treating silent ischemia remains unresolved. The Asymptomatic Cardiac Ischemia Pilot study demonstrated that revascularization was more effective in reducing asymptomatic ischemia than either angina- or ischemia-guided medical therapy. Patients with greater reduction in ischemic episodes had a nonsignificant improvement in cardiac events, and 2-year follow-up data from that study demonstrated improved prognosis with initial revascularization compared with angina or ischemia-guided medical therapy. The Swiss Interventional Study on Silent Ischemia type I

(SWISSI I) randomized 54 type I subset patients to treatment with antianginal medications and aspirin versus risk factor modification only. The drug therapy arm had a significantly lower rate of cardiac death, nonfatal MI, or ACS and consistently lower rates of exercise-induced ischemia. The SWISSI II study randomized 201 patients with type II silent ischemia to PCI versus ongoing anti-ischemic medical therapy. The results showed a significant decrease in rates of cardiac death, nonfatal MI, and subsequent need for revascularization in patients in the PCI group over a 10-year follow-up period. Similarly, in patients with type I silent ischemia, with an ineffective "anginal warning system," it has been suggested that medical therapy and revascularization are reasonable approaches to treat silent ischemia.

F. Prognosis. Myocardial ischemia in patients with CAD, whether symptomatic or asymptomatic, is associated with poor outcomes. The Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome trial found that 20% of patients after non–ST-segment elevation ACS had ischemia identified on AECG, and that the group with at least one episode of ischemia was at increased risk for cardiovascular death and recurrent ischemia. The presence of ischemia is a more reliable prognostic factor than the presence of angina, because cardiac event rates among patients with silent ischemia and symptomatic ischemia are similar. In a report from the Coronary Artery Surgery Study registry, about one in four patients with medically managed CAD who were followed for 7 years suffered from death or MI, and the event rate was similar in the group with silent ischemia and the group with symptomatic ischemia on exercise ECG testing. Patients with frequent and accelerating episodes of ST-segment depression on AECG monitoring are at higher risk for subsequent cardiac events than patients with few or no such episodes. In the Copenhagen Holter study, asymptomatic healthy patients between the ages of 55 and 75 years with ischemic changes on AECG had a threefold higher risk of subsequent cardiac events over a 5-year follow-up period. It has not been proven conclusively, however, that detection of silent ischemia is an independent risk factor for future cardiac events.

II. MICROVASCULAR ANGINA

A. Introduction. Approximately **30% to 40% of patients referred for coronary angiography** in the setting of chest pain do not have obstructive CAD by angiography. About half of these patients have microvascular angina (MVA). MVA is a **syndrome of microvascular dysfunction characterized by inadequate coronary arteriolar vasodilation resulting in reduced coronary blood flow under conditions of increased oxygen demand**. There is a paucity of data on the optimal treatment for MVA. MVA is associated with an increased risk of cardiac events, hospitalization, MI, and coronary revascularization, and the primary goal of treatment is cardiac risk factor modification.

B. Presentation. Angina in the absence of obstructive CAD was previously referred to as Syndrome X. However, these patients constitute a heterogeneous group including those with a variety of conditions such as coronary spasm and noncardiac chest pain. Therefore, the terminology Syndrome X has been largely abandoned. In contemporary practice, MVA refers to the subset of these patients with angina, no obstructive epicardial CAD, and abnormal coronary flow reserve (CFR) on objective testing. Historically, it was felt that syndrome X was more common in women, with a 3:1 preponderance of women to men. However, recent data suggest that MVA is equally prevalent in men and women. Patients with MVA have higher rates of traditional atherosclerotic risk factors such as diabetes mellitus and

hypertension compared with healthy controls. Chronic inflammatory diseases have also been associated with higher rates of MVA.

C. Mechanisms. Angina because of CAD is the result of inadequate myocardial oxygen supply under conditions of increased demand because of a fixed obstructive stenosis of a major epicardial coronary artery. Similarly, MVA is the result of inadequate myocardial oxygen supply under conditions of increased demand. However, in MVA the imbalance between myocardial oxygen supply and demand occurs due to inadequate vasomotor function in the coronary microvasculature, termed coronary microvascular dysfunction (CMD). CMD is the result of both endothelial and nonendothelial-dependent mechanisms, which cause increased vasoconstriction and reduced vasodilation in the coronary microcirculation.

Prior authors have advocated classifying CMD into four distinct groups to clearly delineate the various pathophysiologic mechanisms.

1. Group 1 includes patients with CMD in the absence of myocardial disease or obstructive CAD. These patients have MVA in the setting of atherosclerotic risk factors which produce endothelial dysfunction and remodeling of the coronary microvasculature.
2. Group 2 includes patients with CMD in the setting of myocardial disease such as hypertrophic cardiomyopathy, aortic stenosis, and amyloidosis. These patients have smooth muscle cell dysfunction, vascular remodeling, and myocardial dysfunction causing impediments to the coronary microvasculature.
3. Group 3 have CMD with concomitant obstructive CAD.
4. Group 4 have CMD as a consequence of coronary revascularization. Group 4 patients are often encountered in the cardiac catheterization lab after PCI with resultant “no reflow” phenomenon because of distal embolization of atherosclerotic plaque into the distal microvasculature.

D. Diagnosis. Whereas epicardial CAD can be reliably detected by both functional (nuclear MPI, exercise ECG, stress echocardiography) and anatomic (coronary angiography, computed tomography) imaging strategies, the **detection of MVA requires functional assessment of the coronary microvasculature. CFR is the predominant method for detecting patients with MVA because of CMD.**

CFR is the ***ratio of myocardial blood flow (MBF) during peak stress or vasodilation compared to MBF at rest.***

CFR can be measured

1. Invasively in the cardiac catheterization lab using intracoronary Doppler or
2. Noninvasively by positron emission tomography (PET) or contrast-enhanced MRI assessments of myocardial perfusion reserve. Additionally Doppler echocardiography has been used to measure CFR with promising results. The normal values of CFR are debated, but previous studies have used a cut-off of CFR <2.5 or <2.0 to identify patients with CMD.

E. Therapy. There is a paucity of evidence-based therapies for MVA because of a lack of literature in this area. In a 2015 systematic review of therapies for MVA, only 8 studies with an average of 11 patients per study were identified. The tested strategies included ACE inhibitors, statins, nitric oxide inhibitors, calcium channel blockers, estrogens, and α-blockers, but the small number of patients in these studies precludes firm conclusions. Therefore, the optimal treatment for MVA is unclear. At this time, the **primary goal** of the therapy in patients with MVA should be **symptom control** and **cardiac risk factor modification**, although whether these measures improve outcomes in patients with MVA is unknown.

F. Prognosis. Historically, the prognosis for patients with angina and normal coronary arteriograms was generally thought to be favorable with good long-term outcomes in multiple studies. However, in contemporary studies, **patients with MVA have been shown to have poor prognosis with increased rates of major adverse cardiac events, stroke, heart failure, and death.** Additionally ***patients with the lowest CFR appear to have the worst outcomes.*** One recent study of patients with CMD (defined as PET MPI showing CFR <2.0) reported a hazard ratio of 0.80 (confidence interval 0.75 to 0.86, $p < 0.0001$) for each 10% reduction in CFR.

III. STRESS CARDIOMYOPATHY

A. Introduction. Stress cardiomyopathy is a syndrome of **transient left ventricular dysfunction which occurs in the setting of intense physical or emotional distress**. It is also known as **Takotsubo syndrome**, because the classic finding of apical ballooning with preserved basal left ventricular systolic function has a similar appearance to the Japanese octopus trap of the same name. The pathophysiology of this syndrome includes catecholamine-induced myocardial dysfunction and CMD. Stress cardiomyopathy is most prevalent among postmenopausal women, and the presentation can often mimic acute MI with chest pain, abnormal ECG findings, and positive cardiac biomarkers. Therefore, the diagnosis of stress cardiomyopathy is often confirmed only at the time of coronary angiography when no obstructive CAD is identified.

B. Presentation. Stress cardiomyopathy is relatively infrequent, affecting only 2% of patients presenting with suspected ACS. An overwhelming majority (90%) of patients with stress cardiomyopathy are women and 90% are older than 50 years of age. Physical stress is a slightly more common trigger than emotional stress in cases of stress cardiomyopathy, and in nearly one-third of cases, no trigger is ever identified. Chest pain and dyspnea are the most common presenting symptoms.

C. Mechanisms. The underlying pathophysiology of stress cardiomyopathy is **catecholamine excess because of activation of the hypothalamic–pituitary–adrenal axis under a condition of extreme physical or emotional stress**. Similar left ventricular dysfunction has been described in the setting of exogenous catecholamine use and other states of excess endogenous catecholamine production such as pheochromocytoma. Catecholamine effects on the cardiac myocyte during stress cardiomyopathy include myocyte hypertrophy, damage to key structural and contractile proteins, and calcium excess. Stress cardiomyopathy is also associated with coronary vasomotor dysfunction at the epicardial and microvascular level with increased vasoconstriction resulting in vasospasm and transient myocardial ischemia. Additionally, systemic response to catecholamine surges includes peripheral vasoconstriction resulting in an acute increase in left ventricular afterload, which may further contribute to left ventricular systolic dysfunction. ***The apex of the left ventricle has a higher proportion of β-adrenergic receptors***, which may account for the typical vulnerability of the left ventricular apex to stress cardiomyopathy.

D. Diagnosis. Stress cardiomyopathy is diagnosed on clinical grounds with characteristic findings of new or transient left ventricular systolic dysfunction, absence of an alternative myopathic process (acute MI, myocarditis, tachycardia, pheochromocytoma), and a history of intense physical or emotional distress. The vast majority of patients with stress cardiomyopathy have elevated cardiac troponin levels, but the elevation in cardiac troponin is typically mild. ECG findings include dynamic ST-segment elevation, and T-wave

inversion. **The ECG findings during stress cardiomyopathy can mimic those of an acute MI.**

1. **Echocardiography.** The characteristic echocardiographic finding is that of severe apical hypokinesis or akinesis with relatively preserved function of the left ventricular base. **However, nonapical variants including mid-ventricular and basal hypokinesis have been reported with less frequency as has involvement of the right ventricle.** Left ventricular ejection fraction is typically severely reduced during the acute phase of stress cardiomyopathy, but in **most patients, left ventricular systolic function recovers within 4 to 6 weeks after the acute presentation.**
2. **Cardiac MRI.** In patients with an abnormal ECG, new left ventricular dysfunction, and positive cardiac biomarkers, cardiac MRI is useful for discriminating stress cardiomyopathy from other syndromes with similar presentation such as myocarditis or ACS with a recanalized coronary obstruction. **In patients with stress cardiomyopathy, cardiac MRI shows no perfusion abnormalities and no evidence of delayed gadolinium enhancement suggestive of scar.** These findings are more typical in patients with acute MI and those with myocarditis.
3. **Cardiac catheterization.** Because there is nearly complete overlap between the clinical presentation of acute MI and stress cardiomyopathy, **a coronary angiogram is required in almost all cases to exclude a culprit coronary lesion** that might account for the clinical findings.

E. Therapy. Treatment of stress cardiomyopathy is multifaceted. The underlying physical or emotional trigger should be identified and treated if possible to try to prevent future episodes. In the acute phase of stress cardiomyopathy, treatment is targeted at electrical and mechanical complications resulting from acute left ventricular dysfunction such as ventricular tachycardia, cardiogenic shock, and dynamic left ventricular outflow tract obstruction using conventional therapies for these complications. In the subacute to chronic phase of stress cardiomyopathy, medical therapy for left ventricular dysfunction is commonly prescribed. ACE inhibitors or angiotensin receptor blockers and β-blockers are widely used as in other cases of left ventricular systolic dysfunction. Unfortunately, there is no proven therapy to prevent recurrence of stress cardiomyopathy.

F. Prognosis. Historically, the prognosis of stress cardiomyopathy was felt to be favorable when compared with acute MI. However, recent reports have identified **in-hospital mortality of nearly 2% to 7% for patients with stress cardiomyopathy, which is similar to the in-hospital mortality of patients with ST-segment elevation MI**. However, the relatively high in-hospital mortality of stress cardiomyopathy may reflect that stress cardiomyopathy is often associated with other noncardiac acute comorbid illnesses. Although left ventricular dysfunction in stress cardiomyopathy is typically transient, it can be associated with lethal dysrhythmias and mechanical failure such as cardiogenic shock or left ventricular outflow tract obstruction. The annual rate of recurrence of stress cardiomyopathy is about 1.5% to 2.9% per year with recurrences more common in patients younger than 50 years of age. There is no treatment for secondary prophylaxis that has proven to be effective.

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CHAPTER 8

Heart Failure with Systolic Dysfunction

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I. INTRODUCTION. Heart failure (HF) is a complex clinical syndrome characterized by impaired myocardial performance and progressive maladaptive neurohormonal activation of the cardiovascular and renal systems leading to circulatory insufficiency and congestion. Currently, acute heart failure syndromes (AHFS) constitute the most common indication for hospitalization in adults over age 65. With the increasing age of the population, improved patient survival with acute coronary syndrome, and reduced mortality from other diseases, the incidence and attendant cost of managing patients with HF will inevitably continue to increase.

A. Terminology

1. Based on the hemodynamic model, **systolic HF** (or **heart failure with reduced ejection fraction**, HFrEF) has been defined by the presence of impaired contractility of the left ventricle, most commonly conveyed by an ejection fraction (EF) of ≤40%. This drop in contractility may be associated with chamber dilation and decreased stroke volume (Fig. 8.1). There is a growing appreciation for the limitations of this classification. The threshold for systolic dysfunction is arbitrary, and it is now clear that patients with HF with preserved EF (HFpEF) suffer similar morbidity and mortality. There is substantial variability in EF determinations made by different imaging modalities. Most importantly, EF correlates poorly with symptoms, cardiac indices, and potential response to medical intervention.

FIGURE 8.1 Pressure–volume loops in normal (dashed line) and heart failure (HF; solid line) patients. **A:** Pressure–volume loops in HF with impaired ejection fraction typically demonstrate a reduction in the end-systolic pressure–volume relationship (ESPVR; i.e., the end-systolic elastance), a representation of contractility. This is typically accompanied by an increase in end-diastolic volume and a reduction in stroke volume (SV) and stroke work (SW; shaded area). At a given ESPVR, a reduction in end-systolic pressure results in an increased SV and reduction in the left ventricular (LV) elastic potential energy (PE; speckled area). **B:** In contrast, patients with HF with preserved ejection fraction have a normal or elevated ESPVR with a left and upward shift in the end-diastolic pressure–volume relationship reflecting decreased myocardial compliance.

2. In practice, HF is a bedside diagnosis that is defined by clinical assessment. Patients may have cardiac dysfunction without symptoms, often referred to as **asymptomatic left ventricular (LV) dysfunction**.

3. Others may have preserved LV systolic function with typical signs and symptoms of HF, best referred to as **HFpEF** (see Chapter 9).
4. The major pathophysiologic process in the progression of HF is **cardiac remodeling**, progressive chamber enlargement with an obligatory reduction in EF. From a histopathologic standpoint, this is associated with myocyte hypertrophy, fibrosis, apoptosis, and necrosis. Molecular alterations including reexpression of a fetal gene program and alterations in excitation–contraction coupling and regulatory proteins occur.
5. In some cases, **myocardial recovery** or **reverse remodeling** is possible with pharmacologic and device therapy.
6. The term **congestive HF** is overused and nonspecific, often being applied to states of hypervolemia unrelated to cardiac dysfunction. Conversely, not all patients with HF have signs and symptoms of congestion or low output.
7. The term **right HF** is used to describe patients with predominantly peripheral signs and symptoms of congestion with a relative paucity of pulmonary congestion.
8. **Acute decompensated HF** or **AHFS** refer to episode(s) of acute or subacute deterioration because of a wide range of precipitants. The vast majority of these events are marked by systemic and pulmonary congestion.

II. PATHOGENESIS.

HF is a progressive disorder initiated by some form of injury. This injury may range from acute disruptions in myocardial function to one of a number of chronic derangements including familial, infiltrative, metabolic cardiomyopathies, or chronic volume or pressure overloading states related to valvulopathies, intracardiac shunts, systemic/pulmonary hypertension, or conduction abnormalities. Regardless of the initial insult, the acute beneficial compensatory mechanisms ultimately become maladaptive.

A. Neurohormonal activation

1. **Activation of the sympathetic nervous system.** Chronic activation of the sympathetic nervous system ultimately results in decreased β-adrenergic receptor responsiveness, decreased norepinephrine stores, and sympathetic innervation of the myocardium. Chronically, these changes contribute to myocyte hypertrophy, fibrosis, and necrosis. Extracardiac effects include increased tubular reabsorption of sodium, activation of the renin–angiotensin–aldosterone system (RAAS), neurogenic and systemic vasoconstriction, and vascular hypertrophy.
2. **Activation of the RAAS.** As HF progresses, renal hypoperfusion and sympathetic stimulation of the kidneys result in increased production of renin by the juxtaglomerular apparatus. Renin cleaves circulating angiotensinogen into the biologically inactive angiotensin I, which is subsequently cleaved by angiotensin-converting enzyme (ACE) to the biologically active angiotensin II. Importantly, renin and ACE-independent pathways can generate angiotensin II. In addition to direct cardiovascular effects, angiotensin II stimulates aldosterone production by the zona glomerulosa within the adrenal cortex, which in turn promotes reabsorption of sodium in exchange for potassium in the distal tubule and collecting ducts of the nephron. Over time, increased aldosterone levels result in the promotion of vascular and myocardial hypertrophy and fibrosis, endothelial dysfunction, and inhibition of norepinephrine uptake.
3. **Other neurohormonal derangements.** Inappropriate production of arginine vasopressin has an antidiuretic effect and augments systemic vasoconstriction. Endothelin, neuropeptide Y, and other peripheral vasoconstrictors further enhance vascular tone.

III. CLASSIFICATION

A. The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines currently classify HF on the basis of the evolution of the disease across a continuum (always progressive, no reversal):

1. **Stage A:** patients at high risk for developing HF without structural heart disease or symptomatic HF
2. **Stage B:** patients with structural heart disease who have not yet developed symptoms of HF
3. **Stage C:** patients with structural heart disease with prior or current symptoms of HF
4. **Stage D:** patients with refractory end-stage HF who require specialized advanced treatment

B. The **New York Heart Association (NYHA) functional classification**, although subjective and vague, remains the most commonly used standard by which the severity of functional impairment is graded (Table 8.1).

C. The **Killip classification** grades the severity of acute decompensated HF in the post–acute coronary syndrome setting and is predictive of 30-day mortality.

1. **Killip I:** patients with no clinical evidence of HF
2. **Killip II:** patients with mild signs of HF: S_3, elevated jugular venous pressure (JVP), or pulmonary crackles
3. **Killip III:** patients with acute pulmonary edema
4. **Killip IV:** patients with cardiogenic shock

IV. ETIOLOGY.

It is essential to make every effort to identify the specific etiology of HF because it may have implications for management and prognosis. Whereas ischemic cardiomyopathy is by far the most common cause of systolic HF, a diverse array of disease states can culminate in this phenotype (Table 8.2).

A. Ischemic cardiomyopathy accounts for almost half of the cases of systolic HF in industrialized countries. It is defined as **cardiomyopathy in the presence of prior extensive myocardial infarction, hibernating myocardium, or severe coronary artery disease**. However, the mere ***presence of obstructive coronary artery disease does not equal ischemic cardiomyopathy because it is possible to have coronary artery disease superimposed with a nonischemic etiology of HF***. A careful assessment of the coronary anatomy, ischemic burden, and the presence of infarcted and viable myocardium must be made and an assessment of the proportionality of these findings to the degree of myocardial dysfunction should be determined. The risks and benefits of percutaneous or surgical revascularization should be assessed in all patients with ischemic cardiomyopathy. Extensive observational data have suggested a benefit for coronary artery bypass grafting (CABG) compared with medical therapy alone in moderate to severe LV systolic dysfunction. Registry data suggest that CABG is superior to percutaneous coronary intervention in patients with reduced EF. Recently released 10-year follow-up data from the Surgical Treatment for Ischemic Heart Failure trial demonstrated a significant reduction in all-cause mortality, cardiovascular death, and HF hospitalization in the CABG plus medical therapy cohort compared with the medical therapy alone in patients with an EF <35%. Notably, patients with left main trunk disease and severe angina were excluded from the study and these patients should continue to be treated aggressively with revascularization.

TABLE 8.1 New York Heart Association Functional Classification

Class	Description

TABLE 8.1 New York Heart Association Functional Classification

I	Patients have cardiac disease but without resulting limitations of physical activity. Ordinary ph fatigue, palpitations, dyspnea, or anginal pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfort results in fatigue, palpitations, dyspnea, or anginal pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are co physical activity causes fatigue, palpitations, dyspnea, or anginal pain
IV	Patients have cardiac disease resulting in an inability to carry on any physical activity witho insufficiency or of the anginal syndrome may be present even at rest. If any physical activity i

TABLE 8.2 Etiologies of Heart Failure

Ischemic cardiomyopathy
Idiopathic cardiomyopathy
Familial cardiomyopathy
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Arrhythmogenic heart disease
Valvular heart disease
Hypertension
Inflammatory (lymphocytic, eosinophilic, giant cell myocarditis)
Amyloidosis
Sarcoidosis
Infectious (Chagas disease, Lyme disease, HIV, enterovirus, adenovirus, CMV, bacterial or fungal inf
Toxins (alcohol, catecholamines, cocaine, anthracyclines, chloroquine, and other chemotherapeutics,
Endocrine (thyroid diseases, adrenal insufficiency, pheochromocytoma, acromegaly, diabetes mellitu
Stress-induced cardiomyopathy
Peripartum cardiomyopathy
LV noncompaction
Mitochondrial cardiomyopathy
Fibroelastosis
Familial storage disease (hemochromatosis, glycogen storage disease, Hurler syndrome, Anderson–

TABLE 8.1 New York Heart Association Functional Classification
Electrolyte deficiency syndromes (hypokalemia, hypomagnesemia)
Nutritional deficiencies (L-carnitine, iron, thiamine, and selenium deficiency)
Familial Mediterranean fever
Systemic diseases
Connective tissue disorders (SLE, polyarteritis nodosa, rheumatoid arthritis, scleroderma, dermatomy
Muscular dystrophies (Duchenne, Becker, myotonic, limb girdle)
Neuromuscular (Friedreich ataxia, Noonan disease)

B. CMV, cytomegalovirus; HIV, human immunodeficiency virus; LV, left ventricular; SLE, systemic lupus erythematosus.

C. Dilated cardiomyopathy. Heterogenous cohort of patients with systolic dysfunction not related to underlying coronary artery disease. In 20% to 30% of HFrEF cases, the precise etiology is not established and a diagnosis of nonischemic, dilated, or idiopathic cardiomyopathy is made. Patients with **dilated cardiomyopathy typically have a better prognosis than their ischemic counterparts**.

1. **Subclinical viral myocarditis** can progress to dilated cardiomyopathy. Endomyocardial biopsy sensitivity remains poor but molecular techniques like reverse transcription polymerase chain reaction analysis demonstrates amplification of viral genomes in approximately two-thirds of cases and should be considered when benefits outweigh the risks (see Chapter 11). Any virus can cause myocarditis, but, owing to its ubiquity, coxsackie B virus is the most epidemiologically important.
2. **Familial dilated cardiomyopathy.** It is now recognized that 25% to 50% of cases of dilated cardiomyopathy may have a genetic etiology. Conditions are typically autosomal dominant and show variable penetrance. A detailed **three-generation** family history is essential at the time of initial evaluation. If the family history suggests a genetic predisposition, clinical screening of family members is appropriate and genetic testing can be performed following referral to a genetic counselor. Importantly, only 40% of presumed familial dilated cardiomyopathies have identifiable genetic alterations.
3. **Hypertensive and diabetic cardiomyopathy** are seldom considered as stand-alone diagnoses. Progression from LV hypertrophy to overt dysfunction in hypertensive patients (the so-called burnt-out hypertensive heart) most likely results from progressive microvascular ischemia. Hypertension and diabetes mellitus also contribute significantly to the development of coronary artery disease and ischemic cardiomyopathy.
4. **Cardiotoxic agents.** The list of toxins that can produce cardiomyopathy is extensive. Identification of the toxin and removal of the offending agent may halt the progression of or even reverse LV dysfunction.

a. **Chemotherapeutic agents. Anthracycline** (doxorubicin, epirubicin, mitoxantrone) toxicity can cause myocyte destruction and cardiomyopathy. Patients who receive a cumulative doxorubicin equivalent dose of <400 mg/m^2 are at low risk for this syndrome, whereas those receiving a cumulative dose >700 mg/m^2 have an approximately 20% lifetime risk of developing

cardiomyopathy. However, **cardiotoxicity can occur at any dose**. Doxorubicin is the most cardiotoxic. In an attempt to minimize doxorubicin cardiotoxicity, the agent should be administered via a continuous infusion, not bolus, as a means to lower the peak plasma level and via a liposomal formulation to minimize cardiotoxicity. Alongside standard cardioprotective HF medications, **dexrazoxane** has been approved for patients receiving doxorubicin therapy to minimize cardiotoxicity. Other cardiotoxic drugs that require careful cardiac monitoring include **cyclophosphamide** and **trastuzumab**. Trastuzumab (Herceptin) is now frequently used in the treatment of human epidermal growth factor receptor 2–positive breast cancer and has been associated with cardiotoxicity in 8% to 30% cases, which is reversible following drug cessation in approximately 60% cases and can be rechallenged with close monitoring. Antiangiogenic drugs such as **sunitinib** can also cause cardiotoxicity and uncontrolled hypertension. **5-Fluorouracil** has been associated with both cardiomyopathy and severe coronary vasospasm.

b. **Alcohol** consumption (>5 drinks per day) is thought to represent a common cause of toxin-mediated cardiomyopathy. However, there is limited observational data on the actual incidence of the cardiomyopathy or the volume of alcohol consumption necessary to induce it. Total abstinence from alcohol may result in complete resolution, whereas continued use is associated with a 3- to 6-year mortality exceeding 50%.

c. **Stimulant drugs** including cocaine and methamphetamines may result in the development of HF via multiple derangements including progressive concentric hypertrophy and recurrent myocardial infarction.

d. **Toxin exposures** including lead, arsenic, and cobalt can result in progressive myocardial dysfunction. **Iron overload** from primary or secondary **hemochromatosis** may present with restrictive cardiomyopathy; it typically progresses to a mixed or dilated form. Treatment with chelating agents or phlebotomy may improve cardiac function in both primary and secondary forms.

5. **Inflammatory cardiomyopathy** (i.e., myocarditis) is discussed in detail in Chapter 11.

6. **Tachyarrhythmia-induced cardiomyopathy** can complicate the course of atrial fibrillation, atrial flutter, ectopic atrial tachycardia, and even occult sustained ventricular tachycardia and frequent premature ventricular contractions (>10% to 20% of beats). In general, it is thought that persistent tachycardia in excess of 110 beats/min is required to induce LV dysfunction. This is a critical diagnosis to make, because treatment of the underlying tachyarrhythmia generally results in complete resolution of the cardiomyopathy.

7. **Peripartum cardiomyopathy** is defined as a dilated cardiomyopathy occurring between the last month of pregnancy and up to 5 months postpartum. Approximately 50% of peripartum cardiomyopathy patients improve with standard HF pharmacotherapy but the morbidity and mortality continues to be high for those patients who do not demonstrate myocardial recovery. Risk factors include age >30, multiparity, African American, and hypertension or history of preeclampsia.

8. **Valvular disorders** are common causes of HF secondary to volume or pressure overload or both. Aortic and mitral valve pathology can lead to progressive LV dysfunction (see Chapters 15 and 16). When appropriate, surgical correction is the preferred management of severe valvular lesions, or high-risk candidates could consider a percutaneous approach, for example, transcatheter aortic valve replacement, balloon valvuloplasty, or MitraClip.

9. **Miscellaneous disorders: Thyroid disorders: Hypothyroidism** is common in patients with HF. Severe hypothyroidism (i.e., myxedema) may cause decreased cardiac output and HF.

Bradycardia and pericardial effusion can develop in extreme cases of hypothyroidism. **Hyperthyroidism** can also lead to AHFS, which can be especially problematic in elderly patients with low ventricular reserve. Atrial fibrillation is a common accompanying arrhythmia, occurring in 9% to 22% of patients with thyrotoxicosis. Nonspecific symptoms such as fatigue, weight loss, and insomnia may predominate. Previously stable angina may also become unstable. Patients treated with amiodarone may develop a wide range of thyroid disorders ranging from abnormal thyroid function tests to overt amiodarone-induced thyrotoxicosis or hypothyroidism. Both conditions can occur in otherwise normal thyroid glands.

Thiamine deficiency (beriberi): Although rare in industrialized countries, thiamine deficiency is still prevalent in the developing world. It can also occur in alcoholics or individuals observing fad diets. *Wet beriberi* includes features of **high-output cardiac failure such as marked edema, peripheral vasodilatation, and pulmonary congestion**. The signs and symptoms of *dry beriberi* include **glossitis, hyperkeratosis, and peripheral neuropathy**. The laboratory diagnosis is made by assessing erythrocyte transketolase and 24-hour urine thiamine levels. Severe cases can present with lactic acidosis. Intravenous (IV) therapy with 100 mg of thiamine followed by daily oral supplementation can result in dramatic clinical improvement. Chronic use of high-dose diuretics may be complicated by subclinical thiamine deficiency of unknown significance.

Other nutritional deficiencies: Carnitine and selenium deficiency may result in dilated cardiomyopathy complicating chronic parenteral nutrition.

10. **Anemia:** Acute anemia caused by rapid blood loss is associated with decreased cardiac output because of hypovolemic shock. In contrast, chronic anemia can be associated with symptoms of HF because of compensatory mechanisms. These include fluid retention, increased cardiac output, decreased systemic vascular resistance, and increased 2,3-diphosphoglycerate with a resultant rightward shift in the oxyhemoglobin dissociation curve. Chronic anemia (hemoglobin < 9 g/dL) may exacerbate or augment HF symptoms in patients with preexisting disease. Chronic anemia of severe proportion (hemoglobin < 7 g/dL) may result in high-output HF even in individuals with normal cardiac anatomy. Evaluation and management of the underlying cause and supportive care are advised. Thresholds for transfusion depend on the clinical context and rapidity of blood loss. Iron repletion should be considered in iron-deficient patients with IV iron. FAIR-HF and CONFIRM-HF demonstrated functional improvement with IV iron replacement. (See Section **VII** for current guideline recommendations regarding management of iron deficiency anemia in stage C HF.)
11. **Inherited myopathies** such as Becker or Duchenne muscular dystrophy and myotonic dystrophy represent a group of dystrophinopathies that can be associated with a dilated cardiomyopathy. Friedreich ataxia is most commonly associated with hypertrophic cardiomyopathy, but in rare instances can present with a dilated phenotype. Fabry disease can appear as a hypertrophic cardiomyopathy. It is an X-linked, lysosomal storage disease and will have systemic manifestations including acroparesthesias, renal dysfunction, and angiokeratomas. Mitochondrial cardiomyopathies may also present with dilated cardiomyopathy. Danon disease is an X-linked, glycogen storage disorder associated with a lysosomal associated membrane protein-2 mutation. Dilated cardiomyopathies without conduction disease may be associated with a titin (TTN) mutation. Dilated cardiomyopathies with conduction disease may be associated with Lamin A/C mutations.

12. **Cardiac sarcoidosis** can present with LV dysfunction with regional hypokinesis or aneurysmal dilatation. It is frequently associated with conduction abnormalities and ventricular tachyarrhythmias. The diagnosis can be supported with stereotypical findings on cardiac magnetic resonance (CMR) imaging or positron emission tomography (PET). The diagnosis is rare in the absence of extracardiac manifestations.
13. **Amyloidosis** can impact cardiac function secondary to deposition of insoluble proteins within the myocardial matrix. In early stages, it may be present as HFpEF but in late stages it may present as HFrEF and can have both a dilated and nondilated appearance. Cardiac amyloidosis is primarily due to either transthyretin (TTR)—senile/wild type versus mutant—or primary amyloidosis, which is secondary to a light chain dyscrasia: κ or λ (see Chapter 9).
14. **Chagas disease** caused by the flagellate protozoan *Trypanosoma cruzi* remains a common cause of HF in patients from Latin America. In the chronic symptomatic phase, patients typically present with a syndrome of ventricular dysfunction with regional wall motion abnormalities in the absence of obstructive coronary artery disease. This pattern should prompt *T. cruzi* titers in patients from endemic regions.

V. SIGNS AND SYMPTOMS

A. **There is a wide spectrum of signs and symptoms in** HF **patients.** Subjective changes in signs and symptoms are often difficult to elicit and frequently leave insufficient time lag for therapeutic interventions prior to hospitalization.

1. The most common and earliest presenting symptom is **dyspnea**, typically with exertion. **Orthopnea** is typical with more advanced disease. It is among the most sensitive (90%) and specific (90%) signs of decompensated HF. With further decompensation, paroxysmal nocturnal dyspnea and Cheyne–Stokes respiration may occur.
2. **Fatigue** and **exercise intolerance** are common complaints in patients with HF and may reflect diminished cardiac output. Seldom considered but highly prevalent symptoms include anorexia, **nocturnal cough, insomnia, and depressed mood**.
3. **Syncope** may occur in patients with underlying arrhythmia, severe cardiac dysfunction, or pulmonary arterial hypertension and requires prompt evaluation.
4. **Anorexia**, **abdominal pain**, and **bloating** are common in advanced right HF.

B. **Physical examination** of patients with significant but well-compensated systolic HF may reveal no abnormalities. Physical signs vary according to the degree of compensation, chronicity, and chamber involvement.

1. **Volume overload** is the hallmark of HF. Typical signs of volume overload include the following:

a. **Weight gain** is a sensitive indicator of congestion.
b. **Pulmonary rales** because of accumulation of fluid in the pulmonary interstitium and alveoli secondary to high left atrial pressure are commonly referred to as **acute cardiogenic pulmonary edema**. Importantly, rales may be absent in patients with chronic systolic HF who develop compensatory perivascular and lymphatic changes.
c. **Jugular venous distention or elevated JVP** although not directly reflecting left-sided filling pressures can track these with a reasonable sensitivity (70%) and specificity (79%). JVP should be assessed at a 45° incline with the neck fully exposed. In cases of extreme JVP elevation, the patient may need to be seated upright in order to properly visualize. Five centimeters of water should be added to the vertical distance from the sternal angle to the meniscus of the JVP to account for the distance to the midpoint of the right atrium. Compression of the right upper quadrant and a

resultant positive **hepatojugular reflex** (defined as a sustained increase in JVP of ≥4 cm) increase the sensitivity of the JVP for detecting congestion.

d. **Pedal edema** by some estimates is only present in 30% of patients with decompensated HF and is somewhat nonspecific, because it may reflect venous insufficiency, nephrotic syndrome, hepatic dysfunction, or concomitant treatment with specific medications such as calcium channel blockers or thiazolidinediones.

2. **Ascites and hepatomegaly** may occur. Severe tricuspid regurgitation may be present in the setting of a palpable, pulsatile liver.
3. A holosystolic murmur of mitral regurgitation (MR) is often present in the setting of LV dilatation.
4. **A third heart sound** (S_3 gallop) is best heard with the bell of the stethoscope in the left lateral position and signifies increased LV end-diastolic pressure. Often neglected are the subtle signs of **peripheral hypoperfusion**.
5. **Pulsus alternans** or a low-amplitude pulse in the absence of alternative explanations reflects severely impaired cardiac output.
6. Tachycardia and narrow pulse pressure also suggest diminished cardiac output.
7. Lethargy, pallor, mottled skin, cool extremities, and poor capillary refill are typical signs.
8. **Hypotension** itself may be one of the most important clinical findings in HF. Several studies have demonstrated that a systolic blood pressure <90 mm Hg is a strong predictor of morbidity and mortality.

VI. DIAGNOSTIC EVALUATION

A. **Laboratory work** is used to diagnose potentially reversible causes, identify comorbidities, monitor and correct abnormalities before or during treatment, and assess the disease severity.

1. A **comprehensive metabolic panel** should be assessed on initial evaluation and then subsequently based on clinical judgment. Particular attention should be paid to the presence of hyponatremia, which portends a worse prognosis. **Hypokalemia** is common in the setting of ongoing diuretic therapy. **Hyperkalemia** can be seen in the context of overaggressive potassium repletion and ongoing treatment with renin–angiotensin–aldosterone antagonists, or K-sparing diuretics, or in diabetic patients with associated type IV renal tubular acidosis. Aside from the pragmatic considerations, many real-world registries have identified elevated blood urea nitrogen (BUN) and creatinine as powerful predictors of outcome. Renal function must also be taken into account when considering therapy. In the context of chronic, congestive right HF, liver function testing abnormalities are most consistent with cholestasis.
2. **Anemia** is present in up to 40% of HF patients and is associated with increased mortality and functional impairment. Although frequently because of anemia of chronic disease, a thorough diagnostic evaluation should be performed. Iron deficiency (in the absence of anemia) is also common.
3. The natriuretic peptides **B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP)** are released in the setting of increased ventricular dilation or wall stress. Normal ranges (BNP < 100 pg/mL; NT-proBNP < 125 pg/mL if age < 75 years and <450 pg/mL if age ≥75 years) must be interpreted in the context of associated conditions known to alter levels. ***Increasing age, anemia,* and *worsening renal function* are associated with increased levels.**

a. **Screening for heart failure.** Although cardiac dysfunction has been associated with elevated natriuretic peptide levels, the sensitivity is relatively low in asymptomatic patients and is highly

dependent on the cut-off levels chosen. In general, routine assessment of BNP is not recommended as a screening test for structural heart disease in asymptomatic patients.

b. **Diagnosing heart failure.** The primary use of natriuretic peptides remains the diagnosis of HF in symptomatic patients particularly when the diagnosis is unclear. The high negative predictive value (up to 90%) in this setting allows BNP testing to be useful to rule out a cardiac cause of symptoms. With the growing obesity epidemic, it is important to remember that ***normal natriuretic peptide levels may be present in morbidly obese patients with decompensated HF***. Other noncardiac causes of elevated natriuretic peptides include sepsis, pulmonary disease, pulmonary hypertension, and critical illness.

c. **Management of heart failure.** Although controversial, there is emerging evidence that serial measurements of natriuretic peptides may be beneficial in guiding outpatient HF management and may result in decreased HF–related mortality versus usual care. Post-HF hospitalization assessment or predischarge natriuretic assessment can aid in additional prognostic information. Of note, BNP is a substrate for neprilysin; therefore, if a patient is on an angiotensin receptor blocker neprilysin inhibitor (ARNI), it cannot be used to follow a patient's clinical course. However, NT-proBNP levels will not be impacted.

d. **Determining prognosis of heart failure.** Natriuretic peptide levels correlate with morbidity and mortality in patients with both established HF and other cardiovascular diagnoses (e.g., stable coronary artery disease, acute coronary syndromes, pulmonary hypertension, and atrial fibrillation).

4. **Other biomarkers.** Troponin T or I may be elevated in chronic HF and demonstrate ongoing myocyte injury. Alongside natriuretic peptides and troponins, a growing list of biomarkers assessing systemic inflammation, oxidative stress, extracellular matrix remodeling, myocardial fibrosis, and myocyte injury is commercially available or in development (e.g., soluble ST2, cystatin C, galectin-3). Whereas some of these provide useful prognostic information, it remains unclear on how to best integrate into the diagnosis and management of HF.

5. **Thyroid function testing** is warranted for all patients with a new diagnosis of HF.

6. Iron studies including ferritin, serum iron, and total iron binding capacity (with calculation of percent transferrin saturation) should be performed to screen for hemochromatosis and occult iron deficiency.

7. Standard laboratory screening for **modifiable cardiovascular risk factors** including fasting lipid panel and serum glucose should also be obtained. When clinical suspicion is heightened, consider additional screening for human immunodeficiency virus, rheumatologic processes, and amyloidosis.

B. **The electrocardiogram (ECG)** provides important information pertaining to the cause and management of HF and is a recommended component of the evaluation of any patient with a clinical diagnosis of HF and change in clinical status.

1. It is important to look for evidence of prior myocardial infarction, chamber enlargement and hypertrophy, conduction disease, and supraventricular or ventricular arrhythmias.

2. Specific diagnoses can be suggested in the ECG. Cardiac amyloidosis may classically present with low voltage and a pseudoinfarction pattern in the anterior leads in stark contrast to thickened walls observed on echo. Arrhythmogenic right ventricular (RV) dysplasia may present with epsilon waves or localized prolongation (>110 ms) of the QRS complex in the right precordial leads.

3. The ECG is an important means of assessing **dyssynchrony**. Marked first-degree atrioventricular (AV) block or very short AV delays in the presence of paced rhythms may contribute to AV dyssynchrony. The presence of QRS prolongation >120 ms (particularly left bundle branch block) suggests interventricular dyssynchrony and remains the most important predictor of response to cardiac resynchronization therapy (CRT-D).
4. **Holter or event monitors** are often useful in identifying occult arrhythmia, arrhythmia burden, and conduction abnormalities.

C. Examination of the **chest radiograph** should include an assessment of the heart size, pleura, and the condition of the pulmonary parenchyma. Determination of cardiac size is best restricted to standard posteroanterior projection, because "portable" anteroposterior projection will magnify the cardiac silhouette. The lateral projection is useful to assess for RV enlargement with associated filling of the retrosternal space and pleural effusion(s). A normal cardiac silhouette does not exclude systolic or diastolic dysfunction. The lung field abnormalities may range from mild engorgement of the perihilar vessels to bilateral pleural effusions, Kerley B lines, and frank pulmonary edema.

D. **Echocardiography** is perhaps the most useful diagnostic test in the evaluation of patients with HF. It can provide useful information pertaining to the etiology and prognosis of HF. As described in later sections, echocardiography also plays a key role in guiding HF therapy.

1. **Etiology of heart failure.** Regional wall motion abnormalities occurring in an anatomic coronary artery distribution are suggestive of ischemic cardiomyopathy. However, regional wall motion abnormalities can also be seen in the context of nonischemic dilated cardiomyopathy, stress-induced cardiomyopathy, and infiltrative cardiomyopathies (with inferobasal wall motion abnormalities classically seen in the setting of cardiac sarcoidosis). The presence and severity of valvular stenosis or insufficiency can be assessed as can the relative dysfunction of the right and left ventricles.
2. **Prognosis in heart failure.** The following parameters are useful in assessing the risk of HF-associated morbidity and mortality.

a. **EF and LV dimensions** may not correlate with HF symptoms. However exercise capacity, oxygen consumption, and EF provide valuable prognostic information. Morbidity and mortality are linked to EF and LV volumes. The American Society of Echocardiography recommends EF and LV volumes assessment by Simpson's biplane method.

b. **LV mass.** Cardiac remodeling results in increased LV mass because of eccentric hypertrophy, which worsens prognosis. Eccentric hypertrophy is defined echocardiographically as an LV mass >95 g/m^2 in women and >115 g/m^2 in men with a regional wall thickness (2 × posterior wall thickness/LV end-diastolic dimension) of ≤0.42.

c. **The myocardial performance index (Tei index)** provides a useful assessment of systolic and diastolic function and is equal to the (isovolumic contraction time + the isovolumic relaxation time)/the ejection time. All dimensions are obtained via pulse wave or tissue Doppler. A Tei index of >0.77 in patients with dilated cardiomyopathy is highly predictive of cardiovascular morbidity and mortality.

d. **Measures of diastolic dysfunction.** Many of the measures of diastolic dysfunction detailed in Chapter 9 have powerful prognostic ability in patients with systolic HF. The presence of a restrictive filling pattern ($E/A > 2$, deceleration time < 115 to 150 ms) persisting despite Valsalva maneuver is a particularly ominous finding.

E. Other imaging modalities

1. **Cardiac magnetic resonance imaging** (Chapter 51). CMR offers unparalleled myocardial tissue characterization and allows for myocardial viability assessment. It is an increasingly useful tool in the diagnosis of specific cardiomyopathies (e.g., LV noncompaction, cardiac sarcoidosis, and amyloidosis). The distribution of late gadolinium hyperenhancement representing scar can effectively discriminate between ischemic and nonischemic causes of fibrosis. Cine magnetic resonance imaging provides accurate assessments of chamber volumes and LV and RV systolic function that can be performed in arbitrary tomographic views. Major limitations are incompatibility with implanted electronic cardiovascular devices and the potential for nephrogenic sclerosing fibrosis in patients with preexisting renal insufficiency.
2. **Nuclear imaging.** Single-photon emission computed tomography (SPECT) and PET imaging are primarily of use in ruling out myocardial ischemia and/or viability as well as metabolic activity. **Viability assessment** (i.e., discriminating between scarred and hibernating myocardium) is critical in the assessment of patients with HF and coronary artery disease and the potential for myocardial recovery with revascularization. This can be achieved with PET using concomitant flow and metabolism tracers (typically [^{18}F]fluorodeoxyglucose) or thallium-201 versus technetium-99m SPECT redistribution imaging (see Chapter 50). There is growing evidence that PET is superior to SPECT in patients with systolic dysfunction, and when available it should be used preferentially in patients with a left ventricular ejection fraction (LVEF) <35%. Dobutamine stress echocardiography and CMR are alternative means of assessing viability. Radionuclide ventriculography using multiple-gated acquisition scanning has long served as the gold standard for precise serial measurements of the LVEF (classically in the evaluation of patients receiving cardiotoxic chemotherapeutics). Increasingly, however, it is being surpassed by CMR and three-dimensional echocardiography. A **technetium pyrophosphate scan** is an additional nuclear modality that can be used to assess for TTR (wild type or mutant) amyloidosis with 100% specificity and 97% sensitivity.

F. Right heart catheterization (see Chapter 60). Invasive hemodynamic monitoring is often helpful in the diagnosis and inpatient management of HF. Right heart catheterization can be combined with exercise testing or addition of inotropic or vasodilatory agents to evaluate impact on hemodynamics. Indications for right heart catheterization include short-term management of acute cardiogenic shock, evaluation of patients for cardiac transplantation or mechanical circulatory support, clarification of hemodynamics in the context-specific comorbidities (e.g., suspected RV infarction or mechanical complications of myocardial infarction), and clarification and optimization of medical therapy in patients with recurrent or refractory symptoms.

1. **Cardiac output/index** can be determined by thermodilution or the Fick method using estimated or measured oxygen consumption and a directly measured mixed venous oxygen saturation (MVO_2).
2. **Pulmonary capillary wedge pressure (PCWP)** should be measured in all cases. An inability to normalize the PCWP (<16 mm Hg) with pharmacotherapy was shown in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial to confer a twofold increased risk of mortality.
3. **Right atrial (RA) pressure** is an important indicator of volume status and right heart function. An elevated central venous pressure has been shown to be the most important predictor of

worsening renal function during hospitalizations for acute decompensated HF. RA pressure to PCWP ratio >0.63 or a right ventricular stroke work index <400 portends RV dysfunction.

G. Coronary angiography (see Chapter 64). There are many approaches to determining which patients with systolic HF warrant evaluation by coronary angiography. The Heart Failure Society of America, American College of Cardiology Foundation, and AHA recommend performing coronary angiography in patients with a high pretest probability of underlying ischemic cardiomyopathy and who are candidates for percutaneous or surgical revascularization. At a minimum, patients meeting this description should undergo some form of noninvasive stress testing. Some centers advocate for a baseline coronary angiogram in all patients with newly established systolic HF regardless of risk factors or presentation.

H. Endomyocardial biopsy (see Chapter 61) is indicated only when a specific primary myocardial disease is suspected and other causes of decompensation have been ruled out. AHA/ACC/European Society of Cardiology 2007 writing group identified 14 clinical scenarios in which there is an incremental diagnostic, prognostic (e.g., amyloidosis), or therapeutic (e.g., giant cell myocarditis) value to biopsy that can be weighed against the procedural risk.

I. Cardiopulmonary exercise testing (metabolic stress testing), although not recommended as part of the routine evaluation of patients with HF, should be considered in the context of symptoms out of proportion to clinical exam as an objective measure of disease severity, discriminating between cardiac and pulmonary etiologies of dyspnea, or assessing candidacy for advanced HF therapies: cardiac transplantation or mechanical circulatory support. The following parameters along with inappropriate blood pressure response to exercise are highly predictive of prognosis in patients with established HF.

1. **Peak oxygen consumption (Vo2)** is perhaps the most important parameter in objectively describing functional capacity and prognostication. Normal values based on age and sex are indexed to body weight, with a normal value being >84% predicted. Patients being considered for heart transplantation undergo risk stratification with a metabolic stress test. Patients with a peak V_{O_2} <14 mL/kg/min or <50% predicted are at increased risk for adverse cardiovascular events and, if the limitation is deemed to be cardiac, should be considered for transplantation. Interpretation of the peak V_{O_2} is highly dependent on the adequacy of effort as assessed by the respiratory exchange ratio (RER). The RER is the ratio of V_{CO_2}/V_{O_2} and is, at steady state, an estimate of the respiratory quotient. It signifies the **conversion to anaerobic metabolism** and the sudden rise in CO_2 production occurring with the onset of metabolic acidosis. Failure to achieve an RER >1.05 suggests insufficient effort or premature termination of the study. Up to 50% of HF patients are incapable of achieving an adequate RER, with a modified Bruce treadmill protocol necessitating the use of alternative protocols.
2. **Ventilatory anaerobic threshold** is another means of assessing the adequacy of effort and represents the point at which minute ventilation (VE) increases out of proportion with V_{O_2} (typically occurring at 60% to 70% of peak V_{O_2}).
3. **VE/Vco2 slope** is a dimensionless ratio indicating the relationship between minute ventilation and CO_2 production. The slope is elevated in most patients with HF and is inversely related to cardiac output at peak exercise. A **slope >35** identifies higher risk individuals independently of peak V_{O_2}.

J. Sleep study. Central and obstructive sleep apnea is common in patients with chronic HF. A formal sleep study should be considered in all patients with NYHA II–IV HF. **Continuous**

positive airway pressure (CPAP) in patients with obstructive sleep apnea improves oxygenation and sleep quality and reduces the apnea–hypopnea index. **Adaptive servo-ventilation** therapy has *demonstrated harm* in individuals with HFrEF and is no longer indicated for the treatment of central sleep apnea.

VII. TREATMENT. The effective management of HF relies on appreciating the distinction between acute and chronic therapies.

A. Acute heart failure syndromes. In the United States, AHFS continue to constitute the most common indication for hospital admission in adults over age 65 years. These hospitalizations represent an inflection point in the course and prognosis of the chronic disease, with 90-day and 1-year postdischarge mortality as high as 14% and 37%, respectively. Only 20% of AHFS represent patients with de novo HF. The majority are patients with worsening chronic HF. The initial management goals include symptom improvement, decongestion, and hemodynamic stabilization with optimization of tissue perfusion. It is important to identify and correct any precipitating factors (Table 8.3).

1. Invasive hemodynamic monitoring

a. Pulmonary artery catheter. The **ESCAPE** trial demonstrated that routine use of pulmonary artery catheters did not result in a reduction in subsequent hospitalizations or mortality in patients with AHFS but did result in increased, anticipated adverse events. Invasive hemodynamic guided management should be restricted to scenarios outlined above or where there is need for clarification of cardiac indices and/or filling pressures in critically ill patients. A PCWP of >18 mm Hg suggests cardiogenic pulmonary edema and a cardiac index of <2.0 L/min/m^2 is consistent with cardiogenic shock.

b. Arterial catheter. Continuous blood pressure monitoring with an arterial catheter can be useful in cases with marginal blood pressure and optimizes titration of IV vasodilators.

2. Maximizing oxygenation is vital. All patients with acute cardiogenic pulmonary edema should be positioned upright and receive supplemental oxygen. **Noninvasive positive pressure ventilation (NIPPV)** should be considered in those with ongoing increased work of breathing, respiratory acidosis, or persistent hypoxemia. The Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema trial demonstrated that NIPPV results in more rapid resolution of symptoms and metabolic derangements than CPAP ventilation or standard oxygen therapy. Although there was no evidence of a reduction in short-term mortality, this can be an invaluable tool often forestalling intubation. Patients who fail to respond to NIPPV should be promptly intubated. The use of positive end-expiratory pressure (PEEP) can be effective in improving oxygenation and decreasing cardiac afterload, but high levels of PEEP come at the cost of reduced systemic venous return and subsequently cardiac output particularly in individuals with RV dysfunction.

TABLE 8.3 Common Precipitants of Acute Decompensated Heart Failure

Medication nonadherence
Acute myocardial ischemia, infarction and associated complications: ventricular septal rupture, papillary and cardiogenic shock
Arrhythmias (tachyarrhythmias, bradycardia)
Pulmonary embolus

TABLE 8.3 Common Precipitants of Acute Decompensated Heart Failure

Infections (e.g., pneumonia, urinary tract infection, bacteremia, viremia, endocarditis)
Alcohol consumption or illicit drug use
Uncontrolled hypertension
Acute cardiovascular compromise: myocarditis, aortic dissection, valvular pathology
Drugs that can acutely worsen HF symptoms (e.g., calcium channel blockers, nonsteroidal anti-inflar steroids)
β-Blocker initiation in decompensated state

3.HF, heart failure.

4. **Vasodilators.** In the absence of symptomatic hypotension, IV vasodilators are the first-line therapy for the management of cardiogenic pulmonary edema.

a. **Nitroglycerin** reduces LV filling pressures via venodilation and to a lesser extent via systemic afterload reduction. It may be given rapidly in the emergency setting (0.4 to 0.8 mg, given sublingually every 3 to 5 minutes) and by means of IV infusion in the subacute setting (starting dosage of 0.2 to 0.4 µg/kg/min), with titration every 5 minutes on the basis of symptoms or mean arterial pressure (MAP). Although there is no maximal dose, increasing beyond 300 to 400 µg/min likely yields no additional benefit and should prompt the addition of another vasodilator. Tachyphylaxis can occur with high-dose infusions. Headache is the most common side effect and its use is contraindicated in the setting of recent use of phosphodiesterase-5 (PDE-5) inhibitors.

b. **Sodium nitroprusside (nipride)** is a potent vasodilator with balanced venous and arteriolar effects. It requires careful hemodynamic monitoring. A starting dosage of 0.1 to 0.2 µg/kg/min is used and titrated every 5 minutes to achieve a clinical response while maintaining a MAP >65 mm Hg. Nipride is particularly useful in instances where a rapid and large reduction in afterload is desired (e.g., cardiogenic shock, acute aortic regurgitation, or acute MR). Whereas cyanide and thiocyanate toxicity are rare with short durations of therapy, nipride should be used with caution in patients with severe renal dysfunction, and long-term, high-dose infusions should be avoided. In patients with myocardial ischemia, nitroglycerin or a combination of nitroglycerin and nipride is preferred to avoid the theoretical risk of coronary steal syndrome.

c. **Nesiritide** is an IV vasodilator that gained popularity in the acute care setting because of its ease of use in the absence of invasive hemodynamic monitoring. Typical dosing starts with 2 mg/kg delivered by IV bolus followed by an infusion at a rate of 0.01 mg/kg/min for up to 48 hours. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial demonstrated no effect on death or rehospitalization for HF at 30 days in patients treated with Nesiritide when compared to conventional therapy. Although providing some reassurance regarding previous safety concerns, these results have led most experts to discourage its use based on lack of efficacy.

5. **Diuretics.** In addition to their ability to gradually reduce intravascular volume, diuretics have an immediate vasodilatory effect, which may be responsible for their prompt symptom relief. Reductions in filling pressures may be associated with augmented forward flow because of optimization of LV and RV mechanics. Because many patients with acute cardiogenic pulmonary edema do not have total body salt and water excess, the judicious use of diuretics is

recommended. Often, filling pressures normalize with the use of vasodilators alone. Patients without chronic exposure to loop diuretics usually respond to 20 to 40 mg of IV furosemide. Patients undergoing long-term furosemide therapy typically need an IV bolus dose at least equivalent to their oral dose (Diuretic Optimization Strategies Evaluation [**DOSE**] trial). Rather than an arbitrary therapeutic goal of net fluid balance or an estimated dry weight, frequent clinical assessments of volume status should guide therapy and define the point at which conversion to an oral maintenance regimen should occur. Nevertheless, up to 30% of patients with AHFS continue to have symptoms of congestion at the time of discharge. Important adverse effects include hypotension, hypokalemia, hypomagnesemia, and hypocalcemia. There is also extensive evidence suggesting that IV diuretics may result in at least transient neurohormonal activation, which is theoretically disadvantageous. Electrolyte repletion is best achieved with scheduled doses of potassium and magnesium supplements to prevent severe deficits. DOSE demonstrated no benefit of continuous or bolus dose IV diuretic administration and no detriment from high doses (an IV dose 2.5 times the patients' chronic oral dose of furosemide). If a continuous diuretic infusion is opted for, it should be preceded by a bolus dose to achieve therapeutic threshold, as should any subsequent continuous dose titration. Escalating diuretic dose requirement should raise suspicion of resistance and can be addressed with the addition of sequential nephron blockade with a thiazide diuretic (hydrochlorothiazide, metolazone, or chlorothiazide) for synergistic effect. Some degree of worsening renal function must often be tolerated in order to achieve adequate decongestion. However, if progressive renal failure occurs despite persistent congestion, ultrafiltration (UF) or additional pharmacologic intervention(s) may be warranted.

6. **Inotropic therapy.** When signs and symptoms of decompensated HF persist despite administration of vasodilators and diuretics, IV inotropes may be considered. Their use should be restricted to patients with clear clinical or direct hemodynamic evidence of refractory elevated filling pressures and reduced cardiac indices. For patients without significant hypotension, dobutamine or milrinone can be used to augment cardiac output. Both drugs are associated with increased myocardial oxygen demand and cardiac arrhythmias and should be used with extreme caution in patients with ischemia and preexisting arrhythmias. Both drugs may cause hypotension, although this is more common with loading doses of milrinone. ***There is no evidence to support benefit with the use of chronic or intermittent infusion of inotropic agents, and in fact, there is extensive observational data suggesting a trend toward increased postdischarge mortality***. Use is typically confined to the acute care setting as a bridge to decision making, transplant, or mechanical circulatory support or as definitive palliative therapy in patients who are not candidates for advanced therapies. In cases of severe hypotension (especially as a result of administration of vasodilators or β-blockers), temporary use of vasopressors such as dopamine or norepinephrine may be necessary. In contrast to the conventional wisdom, recent prospective data suggest that norepinephrine is not inferior to dopamine in the setting of cardiogenic shock.

a. **Dobutamine** acts on β-1 and to a lesser extent on β-2 and α-1 adrenergic receptors. It has a short half-life (~2 minutes). Infusions are usually started at 2.5 to 5.0 μg/kg/min. On the basis of hemodynamic response, it may be titrated by 1 to 2 μg/kg/min every 30 minutes until the desired effect or a dosage of 10 μg/kg/min is reached.

b. **Milrinone** is a PDE-III inhibitor that acts as a potent inodilator with a longer half-life (~ 2 to 3 hours and is renally cleared). For patients who need an immediate inotropic response, a loading

dose of 50 µg/kg over 10 minutes is followed by an infusion of 0.125 to 0.75 µg/kg/min. Because it does not target β-receptors, milrinone may be more effective than dobutamine in the setting of recent or chronic β-blocker use.

7. **Ultrafiltration** has been used as an alternative to pharmacologic diuresis in acute decompensated HF. The UF versus intravenous diuretics for patients hospitalized for acute decompensated congestive heart failure study demonstrated that UF was safe and resulted in a reduced need for IV diuretics and inotropes. However, **CARRESS-HF** demonstrated a stepped pharmacologic approach to AHFS with worsening renal function was superior to UF. Currently the use of UF is reserved for patients that are refractory to IV diuretic therapy.
8. **Vasopressin antagonists.** The oral vasopressin receptor 2 antagonist tolvaptan was shown to be safe and results in short-term symptom improvement in patients hospitalized with acute decompensated HF. However, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan trial failed to demonstrate an improvement in morbidity or mortality in patients with AHFS. Tolvaptan and the nonselective IV vasopressin receptor inhibitor conivaptan are both approved for the management of hypervolemic or euvolemic hyponatremia that can accompany decompensated HF but neither has demonstrated benefit with regards to morbidity or mortality.
9. **Temporary mechanical circulatory support.** The use of temporary and permanent mechanical circulatory support is described in detail in Chapter 12. Patients with refractory cardiogenic shock and cardiogenic pulmonary edema may benefit from the temporary use of intra-aortic balloon counterpulsation or an alternative temporary means of mechanical circulatory support (i.e., venoarterial extracorporeal membrane oxygenation, Impella, or TandemHeart) may facilitate bridging to stabilization or further decision making.

Transition to chronic pharmacotherapy is implemented once clinical stability is achieved. Generally, vasodilators (ACE inhibitors [ACEis], angiotensin II receptor blockers [ARBs], ARNIs, or hydralazine and isosorbide dinitrate) are reintroduced first in concert with weaning off IV vasodilators. If β-blockers were held due to cardiogenic shock, they can be cautiously reintroduced in stable, euvolemic patients.

B. Chronic medical therapies. The cornerstone of chronic medical therapy is to prolong survival and improve quality of life.

1. **ACEis** have been shown to reduce morbidity and mortality among patients with systolic HF. The mechanism of long-term benefit is related to attenuation of the renin–angiotensin system (RAS). In addition, ACEi improve symptoms, clinical status, and exercise capacity.

a. **Use of an ACEi is first-line therapy for asymptomatic and symptomatic LV dysfunction.** The dose of the ACEi should be increased to the target doses demonstrating clinical benefits in trials (Table 8.4). Although there are theoretical benefits of using "tissue" inhibitors (e.g., quinapril and ramipril), there are no data to support their preferential use. Relative contraindications include hyperkalemia (potassium > 5.5 mEq/L), renal insufficiency (creatinine > 3.0 mg/dL), and hypotension (systolic blood pressure < 90 mm Hg) and should be gauged on a case-by-case basis. It is not advisable to stop ACEis in patients with systolic HF, even when there is complete resolution of symptoms.

TABLE 8.4 Drug Dosing for Common Medical Therapies for Chronic Heart Failure

Drug	Start (mg)	Target (m

TABLE 8.4 Drug Dosing for Common Medical Therapies for Chronic Heart Failure

ACE Inhibitors		
Captopril (Capoten)	6.25–12.5 tid	50 tid
Enalapril (Vasotec)	2.5–5 bid	10 bid
Lisinopril (Prinivil, Zestril)	2.5–5 qd	20 qd
Ramipril (Altace)	1.25–2.5 bid	5 bid
Quinapril (Accupril)	5 bid	20 bid
Fosinopril (Monopril)	2.5 or 5 bid	20 bid
Benazepril (Lotensin)[a]	2.5 or 5 bid	20 bid
Moexipril (Univasc)[a]	7.5 qd	30 qd
Trandolapril (Mavik)	1 qd	4 qd
Angiotensin Receptor Blockers		
Candesartan (Atacand)	16 qd	32 qd
Valsartan (Diovan)	80 qd	160 qd
Losartan (Cozaar)[a]	12.5–25 qd	50 qd
Irbesartan (Avapro)[a]	150 qd	300 qd
Telmisartan (Micardis)[a]	40 qd	80 qd
Hydralazine/Isosorbide Dinitrate		
Hydralazine	25 qid	50–75 qid
Isosorbide dinitrate	10–20 tid	20–80 tid
Hydralazine–isosorbide dinitrate (BiDil)	25/37.5 tid	50/75 tid
Aldosterone Antagonists		
Spironolactone (Aldactone)	12.5–25 qd	25 qd
Eplerenone (Inspra)	25 qd	50 qd
Loop Diuretics[c]		
Furosemide (Lasix)	10 qd (IV)	As require
	20 qd (PO)	As require
Bumetanide (Bumex)	1 qd	As require

TABLE 8.4 Drug Dosing for Common Medical Therapies for Chronic Heart Failure		
Torsemide (Demadex)	10 qd	As require
Ethacrynic acid (Edecrin)	50 qd	As require
Thiazide Diuretics		
Hydrochlorothiazide (HCTZ)	25 qd	As require
Metolazone (Zaroxolyn)	2.5 qd	As require
Chlorthalidone	12.5 qd	As require
Chlorothiazide (PO or IV)	250–500 (PO) qd/bid 500–1,000 (IV)	As require n/a
Potassium-Sparing Diuretics		
Triamterene (Maxzide)	50 qd	As require
Amiloride	5 qd	As require
β-Blockers		
Carvedilol (Coreg)	3.125 bid	25 bid
Carvedilol phosphate (Coreg CR)	10 qd	40 qd
Metoprolol succinate (Toprol XL)	25 qd	150–200
Bisoprolol (Zebeta)[a]	1.25 qd	8.6 qd
Nebivolol (Bystolic)[a,b]	1.25 qd	10 qd
Neprilysin Inhibitor + Angiotensin Receptor Blockers		
Sacubitril/Valsartan (Entresto)	24/26 bid	97/103 bi
I_f Current Inhibitor		
Ivabradine (Corlanor)	5 bid	As require

b. ACE, angiotensin-converting enzyme; IV, intravenous; PO, orally.

c. [a] Not yet approved by the Food and Drug Administration (FDA) for management of heart failure.

d. [b] Approved in Europe, not yet approved by the FDA for management of heart failure. SENIORS trial demonstrated all-cause mortality benefit in patients over 70 years of age.

e. [c] Oral to IV conversion for furosemide is approximately 2:1. Oral to IV conversion for all other loop diuretics is 1:1.

f. After initiation, close monitoring for **hyperkalemia** and **renal insufficiency** is warranted.

1. **(1) Hypotension** is common, especially with first dose in a volume-depleted patient (e.g., after aggressive diuresis). This may require downtitration of diuretic doses and other vasodilator therapy.

Because of its short half-life, captopril is usually used in the acute setting (e.g., after myocardial infarction).

2. **(2) Renal insufficiency** and **hyperkalemia** may occur when ACEis are given in the setting of volume depletion. **It is crucial to discontinue other nephrotoxic agents (e.g., nonsteroidal anti-inflammatory agents)** and ensure adequate kidney perfusion. **If BUN or creatinine levels increase by** <50%, ACEis can be continued safely; if they increase by **>50%, the ACEi dose should be halved; if they increase by >100%, the ACEi should be held and switched to hydralazine and isosorbide dinitrate**. In the case of hyperkalemia, discontinuation of potassium supplementation, K-sparing diuretic, and reducing the ACEi dose is usually effective.

g. Unique side effects of ACEis are cough and angioedema.

1. **(1)** The **cough** associated with ACEis is related to increased levels of bradykinin and seen in ~20% of patients. It tends to be nonproductive and involuntary, rarely resolving with altering the dose or specific agent. All attempts should be made to identify an alternative cause of cough before discontinuing ACEis.

2. **(2) Angioedema** is a rare complication of ACEis (0.4%). It involves soft tissue edema of the lips, face, tongue, and, occasionally, the oropharynx and epiglottis. Angioedema typically begins within 2 weeks of initiation of ACEi therapy, but some patients present with this complication months to years after starting therapy. **Angioedema is an absolute contraindication to the use of any type of ACEi**.

2. **ARBs** are specific receptor antagonists to the angiotensin II type 1 receptors. Although they theoretically provide more complete inhibition of the deleterious effects of angiotensin II than do ACEis, clinical trials have not demonstrated superiority in patients with HF. In general, ARBs are used and monitored in the same manner as ACEis. These drugs are reserved for patients who are ACEi intolerant, although in practice, they are used extensively. ARBs have a similar side-effect profile to ACEis (e.g., hypotension, renal insufficiency, and hyperkalemia). There appears to be a <10% incidence of cross-reactivity for ACEi-associated angioedema in patients receiving ARBs. However, consideration for the use of these agents must be weighed against the life-threatening nature of this complication. Whereas the addition of an ARB is reasonable in patients on target doses of ACEis and β-blockers with persistent symptoms, it is preferable to add an aldosterone antagonist first to get added morbidity and mortality benefit. ARBs should not be added to an ACEi in the postmyocardial infarction period. Valsartan and candesartan are the best studied ARBs in patients with HF and should be used preferentially.

3. The combination of **hydralazine** and **isosorbide dinitrate** may provide a reduction in morbidity and mortality in selected HF patients. A fixed dose combination of hydralazine and isosorbide dinitrate (BiDil) demonstrated a substantial reduction in mortality when added to African-American patients on optimal medical therapy including ACEis and β-blockers in the African-American Heart Failure Trial. This combination is also indicated in patients intolerant of ACEis or ARBs or ARNI or in patients receiving maximal RAS inhibition therapy in need of additional vasodilator therapy. Side effects of hydralazine may include reflex tachycardia and rarely drug-induced lupus erythematosus.

4. **β-blockers. First-line therapy for chronic symptomatic patients with HF (NYHA class I, II, III, or stable class IV)** because of their consistent mortality and morbidity benefits.

a. It is often customary to start ACEis before β-blockers. This in part reflects the fact that all major β-blocker trials demonstrated their benefit on a background of therapy with ACE inhibition. Furthermore, whereas ACEis provide immediate beneficial hemodynamic effects, β-blockers may

acutely result in diminished LVEF and cardiac output, which may be poorly tolerated in decompensated patients. In some instances (e.g., postmyocardial infarction and comorbid tachyarrhythmias), β-blockers may be particularly beneficial and should be started before or concurrently with ACEis. β-Blockers should typically not be initiated or titrated in the setting of acutely decompensated HF.

b. Current ACC/AHA guidelines recommend bisoprolol, carvedilol, and metoprolol succinate for the medical treatment of chronic HF. Although atenolol and metoprolol tartrate are widely available and relatively inexpensive, there is no evidence to support their use. β-Blockers with intrinsic sympathomimetic activity (pindolol and acebutolol) should be avoided.

c. Relative contraindications to β-blocker therapy are a heart rate <60 beats/min, symptomatic hypotension, more than minimal pulmonary or systemic congestion, signs of peripheral hypoperfusion, a PR interval >0.24 seconds, second- or third-degree AV block, a history of severe reactive airway disease, and peripheral arterial disease with resting limb ischemia. It is important to note that these are relative contraindications, and particularly in the setting of reactive airway disease and peripheral arterial disease, the risks of β-blocker therapy must be weighed against their known benefits.

d. Current recommendations are to start β-blockers in those who are clinically euvolemic. The general principle is to "start low and go slow." The initial dose is **slowly uptitrated every 2 to 4 weeks over 3 to 4 months to achieve target doses**, provided that the patient can tolerate side effects. It is imperative to maintain contact with the patient and adjust vasodilator or diuretic therapy during titration. It is not advisable to stop β-blockers in patients with a history of HF, even if there is complete resolution of symptoms and LV dysfunction.

e. Every effort should be made to achieve target doses, but it is clear that even low doses of these drugs provide mortality and morbidity benefit.

f. Side effects of β-blockers include the following:

1. **(1) Dizziness** and **light-headedness** are common and may be related to hypotension or heart block. Hypotension can be managed by staggering the timing of drug administration. In practice, carvedilol (with its nonselective, β_1-blocking vasodilator effects) may have greater blood pressure lowering than selective β_1-agents such as metoprolol succinate.
2. **(2) Significant bradycardia** mandates dose reduction of β-blockers and other rate-lowering agents such as digoxin and amiodarone. **Advanced heart block** is a contraindication to β-blockers unless a permanent pacemaker is present.
3. **(3) Worsening HF** is still an important adverse effect of β-blockers. Intensification of diuretic therapy and dose reduction or slower titration may be necessary.

5. Aldosterone receptor antagonists have long been used as weak, potassium-sparing diuretics in patients with HF. The concept of incomplete RAS blockade by ACEi or ARB led to studies demonstrating significant pleiotropic effects of aldosterone antagonism in patients with advanced HF including antifibrotic effects and reduction in sudden cardiac death. Results from the Randomized Aldactone Evaluation Study (**RALES**), Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (**EPHESUS**), and Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (**EMPHASIS-HF**) trial have demonstrated substantial mortality and morbidity benefit in stage C HF.

a. Aldosterone inhibitors are indicated in patients with HFrEF and NYHA class II–IV symptoms receiving ACEi/ARB/ARNI and β-blockers that do not have significant renal dysfunction (creatinine clearance > 30 mL/min) or hyperkalemia (potassium < 5 mEq/L). Their use is also

indicated in patients with postinfarction LV dysfunction (LVEF ≤ 40%) with any HF symptoms or history of diabetes mellitus.

b. In most cases, potassium supplementation should be reduced or discontinued. A basic metabolic panel should be checked within 1 week after initiation and monitored at regular intervals.

c. The most common and life-threatening side effect of aldosterone antagonists is hyperkalemia, which is particularly problematic in patients with concomitant renal insufficiency and diabetes mellitus (type IV renal tubular acidosis). Gynecomastia and galactorrhea may occur with spironolactone.

d. Whereas clinical trials used either spironolactone (RALES) or eplerenone (EPHESUS and EMPHASIS-HF), most experts believe that aldosterone inhibitors work via class effect. Our approach is to initiate treatment with spironolactone because of its low cost and transition to eplerenone only in the setting of significant gynecomastia.

6. **Diuretics** are used to maintain euvolemia and to improve symptoms, but their overuse can result in volume contraction, hypotension, resistance, and renal dysfunction.

a. An effective and inexpensive initial regimen includes 20 to 120 mg of furosemide taken orally each day. If furosemide doses higher than 120 mg/d are needed, a second evening dose is typically prescribed. If this regimen fails, sequential nephron blockade with a thiazide diuretic can provide synergistic benefit.

b. More expensive loop diuretics (e.g., torsemide and bumetanide) have superior bioavailability and may be more effective in diuretic-resistant patients. Torsemide in particular may have unique benefits in the form of antifibrotic effects and minimization of the postdiuretic sodium retention that complicates the use of loop diuretics with shorter half-lives.

7. **Digoxin** is reasonable to use in patients with persistent HF symptoms despite appropriate, optimized guideline-directed medical therapy (GDMT) and/or in patients with atrial fibrillation to control ventricular rate.

a. Despite a fairly narrow therapeutic window, digoxin is safe and significantly reduces HF hospitalizations. A typical starting dose of 0.125 mg of digoxin daily is appropriate in patients with normal renal function.

b. Whereas the **Digitalis Investigation Group trial** demonstrated the best clinical outcomes in patients with a serum digoxin concentration of 0.5 to 0.8 ng/mL, routine measurement of levels is not recommended in the absence of concern for toxicity.

8. Recently approved novel drugs for the treatment of chronic systolic HF:

a. **Ivabradine** is an I_f current inhibitor within the sinus node; inhibition leads to rate reduction and subsequently increases stroke volume while preserving AV nodal conduction and contractility. Addition should be considered in HFrEF individuals, NYHA II–III receiving GDMT, including maximally tolerated dose of BB and have a heart rate >70 beats/min. The SHIFT trial demonstrated overall significant reduction in all-cause HF and cardiovascular admission in individuals with HFrEF and sinus rhythm with rate over 75 beats/min (see Table 8.4 for dosing).

b. **Sacubitril/valsartan (ARNI) is first-line therapy for symptomatic HFrEF.** RAS blockade can be achieved via ACE or ARB or ARNI in conjunction with additional GDMT. **Sacubitril/valsartan** is a combination pill that consists of a neprilysin inhibitor with angiotensin receptor blocker. Inhibition of neprilysin leads to the inhibition of natriuretic peptides and additional vasoactive peptides subsequently augmenting natriuresis and decreasing sympathetic tone, aldosterone, and cardiac fibrosis/hypertrophy. PARADIGM-HF demonstrated a 20% reduction in cardiovascular death or first HF hospitalization (see Table 8.4 for dosing). There

should be a minimum 36-hour washout period between discontinuation of ACEi and administration of ARNI to avoid angioedema.

9. Other drugs and interventions of importance.

a. Statins should be used in the secondary prevention of atherosclerotic cardiovascular disease without regard to the presence of HF. There is no evidence of benefit in HF patients without coronary artery disease.

b. Aspirin clearly prevents reinfarction and other vascular events in patients with known coronary artery disease; there is growing evidence from observational and randomized studies that it may worsen outcomes in HF patients via inhibition of prostaglandin synthesis and the resultant adverse hemodynamic and renal effects. This remains a controversial subject and the decision of whether to use aspirin or not should be made on a case-by-case basis. It should likely be avoided in patients without coronary disease who have refractory HF symptoms.

10. Electrolyte supplementation is among the most important and least emphasized areas in chronic HF management. Potassium depletion is common with diuretic therapy, whereas hyperkalemia can be caused by RAS inhibitors or worsening renal insufficiency. In general, oral potassium supplementation is necessary to maintain serum potassium level in the ideal range of 4.0 to 5.0 mEq/L. Magnesium, thiamine, and calcium depletion are also common with long-standing diuretic therapy.

11. Device therapy. Chapters 55 and 56 provide detailed coverage of the indications, contraindications, and clinical issues related to implantable cardioverter defibrillators (ICD) and CRT-D.

a. Device monitoring. Currently implanted electrical cardiovascular devices including ICD and CRT-Ds have the capability to remotely monitor a variety of electrophysiologic (e.g., heart rate variability, atrial arrhythmia burden and rate, ventricular tachycardia, % biventricular pacing, and average heart rate) and physiologic (e.g., patient activity and intrathoracic impedance) parameters with prognostic value. Several implantable hemodynamic monitors (e.g., CardioMEMs) are under development for use in patients with advanced HF. How to best integrate device monitoring into a comprehensive approach to HF disease management remains to be established.

C. Chronic nonmedical therapies

1. Patient education and disease management programs remain the most effective treatment strategy for patients with systolic HF. Sodium restriction (<2,000 mg daily) and medication compliance are crucial to reducing hospitalizations. Control of blood pressure, serum glucose, and lipid levels should be emphasized. Some highly motivated patients can perform self-monitoring (i.e., daily weights and symptom assessment) and care (i.e., titration of diuretics) analogous to the chronic management of diabetes.

2. Exercise training. There is a clear body of evidence supporting the fact that exercise training improves endothelial function and functional capacity in patients with chronic HF. HF-ACTION failed to demonstrate a reduction in all-cause mortality and hospitalization; but demonstrated significant improvement in self-reported health status. A supervised cardiac rehabilitation program should be advised when available.

D. Advanced therapies. Mechanical circulatory support and orthotopic heart transplantation are therapies currently reserved for patients with ACC/AHA stage D HF refractory to other therapies. These are described in detail in Chapters 12 and 13, respectively.

VIII. PROGNOSIS.

HF is associated with high rates of morbidity and mortality. In the Framingham Heart study, patients with HF had mortality rates four to eight times those of

age-matched controls. A patient with NYHA class IV HF has a 1-year survival between 30% and 50%—a mortality rate comparable to that of advanced malignancies. Several risk scores have been developed to characterize the risk of HF hospitalization and mortality. The Seattle Heart Failure Model is perhaps the most widely used of these and incorporates demographic, clinical, pharmacologic, and laboratory data to provide accurate 1-, 2-, and 3-year survival estimates. Table 8.5 lists some common clinical predictors of poor survival in systolic HF.

TABLE 8.5 Common Clinical Predictors of Poor Prognosis in Systolic Heart Failure

Increased age
Increased New York Heart Association functional class
Severely reduced LV ejection fraction (<25%), extensive cardiac remodeling (LVIDd > 65 mm), or r
Concomitant diastolic dysfunction (particularly irreversible restrictive filling, stage IV diastolic dysfu
Reduced RV function
Atrial fibrillation, elevated average heart rate, and reduced heart rate variability
Low peak VO_2 with maximal exercise (14 mL/min/kg), low heart rate response to exercise, increase response to hypoxia), and high VE/VCO_2
High plasma BNP and N-terminal proBNP levels
High levels of other cardiac and neurohormonal biomarkers including norepinephrine, renin, arginin tumor necrosis factor, cardiac troponin T and I, and C-reactive protein
Anemia
Low systolic blood pressure
Renal insufficiency (creatinine clearance < 60 mL/min)
Attenuated response to diuretics and lack of hemodynamic and structural improvement (reverse re
Persistent signs of congestion and fluid retention or failure to normalize filling pressures (PCWP < therapy
Serum sodium < 135 mg/dL
Cardiac dyssynchrony (QRS > 130 ms, left bundle branch block)
Depression
Nocturnal Cheyne–Stokes respiration and obstructive sleep apnea

IX.BNP, B-type natriuretic peptide; CVP, central venous pressure; LV, left ventricular; LVIDd, left ventricular internal dimension at diastole; PCWP, pulmonary capillary wedge pressure; RV, right ventricular; VE, ventilation.

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USEFUL WEB SITES

HFSA Heart Failure Guidelines: http://www.hfsa.org/heart-failure-guidelines-2/
Seattle Heart Failure Model: http://depts.washington.edu/shfm/

CHAPTER 9

Heart Failure with Preserved Ejection Fraction and Restrictive Cardiomyopathy

Antonio L. Perez
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I. INTRODUCTION

A. Epidemiologic studies suggest that nearly one-half of patients with heart failure have a preserved ejection fraction (EF); the proportion in those hospitalized has been reported to range from one-quarter to half. The survival of patients with heart failure and preserved EF was once thought to be better than those with a decreased EF, but current evidence suggests similar mortality rates.

Heart failure with preserved ejection fraction (HFpEF) has become the preferred term in the literature. This clinical entity historically has also been referred to as diastolic heart failure. In this chapter, we focus on HFpEF and provide a brief discussion of the restrictive cardiomyopathies, which are important differential diagnoses in patients presenting with heart failure and an EF measured in the normal range.

B. Definition. The 2013 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) Guideline for the Management of Heart Failure defines HFpEF as the clinical syndrome that includes **(1) signs and symptoms of congestive heart failure; (2) left ventricular ejection fraction (LVEF) > 50%; and (3) evidence of diastolic dysfunction as determined by Doppler echocardiography, cardiac catheterization, and natriuretic peptide measurement** (Table 9.1). Findings on diagnostic testing that suggest the presence of diastolic dysfunction include: (1) pulmonary capillary wedge pressure (PCWP) > 12 mm Hg or left ventricular end-diastolic pressure (LVEDP) > 16 mm Hg; (2) unequivocal echocardiographic evidence of elevated LV filling pressure (E/e′ > 15); (3) lateral e′ velocity < 10 cm/s or septal e′ velocity < 8 cm/s; (4) abnormal mitral inflow Doppler pattern suggesting impaired relaxation (E/A < 1), E/A pseudonormalization or restrictive physiology (E/A > 2); and (5) elevated natriuretic peptide plasma levels (N-terminal prohormone of brain natriuretic peptide [NT-proBNP] > 220 pg/mL or BNP > 200 pg/mL).

TABLE 9.1 Diagnostic Criteria for Heart Failure with Preserved EF

Clinical Presentation	Signs and Symptoms of Congestive Heart Failure
Left ventricular function	EF > 50%

TABLE 9.1 Diagnostic Criteria for Heart Failure with Preserved EF

Evidence suggesting diastolic dysfunction on diagnostic testing	1. LVEDP > 16 mm Hg or PCWP > 12 mm Hg 2. E/e′ > 15 3. Lateral e′ velocity < 10 cm/s or septal e′ velocity < 8 c 4. Abnormal mitral inflow Doppler pattern suggesting pseudonormalization or restrictive physiology (E/A > 2 5. Elevated plasma natriuretic peptide levels (NT-proBN

C.BNP, β-natriuretic peptide; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N-terminal prohormone of BNP; PCWP, pulmonary capillary wedge pressure.

D.Pathophysiology. Most pathophysiologic abnormalities in patients with HFpEF are related to diastolic function. There are two major determinants of diastolic function: LV relaxation and LV stiffness. LV relaxation relates to the cellular mechanisms involved with actin–myosin cross-bridge detachment. This requires intracellular calcium uptake into the sarcoplasmic reticulum, an energy- or adenosine triphosphate (ATP)-dependent process. Thus, ischemia, which would decrease intracellular availability of ATP, would prolong the time required for ventricular relaxation. LV stiffness relates to the compliance of the myocardial tissue. One determinant of this is the extracellular matrix. For example, increase in fibrosis and collagen deposition, as in patients with hypertensive heart disease, leads to an increase in LV stiffness. Restrictive cardiomyopathies share a similar pathophysiology, with increased LV stiffness; however, these differ in the pathology underlying the change in ventricular compliance: extracellular amyloid deposition (cardiac amyloidosis); endocardial fibrosis from eosinophilic injury (Loeffler endocarditis and endomyocardial fibrosis); intracellular lysosomal engorgement with sphingolipids (Fabry disease); and others.

A number of other pathophysiologic mechanisms have been implicated in patients with HFpEF. These include arterial stiffness, the relationship between arterial and ventricular stiffness, and chronotropic incompetence. The implications and relative importance of these mechanisms are still unclear.

II.CLINICAL PRESENTATION

A.Demographics. When compared with patients with heart failure with reduced ejection fraction (HFrEF), those with HFpEF tend to be **older**and are more likely to be **female**. Associated comorbidities include hypertension, diabetes, obesity, and chronic kidney disease.

B.Symptoms. Analogous to HFrEF, HFpEF spans the spectrum of asymptomatic or subclinical disease to chronic congestive heart failure. The symptoms of HFpEF are indistinguishable from those of HFrEF. Some patients present with only exertional fatigue or dyspnea. Other patients experience overt symptoms of left-sided (dyspnea, orthopnea, and paroxysmal nocturnal dyspnea) and right-sided (edema and abdominal bloating) heart failure.

C.Signs. The signs of HFpEF are similar to those of HFrEF. Patients should be evaluated for typical signs of right-sided (elevated jugular venous pressure, hepatic congestion, ascites, and lower extremity edema) and left-sided (pulmonary edema and pleural effusion) congestion. The presence of an S4 usually signifies a stiff left ventricle. In contrast to patients with dilated cardiomyopathy, the location of the apical impulse is usually close to the midclavicular line, signifying a normal-sized ventricle. In addition, a hypertrophied ventricle will often have a stronger impulse than a ventricle of normal thickness. This may be appreciated on

examination in patients who do not have thick chest walls. In patients with exertional symptoms alone, these signs may not be present as the manifestation of their diastolic dysfunction may occur only during exercise.

The presence of severe right-sided heart failure features, particularly ascites and hepatic congestion, should raise suspicion for restrictive cardiomyopathy, constrictive pericarditis, or both. In these patients, clinical findings of multiorgan disease may provide additional insights into the etiology of their cardiomyopathy. Kussmaul sign, a paradoxical elevation in the mean jugular venous pressure during inspiration, has been classically described in constrictive pericarditis. However, it can also be present in patients with restrictive cardiomyopathy as well as other pathologies involving the right heart (e.g., severe right ventricular [RV] systolic dysfunction and dilatation with secondary tricuspid regurgitation).

III.LABORATORY EXAMINATION AND BASIC INVESTIGATIONS

A.Electrocardiogram (ECG). ECG is an insensitive test for HFpEF. The most important finding is the amplitude of QRS voltage. The presence of elevated voltage and other criteria for left ventricular hypertrophy (LVH) can suggest a possible etiology of HFpEF. Conversely, in a patient who has increased wall thickness (typically identified by echocardiography) but has low voltage or infarction patterns on ECG ("pseudoinfarction"), infiltrative cardiomyopathy should be considered.

B.Chest radiograph. The chest x-ray has few specific findings for HFpEF. In a posterior–anterior film, a normal-sized heart (lateral heart width less than two-thirds of a hemithorax) may be a clue to a normal-sized left ventricle. Otherwise, the findings are the same as in HFrEF: fluffy alveolar opacities (alveolar pulmonary edema), increased interstitial markings (increased interstitial fluid), pulmonary vascular redistribution (increased pulmonary venous pressure), and pleural effusions.

C.Specific laboratory investigations. Natriuretic peptide assessment can be helpful in establishing the diagnosis of HFpEF. When compared with patients with systolic heart failure, the elevation in BNP or NT-proBNP is generally lower. In patients with undifferentiated dyspnea, a normal BNP or NT-proBNP would argue against the presence of any heart failure syndrome.

IV.DIFFERENTIAL DIAGNOSIS.

The two most common clinical presentations of HFpEF are congestive heart failure and exertional dyspnea (without physical examination findings of heart failure). In a patient presenting primarily with exercise intolerance or exertional dyspnea, HFpEF should be considered in addition to coronary artery disease (CAD), primary lung disease, anemia, etc.

In a patient who has an established clinical syndrome of heart failure, the differential diagnosis is typically narrowed following echocardiography. HFpEF is the most likely diagnosis in a patient with preserved EF and a normal-sized left ventricle. Other diagnoses to consider include restrictive cardiomyopathy, hypertrophic cardiomyopathy (HCM), valvular heart disease, and constrictive pericarditis. Here, we primarily discuss HFpEF and restrictive cardiomyopathy.

A.Heart failure with preserved EF. Heart failure without another obvious cause, particularly in the context of advanced age, hypertension, obesity, chronic kidney disease, and diabetes, should lead to an early consideration for HFpEF. In such patients, myocardial ischemia may play some role in the manifestation of heart failure. This is particularly true for patients presenting with acute heart failure or flash pulmonary edema. In the absence of dynamic

valvular regurgitation, ischemia leading to pulmonary edema usually denotes a large amount of myocardium at risk. This type of presentation certainly warrants aggressive investigation for obstructive coronary disease and, when applicable, revascularization.

B. HCM. The diagnosis of HCM is usually made in the presence of LVH, without concomitant hypertension or aortic stenosis. There are many manifestations of HCM, one of which is a "restrictive" phenotype that presents predominantly with diastolic heart failure. Distinction between HCM and other restrictive cardiomyopathies is not always clear, but it should be considered in certain scenarios: examples of this would include family members with HCM (particularly with an identified gene mutation), the typical reverse curve morphology of the interventricular septum, predilection for sudden death or ventricular tachyarrhythmia, and/or the presence of LV outflow tract obstruction.

C. Restrictive cardiomyopathies. Restrictive cardiomyopathies represent a group of disorders in which ventricular stiffness is increased by mechanisms and pathologies other than those related to the more common HFpEF. This may be a result of infiltrative, inflammatory, or metabolic diseases. The most common etiology of restrictive cardiomyopathy is cardiac amyloidosis.

1. Cardiac amyloidosis. Amyloidosis refers to the deposition of amyloid, or an abnormal protein, in organ tissue. There are several causes, and the following are the most important ones that manifest with cardiac involvement.

a. Primary amyloidosis is caused by a primary hematologic malignancy. Monoclonal plasma cells produce a light chain immunoglobulin; deposition into cardiac tissue is variable. Early stages show subclinical diastolic dysfunction (usually seen on echocardiography); later stages show severe restrictive cardiomyopathy. Traditionally, patients presenting with heart failure are felt to have a very poor prognosis with limited treatment options. However, tertiary center experience suggests that achieving remission of the malignancy with chemotherapeutics may positively impact a patient's heart failure symptoms.

b. Familial amyloidosis involves the inheritance of a gene that produces a mutant form of transthyretin, a serum protein carrier of thyroxine and retinol. The protein is produced in the liver and is deposited in the kidneys, the heart, and the nerves. Some centers may offer cardiac transplantation to selected patients.

c. Senile amyloidosis is similar to familial amyloidosis in that it is related to the deposition of a pathologic variant of transthyretin. This usually occurs in older men.

2. Endomyocardial fibrosis. Endomyocardial fibrosis is an idiopathic restrictive cardiomyopathy that occurs in areas close to the equator, such as equatorial Africa, South America, and Asia. It usually affects children and young adults. Histologically, it is characterized by granulation tissue, collagen, and extensive connective tissue lining the endocardium. It affects both ventricles (50%), left ventricle (40%), or isolated right ventricle (10%) and is associated with a 2-year mortality rate of up to 50%. Atrial fibrillation, mitral regurgitation (MR), and thromboembolism are common. The response to medical treatment is poor. Endocardial decortication may be beneficial for those with New York Heart Association (NYHA) class III or IV symptoms. This technique has high operative mortality (15% to 20%) but, when successful, reduces symptoms and may favorably affect survival.

3. Loeffler (eosinophilic) endocarditis. Loeffler endocarditis is more commonly seen in temperate climates and generally occurs as part of the idiopathic hypereosinophilic syndrome. It typically manifests in middle age. Features include eosinophilia, restrictive cardiomyopathy,

and nervous system and bone marrow involvement. Left ventricular mural thrombus frequently occurs. Aside from conventional heart failure medications (including anticoagulation), corticosteroids and hydroxyurea are useful treatment options. Endocardial decortication may be required for advanced fibrotic disease.

4. **Idiopathic restrictive cardiomyopathy.** Idiopathic restrictive cardiomyopathy is a diagnosis of exclusion. It usually occurs sporadically, but may be inherited with an autosomal dominant pattern in association with distal skeletal myopathy and occasionally a heart block. Echocardiography reveals near-normal LV dimensions and systolic function, biatrial enlargement, and variable hypertrophy. Endomyocardial biopsy is unremarkable or shows nonspecific changes. The condition may manifest at any age throughout childhood or adult life. Survival time varies, with a mean survival of 9 years. Cardiac transplantation may be indicated in selected patients.
5. **Sarcoidosis.** Cardiac sarcoidosis can present with restrictive cardiomyopathy, but much more commonly it produces a dilated cardiomyopathy phenotype. Associated cardiac manifestations include conduction disease and ventricular tachyarrhythmia.
6. **Radiation carditis.** Radiation heart disease affects almost all components of the heart. Direct myocardial involvement, usually in the form of diastolic dysfunction, can be underappreciated, particularly when there is concomitant valvular, coronary, and/or pericardial disease. Separating the relative contributions of multiple pathophysiologic mechanisms in a given radiation patient can be challenging. These patients are at risk for suboptimal outcomes after surgery to correct valvular, coronary, or pericardial disease because of their primary restrictive myocardial disease.
7. **Metabolic storage diseases** are characterized by intracellular deposition of substances within the myocyte, resulting in increased myocardial stiffness.

a. **Hemochromatosis**, or iron overload, can cause restrictive cardiomyopathy. However, when cardiac manifestations occur, the phenotype is usually dilated cardiomyopathy.
b. **Glycogen storage diseases.** Types II, III, IV, and V glycogen storage diseases may present with cardiac manifestations, usually as asymptomatic increase in LV thickness.
c. **Gaucher disease.** Gaucher disease is caused by a deficiency in β-glucosidase, which leads to cerebroside deposition into multiple organs (spleen, liver, brain, bone marrow, lymph nodes, and heart). In the heart, this can cause increased ventricular thickness with diastolic dysfunction, LV systolic dysfunction, pericardial effusion, and valvular disease. This can be treated with enzyme replacement.
d. **Fabry disease** is a lysosomal storage disease caused by a deficiency in α-galactosidase (X-linked, recessive trait). This leads to glycosphingolipid accumulation in the kidney, the skin, and the heart. Cardiac manifestations include increased LV thickness, diastolic dysfunction, atrioventricular block, and MR. This can be treated with enzyme replacement.

V. DIAGNOSTIC TESTING

A. **Echocardiography** is the primary imaging modality for evaluating a patient with a clinical syndrome of congestive heart failure. It is the modality of choice when evaluating LV diastolic function. The most commonly used parameter in clinical practice is the Doppler interrogation of the transmitral flow pattern and tissue Doppler evaluation of annular velocity to determine the E/e′ ratio. There are numerous other 2D and Doppler findings that are critical to diagnosis, including chamber size and wall thickness.

1. **Transmitral flow pattern.** In sinus rhythm, using pulsed wave Doppler across the mitral inflow tract generates two waves: the early E wave, corresponding to rapid ventricular filling as the mitral valve opens, and the A wave, which reflects atrial contraction. The E-wave deceleration time is the time from peak E inflow velocity to decay to zero. With age, hypertension, or ischemia, the viscoelastic properties of the ventricle decrease, and the E wave decreases in amplitude, has a gentler slope, and has a longer deceleration time. The atrial kick is proportionately greater, and E–A reversal may occur. However, multiple other factors can impact the E/A ratio, and recent guidelines have abandoned this as a sensitive measure of diastolic dysfunction. Recent guidelines advocate using left atrial (LA) size, septal and lateral mitral annular velocity (E′), and tricuspid regurgitant velocity to identify those with Grade 1 diastolic dysfunction. With progression of diastolic dysfunction, LA pressure rises further to compensate, and the E wave becomes more prominent than the A wave (i.e., pseudonormalization or grade 2 diastolic dysfunction). As diastolic dysfunction progresses, the LV stiffness increases and the deceleration time shortens, reflecting rapid equilibration of LA/LV pressures during early diastole. When the deceleration time is < 160 ms and the E/A ratio is > 2, the patient is considered to have grade 3 diastolic dysfunction.

   Although the transmitral flow pattern is one of the primary ways of evaluating diastolic function, it has several limitations. It can be difficult to differentiate normal diastolic function from the "pseudonormal" pattern of grade 2 diastolic dysfunction, as they both have E/A ratios > 1. Also, the transmitral flow pattern can often be difficult to interpret or is uninterpretable in common scenarios, including atrial fibrillation, tachycardia (fusion of E and A waves), and mitral valve disease (MR ≥ 3+, mitral stenosis, and mitral prosthesis).
2. **Tissue Doppler imaging (TDI) of the mitral annular velocity.** In the evaluation of LV diastolic function, TDI is used to measure the velocity of movement of the septal and lateral aspects of the mitral annulus. The myocardial velocities have three main components: systolic wave (S′), early diastolic wave (e′), and late diastolic wave (a′). In the earliest stages of diastolic dysfunction, the diastolic velocities of annular motion decrease. Normally, the lateral annulus tends to have higher velocities than the septal mitral annulus. Septal e′ < 8 cm/s and/or lateral e′ < 10 cm/s suggests the presence of diastolic dysfunction.

   Unlike the transmitral flow pattern, there is no "pseudonormalization" pattern with annular velocity, making it easier to differentiate normal from abnormal diastolic function. The mitral annular TDI should be used with caution when other conditions that may affect annular velocity independent of ventricular relaxation coexist, such as infarction of the septum or lateral wall or constriction with pericardial adhesion of the lateral wall.
3. **E/e′.** The ratio of the E velocity (obtained from the transmitral flow pattern) and the e′ (obtained from TDI, primarily of the lateral mitral annulus) can be used to estimate filling pressure, as there is a rough correlation with invasive hemodynamics (PCWP). This correlation is better with patients with depressed EF but is reasonable in patients with normal EF. Extreme values are most helpful. E/e′ < 8 correlates with normal LV filling pressures. E/e′ > 15 correlates with PCWP > 12 mm Hg; higher values are more specific for this. Unfortunately, there are many patients that fall into the intermediate zone, where E/e′ > 8 but < 15. For these patients, the presence of elevated filling pressure cannot be determined by this method alone. Echocardiographic guidelines suggest using the presence of LA enlargement (LA volume index

> 34 mL/m^2). Plasma BNP or NT-proBNP can be helpful in equivocal cases to determine whether or not there is corroborating evidence for elevated pressures.

In patients with predominantly exertional symptoms, it may be useful to perform exercise echocardiography to evaluate for the presence of diastolic dysfunction during exercise, particularly when this is not evident at rest. The sonographer should obtain LV images in multiple views following stress. Once the 2D information has been acquired, Doppler studies, including the transmitral flow pattern and the TDI of the septal and lateral mitral annulus, should be recorded. The diastolic abnormalities usually persist after tachycardia subsides. Therefore, Doppler data should be recorded for a period of time following stress to reduce the likelihood of E- and A-wave fusion, which can make the E-wave velocity difficult to interpret. If E/e′ following stress is > 15, exertional increase in LV filling pressures is likely.

B. Invasive hemodynamic assessment. Invasive hemodynamic assessment is not routinely performed but is indicated when noninvasive studies cannot adequately assess filling pressures. The PCWP (> 12 mm Hg) or LVEDP (> 16 mm Hg) should be measured. Other diastolic parameters, including Tau (τ), the time constant of isovolumic relaxation, are rarely measured in clinical practice.

When restrictive cardiomyopathy is considered, detailed hemodynamics may be of greatest value in directing management but are often less helpful in differentiating between possible diagnoses. Findings such as elevated and equalized diastolic pressures in four chambers (within 5 mm Hg), M pattern of the right atrial pressure waveform, “dip and plateau” of the ventricular diastolic pressures, equalization of LVEDP/RVEDP, and Kussmaul sign occur in a number of pathologies, including restrictive cardiomyopathy, constrictive pericarditis, severe RV failure, and severe tricuspid regurgitation.

C. Magnetic resonance imaging (MRI). In most patients with HFpEF, cardiac MRI is usually not required. It can be useful to measure ventricular function, mass, and volumes when echocardiography is not diagnostic. It is also helpful in establishing or excluding specific conditions such as constrictive pericarditis, sarcoidosis, amyloidosis, or hemachromatosis.

D. Endomyocardial biopsy. Endomyocardial biopsy is used in selected circumstances, particularly when there is a high suspicion of a disorder whose diagnosis will profoundly impact management and prognosis. The most common indication in restrictive cardiomyopathy is to evaluate for cardiac amyloidosis. Biopsy in this setting can determine the presence of amyloid as well as differentiate between the different types of amyloid. The yield of endomyocardial biopsy for patchy diseases, such as sarcoidosis, is low.

VI. THERAPY.

Numerous trials have evaluated the effects of medical therapy in HFpEF, including studies of angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and mineralocorticoid antagonists in patients with HFpEF. Unfortunately, none of these trials have shown a clear mortality benefit. There has been variable effect of these medications on morbidity endpoints, including heart failure hospitalizations, symptoms, and LVH regression. The relevance of some of these trials is in question, as their entry criteria included patients with LV dilatation and LVEF < 50%, a population that may be different from HFpEF patients with LVEF > 50%. Hypertension and congestion management remain the mainstay of therapy. Based on the results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Programme (CHARM-P) and Treatment of Preserved Cardiac Function Heart Failure with

an Aldosterone Antagonist (TOPCAT) trials, candesartan and spironolactone, respectively, have been shown to reduce hospitalization in HFpEF. The ACC/AHA Guidelines for Management of Heart Failure (2013) recommendations for management of HFpEF are listed in Table 9.2.

TABLE 9.2 ACC/AHA Guideline Recommendations for Pharmacologic Therapy of HFpEF

Class I Recommendations	
Systolic and diastolic hypertension	Physicians should control hypertension in accordance with publ
Diuretics	Physicians should use diuretics to control symptoms of volume
Class IIa Recommendations	
Coronary revascularization	In patients with CAD in whom ischemia has an adverse effect o directed medical therapy (level of evidence: C)
Atrial fibrillation	Management of AF according to guidelines reasonable to impro
β-Blockers, ACE inhibitors, and ARBs	Use of these drug classes to treat hypertension in HFpEF patien
Class IIb Recommendations	
ARBs and hospitalization	ARB therapy can be considered to reduce hospitalizations (leve
Class III: No Benefit Recommendation	
Nutritional supplements	Routine use is not recommended for HFpEF patients (level of ev

VII. ACC, American College of Cardiology; ACE, Angiotensin-converting enzyme; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; CAD, coronary artery disease; HFpEF, Heart failure with preserved ejection fraction.

VIII. Adapted from Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239.

A. **Salt restriction.** Sodium restriction is a reasonable dietary recommendation in patients with symptomatic HFpEF, in order to reduce congestion. Daily sodium intake should not exceed 2,000 mg in these patients.

B. **Diuretics.** Diuretics should be used for symptomatic treatment of edema and pulmonary congestion. Chronic use of loop diuretics may lead to diuretic resistance; in this scenario, a thiazide- or potassium-sparing diuretic may be used to augment diuresis. For this indication, hydrochlorothiazide (usually 25 to 50 mg, given once or intermittently) is effective within the first day. Patients may also present with significant bowel edema, rendering diuretics with poor oral absorption ineffective. In these patients, torsemide, which has a better oral absorption profile, is a reasonable option. Diuresis is often limited by the occurrence of prerenal azotemia. This is particularly common in HFpEF or restrictive cardiomyopathy

patients with systemic disorders that have concomitant effects on the kidney, including hypertension, diabetes, or amyloidosis. In these cases, balancing congestive symptoms and azotemia can be challenging. On occasion, the patient may only achieve symptomatic relief after aggressive diuresis, even to the point where the blood urea nitrogen and/or creatinine is at levels higher than baseline values.

C. **Angiotensin receptor blockers.** CHARM-P and Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) are two major trials that evaluated the use of ARBs in the HFpEF population. CHARM-P, which randomized candesartan versus placebo, also failed to show a difference in its primary combined endpoint of cardiovascular death and heart failure hospitalization. Candesartan therapy did, however, reduce heart failure hospitalization in comparison to control. I-PRESERVE enrolled patients with LVEF ≥ 45% and randomized patients to irbesartan versus placebo. This trial showed no difference in the primary endpoint of mortality and heart failure hospitalizations between ARB therapy and placebo groups.

D. **ACE inhibitors.** The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial randomized patients with LVEF ≥ 40% to perindopril versus placebo. The primary endpoint of all-cause mortality and unplanned heart failure hospitalization was not met, but after 1 year, there appeared to be a statistically significant decrease in heart failure hospitalizations in the active treatment arm.

E. **β-Blockers.** The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial randomized nebivolol versus placebo in all patients with congestive heart failure. Thirty-five percent of the patients had LVEF > 35%. In the overall trial, the nebivolol group demonstrated a significant decrease in the primary endpoint of mortality and heart failure mortality. In the subgroup analysis, the improvement appeared to hold in the group with LVEF > 35%. The Japanese Diastolic Heart Failure Study (J-DHF) randomized heart failure patients with EF > 40% to treatment with or without carvedilol, in an open label study. The trial did not show a significant difference in cardiovascular death and unplanned hospitalization between the two groups. The median prescribed dose of carvedilol achieved was only 7.5 mg, below the trial's target 20 mg/d dose. The subgroup treated with >7.5 mg/d did experience a significant reduction in the primary endpoint compared to control.

F. **Digoxin.** The Digitalis Investigation Group (DIG) trial evaluated the use of digoxin in patients with heart failure. A subgroup of that trial examined patients with LVEF > 45%. There was no significant difference in mortality in this subgroup. There was a nonsignificant trend toward decreased heart failure hospitalizations but an increased trend toward unstable angina hospitalizations in those treated with digoxin.

G. **Spironolactone.** The TOPCAT trial randomized heart failure patients with EF ≥ 45% to receive spironolactone or placebo. The international trial which enrolled patients from North and South America as well as Eastern Europe showed that spironolactone reduced hospitalizations, but had no effect on the primary outcome of cardiovascular death, aborted cardiac arrest, or heart failure hospitalization. Interestingly, subgroup analysis revealed a significant reduction in the primary outcome in patients enrolled in North and South America, but not those enrolled from Eastern Europe (who were younger and had less diabetes, chronic kidney disease, and atrial fibrillation than North and South American patients). The Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-HF) trial randomized heart failure patients with EF > 50% to spironolactone versus placebo; at 12 months, there was no

significant difference between the groups in the coprimary endpoints of changes in diastolic function by echocardiography (E/e′) and maximal exercise capacity (peak VO_2) on cardiopulmonary exercise testing (CPET).

H. Sildenafil. The Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial that randomized outpatients with HFpEF (EF ≥ 50%) to 24 weeks of sildenafil or placebo showed no significant improvement in VO_2 max on CPET or 6-minute walk test.

I. Nitrates. The Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT) trial randomized HFpEF patients (EF ≥ 50%) to isosorbide mononitrate or placebo for 6 weeks, with subsequent cross-over to the other group for an additional 6 weeks. The trial revealed no significant change in daily activity level, 6-minute walk disease, quality of life scores, or NT-proBNP levels with nitrate therapy compared to placebo.

J. Angiotensin receptor/neprilysin inhibitor. The angiotensin/neprilysin inhibitor sacubitril/valsartan has been shown to significantly reduce mortality in HFrEF patients in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. The Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) is an ongoing study comparing the effects of sacubitril/valsartan versus valsartan in heart failure patients with EF ≥45%.

IX. PRACTICAL APPROACH TO HFPEF AND RESTRICTIVE CARDIOMYOPATHIES

A. Exertional dyspnea only. In these patients, HFpEF should be in the differential diagnosis. Resting echocardiogram should be performed, with particular attention paid toward the presence of resting diastolic dysfunction. If this is absent, one can consider exercise echocardiography to determine exercise-induced diastolic dysfunction. BNP or NT-proBNP should also be measured. Even in the presence of this diagnosis, specific treatment or change in management is uncertain. Hypertension should be medically treated. Therapy with spironolactone may be considered.

B. Congestive heart failure. For patients presenting with overt signs of congestive heart failure, echocardiography should be used to narrow the differential diagnosis. In the absence of findings to support LV systolic dysfunction, valvular disease, or constrictive pericarditis, one should consider HFpEF if there is evidence of diastolic dysfunction and elevated LV filling pressures. This is determined by unequivocal echocardiographic evidence (E/e′ > 15); equivocal echocardiographic evidence (E/e′ > 8 and < 15) + elevated plasma natriuretic peptides (NT-BNP > 200 pg/mL or BNP > 200 pg/mL); or invasive hemodynamics (PCWP > 12 mm Hg, LVEDP > 16 mm Hg), in addition to mitral inflow Doppler pattern. If the above findings are met and the patient fits the appropriate risk profile (elderly, female, hypertension, chronic kidney disease, diabetes, and obese), then HFpEF is a reasonable diagnosis.

Restrictive cardiomyopathy should be entertained when patients present with significant right-sided heart failure symptoms (ascites, hepatic congestion, and severe edema), have multiorgan presentations (amyloidosis—orthostasis and renal failure; Fabry's—renal and skin involvement), or do not fit the typical risk profile for HFpEF (young and no hypertension). In these patients, additional, focused testing should be performed to establish the etiologic diagnosis. This may include cardiac MRI, nuclear imaging, and in selected circumstances endomyocardial biopsy.

C.Treatment. To date, there has been no class of medications that has been clearly established to have mortality benefit for patients with HFpEF. Because hypertension contributes to HFpEF pathophysiology in most patients, elevated blood pressure should be treated according to the established guidelines. It is reasonable to use β-blockers, ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists for this purpose. Candesartan and spironolactone have been shown to reduce hospitalization in clinical trials. Loop diuretics should be used for symptomatic benefit; they can be combined with thiazide diuretics to treat diuretic-resistant patients. The importance of concomitant obstructive CAD is unclear in asymptomatic patients. Revascularization should be reserved for patients in whom ischemia is thought to play a major, adverse role in cardiac function (Table 9.2).

For patients with restrictive cardiomyopathy, treatment should be directed toward the specific etiology, where these therapies exist. The presence of congestive heart failure may portend a worse prognosis in patients with restrictive cardiomyopathy. Diuretics are used for symptomatic relief. β-Blocker therapy must be used cautiously in these patients, as they may depend on their heart rate to maintain their cardiac output. In selected candidates, evaluation for left ventricular assist device implantation and cardiac transplantation can be pursued.

X.PROGNOSIS. The prognosis in symptomatic patients with HFpEF is not as well characterized as our understanding of the natural history of HFrEF. Although population-level data suggest similar mortality risk in HFrEF and HFpEF, analyses from clinical trials and observational cohorts suggest lower mortality in HFpEF than in HFrEF. It is well known, however, that HFpEF patients experience increased risk of death in comparison to those without heart failure. Furthermore, patients with a history of HFpEF and heart failure hospitalization experience even worse survival, with 20% to 30% of these patients dying within 1 year of discharge. Importantly, HFpEF and HFrEF patients experience similar morbidity, with comparable rates of hospitalization and readmission, poor performance on objective measures of functional status such as 6-minute walk test, and reduced quality of life questionnaire scores.

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GUIDELINES

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CHAPTER 10

Hypertrophic Cardiomyopathy

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I. INTRODUCTION. Hypertrophic cardiomyopathy (HCM) is generally defined as the presence of left ventricular (LV) hypertrophy (LVH) of a nondilated LV in the absence of another cardiac or systemic disease which could explain the degree of LVH. There are many causes of LV wall thickening; however, these diseases can typically be identified by a history of significant hypertension or severe aortic stenosis, or due to multisystem organ involvement (e.g., skeletal muscle weakness in Danon disease; Table 10.1).

Whereas there are many alternative names for HCM, including *idiopathic hypertrophic subaortic stenosis*, *hypertrophic obstructive cardiomyopathy*, and *muscular subaortic stenosis*, the World Health Organization recommends that HCM should be used because it does not imply that LV outflow tract (LVOT) obstruction is an invariable component of the disease. HCM is a heterogenous disease with a spectrum including patients who are asymptomatic with or without obstruction, who develop heart failure symptoms, angina, or arrhythmias, and who suffer from sudden death.

II. CLINICAL PRESENTATION

A. Natural history

1. The **histologic features** of HCM are disarray of cell-to-cell arrangement, disorganization of cellular architecture, and fibrosis. The most common sites of ventricular involvement are, in decreasing order, the septum, apex, and mid-ventricle. One-third of patients have wall thickening limited to one segment.
2. The **prevalence** of HCM is ~1 in 500 in the general population, and it appears to be inherited. It is a leading cause of sudden death among athletes aged <35 years.

B. Signs and symptoms

1. **Heart failure.** Symptoms, which include dyspnea, dyspnea on exertion, paroxysmal nocturnal dyspnea, and fatigue, are largely a consequence of two processes: elevated LV diastolic pressure caused by diastolic dysfunction and dynamic LV outflow obstruction.

a. Events that accelerate heart rate, decrease preload, shorten diastolic filling time, increase LV outflow obstruction (i.e., exercise and tachyarrhythmias), or worsen compliance (i.e., ischemia) exacerbate these symptoms.

b. Between 5% and 10% of patients with HCM progress to severe LV systolic dysfunction, characterized by progressive LV wall thinning and cavity enlargement.

2. **Myocardial ischemia.** Myocardial ischemia occurs in obstructive and nonobstructive HCM.

a. The **clinical** presentation is similar to that of ischemic syndromes in persons without HCM. Patients with HCM may have abnormal electrocardiograms (ECGs) at baseline (e.g., inferior q-waves, T-wave inversions) with changes which can be seen in ischemic syndromes. Nuclear stress testing (thallium perfusion or positron emission tomography) has shown that patients with HCM may have reversible or fixed perfusion defects in the absence of epicardial coronary artery disease.

b. The incidence of concomitant atherosclerotic coronary artery disease is estimated to be ~20%. Thus, **mismatch of supply and demand** because of thickened vessels and small vessel disease from increased collagen deposition in the intima and media is considered to be the most likely pathophysiology of ischemia. Contributing factors include the following:

TABLE 10.1 Differential Diagnosis of Left Ventricular Wall Thickening

Long-standing hypertension
Athlete's heart
Aortic stenosis
Amyloidosis
Mitochondrial disease
Fabry disease
Friedreich ataxia
Danon disease
Noonan syndrome
Pompe disease

1. **(1)** Small vessel coronary disease with decreased vasodilator capacity
2. **(2)** Elevated myocardial wall tension as a consequence of delayed diastolic relaxation time and obstruction to LV outflow
3. **(3)** Decreased capillary-to-myocardial fiber ratio
4. **(4)** Decreased coronary perfusion pressure

3. **Syncope and presyncope** are usually a consequence of diminished cerebral perfusion caused by inadequate cardiac output. These episodes are commonly associated with exertion or cardiac arrhythmia.

4. **Sudden cardiac death (SCD).** Risk of SCD is low and <1% per year.

a. HCM is the most common cause of SCD in children and young adults (age < 30 years). Although risk extends into mid-life, rates are lower even with significant risk factors (see Section VI.C.4.b). **Patients with SCD often have no or minimal symptoms prior.** Approximately 60% of deaths occur during periods of inactivity; the remaining deaths occur after vigorous physical exertion.

b. SCD events are generally accepted to be due to sustained ventricular tachyarrhythmias. Proposed arrhythmogenic mechanisms include myocardial disarray and fibrosis, silent ischemia associated with microvascular coronary artery disease, and high sympathetic drive.

III. PHYSICAL EXAMINATION

A. Inspection of the jugular venous system may reveal a prominent *a*-wave that indicates hypertrophy and lack of compliance of the right ventricle. A precordial heave, representing right ventricular (RV) strain, can be found in persons with concomitant pulmonary hypertension.

B. Palpation

1. The **apical precordial pulse is usually laterally displaced and diffuse**. LVH may cause a presystolic apical impulse or palpable fourth heart sound (S_4). A three-component apical impulse may occur, with the third impulse resulting from a late systolic bulge of the left ventricle.
2. The carotid pulse has been classically described as bifid. This **rapid carotid upstroke followed by a second peak** is caused by a hyperdynamic left ventricle.

C. Auscultation

1. S_1 (first heart sound) is usually normal and is preceded by S_4.
2. S_2 (second heart sound) can be normal or paradoxically split as a result of the prolonged ejection time of patients with severe outflow obstruction.

TABLE 10.2 Effects of Maneuvers or Pharmacologic Intervention to Differentiate Murmur of Hyp Aortic Stenosis

Maneuver	Physiologic Effect
Valsalva and standing	Decreases VR, SVR, and CO
Squat and handgrip	Increases VR, SVR, and CO
Amyl nitrite	Increases VR; Decreases SVR and LV volume
Phenylephrine	Increases SVR and VR
Extrasystole	Decreases LV volume
Post-Valsalva release	Increases LV volume

3. AS, aortic stenosis; CO, cardiac output; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MR, mitral regurgitation; SVR, systemic vascular resistance; VR, venous return; ↓, decrease; ↑, increase.

4. The **harsh, crescendo–decrescendo systolic murmur** associated with HCM is best heard at the left sternal border. It radiates to the lower sternal border but not to the neck vessels or axilla.

a. The intensity and duration of the murmur vary with maneuvers which affect preload and afterload which can be used to differentiate it from other systolic murmurs (Table 10.2). During periods of increased venous return, the murmur is of shorter duration and is less intense. In the underfilled ventricle and during periods of increased contractility, the murmur is harsh and of a longer duration.

1. **(1)** The **concomitant murmur of mitral insufficiency** can be differentiated because of its holosystolic, blowing quality that radiates to the axilla.
2. **(2)** A soft, early, decrescendo, **diastolic murmur of aortic insufficiency** is found in ~10% of patients with HCM.

IV. Genetic aspects of HCM. HCM is caused by genetic mutations of sarcomere genes **typically inherited in an autosomal dominant manner**. To date, HCM has been linked to over 1,400 different mutations in at least 11 genes (Table 10.3); however, not all

mutations have the same evidence for pathogenicity, and a probable disease-causing mutation is identified in ~50% of cases currently. Of patients with positive genetic testing, mutations are most commonly found in the genes for **β-myosin heavy chain (MYH7) and myosin-binding protein C (MBPC3)**.

TABLE 10.3 Molecular Genetics of Hypertrophic Cardiomyopathy

Gene	Protein
Thick Filament	
MYH7	β-Myosin heavy chain
MYL2	Regulatory myosin light chain
MYL3	Essential myosin light chain
Thin Filament	
TNNT2	Cardiac troponin T
TNNI3	Cardiac troponin I
TPM1	α-Tropomyosin
ACTC1	α-Cardiac actin
Intermediate Filament	
MYBPC3	Myosin-binding protein C

V. HCM genotype does not necessarily imply that subjects will have the phenotypic traits of HCM because variable penetrance exists, and environmental factors and modifier genes affect whether a particular subject will manifest HCM phenotypically. Current guidelines recommend genetic counseling for patients with known HCM and screening with or without genetic testing for first-degree relatives of patients with HCM. It is reasonable to perform genetic testing in the index patient with HCM to aid in identifying first-degree relatives at risk for HCM. Patients who are genotype-positive, phenotype-negative should undergo periodic screening based on age and clinical status (see Section VII.E).

VI. It is uncertain whether patients with positive genetic testing for a pathogenic mutation have an increased risk for heart failure or SCD.

VII. DIAGNOSTIC TESTING

A. Electrocardiogram. Although most patients have electrocardiographic evidence of disease, there are no specific changes that are pathognomonic for HCM. Common electrocardiographic findings in HCM are listed in Table 10.4. These abnormalities do not correlate with disease severity.

B. Echocardiography is the preferred diagnostic method because of its high sensitivity and low-risk profile. It allows characterization of the site and mechanism of obstruction. Careful assessment for conditions that cause increased wall thickness (aortic or subaortic stenosis, hypertension, infiltrative diseases, etc.) should also be performed.

1. **M-mode and two-dimensional** echocardiographic findings in HCM are listed in Table 10.5. Close evaluation of the extent of hypertrophy should be performed given the role of septal thickness in risk stratification for SCD.

TABLE 10.4 Electrocardiographic Findings in Hypertrophic Cardiomyopathy

Evidence of right and left atrial enlargement
Q-waves in the inferolateral leads
Voltage criteria for large negative precordial T-waves (associated with Yamaguchi or apical HCM)
Left-axis deviation
Short PR interval with slurred upstroke

2. HCM, hypertrophic cardiomyopathy.

TABLE 10.5 Two-Dimensional, M-Mode, and Doppler Echocardiographic Findings in Hypertrophic

Maximal left ventricular diastolic wall thickness >15 mm
Asymmetric left ventricular hypertrophy (septal > posterior wall thickness)
Systolic anterior motion of the mitral valve
Small left ventricular cavity
Resting gradient > 30 mm Hg
Provocable gradients > 50 mm Hg
Septal immobility
Normal or increased motion of the posterior wall
Premature closure of the aortic valve
Reduced rate of closure of the mitral valve in mid-diastole
Mitral valve prolapse with regurgitation

3. **Doppler echocardiography** enables recognition and quantification of dynamic LVOT obstruction as well as the response to various maneuvers.

a. Approximately one-fourth of patients with HCM have a resting pressure gradient between the body and LVOT; approximately half of the patients with normal LVOT gradients at rest will have provocable gradients.

b. The **diagnosis of HCM with obstruction** is based on resting peak instantaneous gradient >30 mm Hg. These gradients correlate directly with the time of onset and duration of contact between the mitral leaflet and the septum, as occurs during systolic anterior motion (SAM) of the mitral leaflet. The earlier and longer the contact occurs, the higher the pressure gradient is.

1. **(1)** Inducing obstruction and, therefore, gradients, in patients believed to have latent obstruction, can be accomplished with substances (e.g., amyl nitrite) or maneuvers (e.g., Valsalva maneuver and exercise) that decrease LV preload or increase contractility. The use of dobutamine is not recommended because it can provoke increased LVOT gradients in normal patients.

c.Recognition of mitral regurgitation (MR)

1. **(1)** Approximately **60% of patients with HCM have structural abnormalities of the mitral valve**, including increased leaflet area, elongation of leaflets, and anomalous insertion of papillary muscles directly into the anterior mitral leaflet.
2. **(2)** When there is no leaflet abnormality, the degree of MR is directly related to the severity of obstruction and lack of leaflet coaptation.

C.Exercise stress testing. Exercise stress echocardiography testing provides significant information regarding functional capacity, exercise-induced symptoms, and prognosis.

1. Quantification of patient functional capacity
2. Determination of presence of provocable LVOT obstruction and correlation with symptoms
3. Prognostication with blood pressure, heart rate, and rhythm response to exercise

D.Magnetic resonance imaging (MRI). Advantages of MRI in the evaluation of HCM include excellent resolution, lack of radiation, inherent contrast, three-dimensional imaging, and tissue characterization. Disadvantages are cost, length of study, and exclusion of patients with contraindications to exposure to magnetism, such as patients with implantable cardioverter–defibrillators (ICDs) or pacemakers.

1. Detection of **LVH** missed by echocardiography, specifically in the anterolateral and basal LV free walls
2. **Myocardial scar**, often found in patients with HCM, can be detected as **delayed hyperenhancement with gadolinium contrast MRI**. More recent studies suggest that the amount of hyperenhancement may be a predictor of SCD.
3. Improved identification of MR, SAM, abnormal papillary muscles, and diastolic dysfunction
4. Differentiation from alternative causes of increased LV wall thickness such as Fabry disease and amyloidosis.

E.Cardiac catheterization is most commonly used for defining coronary anatomy before procedures for septal reduction or MR, or for the evaluation of ischemic symptoms. Invasive hemodynamic assessment may also be used to assess for provocable obstruction for symptomatic patients without obstruction on noninvasive imaging. The characteristic findings of HCM during hemodynamic assessment are listed in Table 10.6 and illustrated in Figure 10.1.

1. Patients with normal epicardial coronary arteries may have myocardial bridges, phasic narrowing during systole, reduced coronary flow reserve, or systolic reversal of flow in the epicardial vessels.
2. **Left ventriculography** usually reveals a hypertrophied ventricle, prominent septal bulge, nearly complete obliteration of the ventricular cavity during systole, SAM, and MR. The **spadelike** appearance of the ventricular cavity is confined to ventricles with **apical involvement.**

VIII.MANAGEMENT STRATEGIES

A.Goals of management. Management of patients with HCM is focused on two major goals: (1) treating symptoms of systolic and/or diastolic heart failure, arrhythmias, angina, and presyncope or syncope and (2) preventing sudden death. The etiologies of symptoms in HCM are multifactorial and include LVOT obstruction, diastolic dysfunction, ischemia, arrhythmias, and MR. Consequently, therapy varies among patients and is designed to target individual symptoms and mechanisms. See Figure 10.2 for a simplified treatment algorithm.

TABLE 10.6 Hemodynamic Findings during Cardiac Catheterization
Subaortic or mid-ventricular outflow gradient on catheter pullback
Spike-and-dome pattern of aortic pressure tracing[a]
Elevated right and left ventricular end-diastolic pressures
Elevated pulmonary capillary wedge pressure
Increased V-wave on wedge tracing[b]
Elevated pulmonary arterial pressure

B. [a] A consequence of outlet obstruction.

C. [b] May result from either mitral regurgitation or elevated left atrial pressure.

D. **FIGURE 10.1** Severe increase in the left ventricular (LV) aortic gradient in the beat after a premature ventricular contraction (PVC) (Brockenbrough–Braunwald–Morrow sign) because of an increase in contractility and decrease in afterload during the post-PVC beat.

E. Medical therapy. General principles for medical therapy focus on medications which have negative inotropic and chronotropic properties and thus improve diastolic filling and decrease myocardial demand. Care should be taken to avoid medications which decrease preload because this can worsen LVOT obstruction.

1. α-Blockers are considered first-line therapy for both obstructive and nonobstructive HCM. Despite the fact that they have not been shown to decrease mortality, they do improve symptoms and exercise tolerance. β-Blockers with additional α-blocking properties, such as carvedilol and labetalol, should be avoided because of their additional vasodilatory properties.

a. The mechanism of action of β-blockers is inhibition of sympathetic stimulation brought about by the negative inotropic and chronotropic properties of the drugs. β-Blockers diminish myocardial oxygen requirements and augment diastolic filling, which mitigate angina and the detrimental effects of LV outflow obstruction, respectively.

2. Calcium channel blockers (CCBs) are considered to be second-line agents that are also effective in reducing the common symptoms of HCM in patients who are unresponsive or intolerant to treatment with β-blockers.

a. CCBs have a negative inotropic effect and reduce the heart rate and blood pressure. They may also have beneficial effects on diastolic function by improving rapid diastolic filling, although possibly at the expense of higher LV end-diastolic pressures. The beneficial effects seem to be limited to the nondihydropyridines **verapamil** and **diltiazem**. Dihydropyridine CCBs (nifedipine, amlodipine) should be avoided because of their significant vasodilatory effects (see below).

FIGURE 10.2 Management algorithm for hypertrophy cardiomyopathy. DDD, dual pacing for both chambers, dual-chamber activity sensing, and dual response; HCM, hypertrophic cardiomyopathy. (Adapted from Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. *Circulation*. 2011;124:e783–e831. Reprinted with permission from Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic

cardiomyopathy. *Circulation*. 2011;124(24):e783–e831. Copyright © 2011 American Heart Association, Inc.)

b. Nondihydropyridines can have unpredictable vasodilatory effects and should be administered cautiously to patients with considerable outlet obstruction and elevated pulmonary pressures.

3. **Disopyramide**, a class Ia antiarrhythmic agent, may be an effective alternative or adjunct to β-blocker and CCB therapy. Its strong negative inotropic qualities coupled with its ability to suppress ventricular and supraventricular arrhythmias make it an effective treatment when marked outflow obstruction or arrhythmias are manifested. Potential disadvantages are anticholinergic properties, accumulation in patients with hepatic or renal dysfunction, the possibility of augmenting atrioventricular (AV) nodal conduction in the presence of atrial fibrillation, and waning hemodynamic effects with time. It is because of these significant side effects that disopyramide is typically used in a very symptomatic patient when a more definitive procedure is being planned, such as surgical myectomy or alcohol septal ablation. It is not considered to be a long-term treatment for HCM.

4. **Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers** have an unclear role in HCM. Previously they were avoided because of the potential for peripheral vasodilation, and a recent randomized control trial demonstrated no benefit with losartan versus placebo in slowing progression of disease.

5. **Diuretics** should be used cautiously for symptom reduction in the setting of pulmonary edema because high filling pressures are often necessary because of the stiff ventricle, and overdiuresis may reduce LV size and increase obstruction.

6. **Digoxin** should be avoided because of potential worsening of the LVOT obstruction secondary to the positive inotropic effect.

7. **Phenylephrine**, a pure α-agonist that causes vasoconstriction, can be considered in cases of refractory hypotension unresponsive to intravenous fluids. Pressors with positive inotropic effects, such as norepinephrine, dopamine, and dobutamine, can provoke LVOT obstruction and should be avoided.

F. **Nonpharmacologic treatment** is typically reserved for those patients with symptoms despite optimal medical therapy. Patients with symptomatic obstruction and resting or latent gradient of ≥50 mm Hg despite optimal medical treatment are candidates for septal myectomy or alcohol septal ablation. Younger patients with gradients >75 mm Hg and low surgical risk should be considered for septal myectomy even in the absence of symptoms. With severe symptomatic, nonobstructive HCM, cardiac transplantation remains the only option.

1. **Septal myectomy** of HCM has been performed for more than 50 years and is the **procedure of choice for patients with symptomatic obstructive HCM despite maximal medical therapy.**

a. When performed by an experienced surgeon, septal myectomy is considered the most definitive treatment and is associated with a mortality rate of <1% to 2%. It is effective in improving symptoms, resting LVOT gradients, MR, and filling pressures. After myectomy, survival is comparable to the general population when matched by age and gender.

b. Concomitant surgery to address obstruction because of abnormal papillary muscle attachment, mitral valve regurgitation not improved following septal myectomy, or atrial fibrillation with a maze procedure may be performed allowing for a more comprehensive approach compared with alcohol septal ablation.

2. **Alcohol septal ablation**—essentially a controlled infarction of the septum—is an alternative to septal myectomy **generally used in patients who are not candidates for surgical myectomy**. There are no randomized control trials comparing myectomy and septal ablation.

a. **Technique.** In the cardiac catheterization laboratory, a guidewire is advanced through the left main trunk to probe the first or second septal perforator or both. An angioplasty catheter is placed in the proximal portion of the septal branch for vessel isolation. Ultrasonic contrast agents are infused in the cannulated perforator to define the area at risk for infarction. Infusion of 1 to 4 mL of absolute alcohol causes infarction in the zone of septal myocardium served by the cannulated septal branch. In most centers, a temporary ventricular pacing catheter is placed into the RV apex before performing the ablation, in order to manage any transient conduction abnormalities.

b. **Results.** In the majority of patients, there is a marked immediate decrease in the LVOT gradient. This gradient response is thought to be triphasic: immediate reduction (because of stunning), early reappearance, and sustained fall by 3 months after the procedure (because of remodeling). Within this initial period, most patients attain satisfactory symptomatic relief. Risks of the procedure include high-grade AV block with subsequent pacemaker implantation, coronary dissection, large anterior wall myocardial infarction, pericarditis, and electrical instability of the scar that forms as a result of the infarction.

3. **Dual-chamber pacing** was previously used in hopes of alleviating symptoms by altering the timing of septal contraction; however, this was not shown to be beneficial in trials. Dual-chamber pacing should only be considered in patients with medically refractory symptoms who are not candidates for septal reduction therapy.

4. **Special management considerations**

a. **Atrial fibrillation** occurs in up to a third of patients with HCM and can worsen heart failure symptoms and increase risk of thromboembolic stroke. Loss of atrial systole and decreased diastolic filling times because of rapid ventricular rates can lead to acute hemodynamic decompensation and pulmonary edema because of LV diastolic dysfunction. Risk of stroke is ~0.8% per year and all patients with HCM-associated atrial fibrillation should be on anticoagulation therapy unless contraindicated.

1. **(1) Acute paroxysms** of atrial fibrillation are best managed with prompt cardioversion with transesophageal echocardiogram to exclude atrial thrombus. The 2014 ACC/AHA/HRS Guidelines for the Management of Patients with Atrial Fibrillation state that disopyramide and amiodarone are reasonable for maintenance of sinus rhythm, whereas it is uncertain whether other class III agents, such as dofetilide, sotalol, and dronedarone, should be used given the paucity of safety data. Some recommend reserving their use for patients with ICDs.
2. **(2) Chronic atrial fibrillation** may be well tolerated if the heart rate is controlled with β-blockers or calcium channel antagonists.
3. **(3) Maze or radiofrequency ablation.** For patients who do not tolerate atrial fibrillation and cannot be maintained in sinus rhythm with antiarrhythmic medications, catheter ablation, maze, or AV nodal ablation and implantation of a dual-chamber pacemaker may be an option.

b. **Risk stratification for sudden death** and subsequent ICD implantation for primary prevention of SCD in high-risk patients continues to be one of the more challenging aspects for the management of patients with HCM. Table 10.7 lists the established factors for risk stratification. Additional risk factors (e.g., scar burden as determined by late gadolinium contrast on MRI) continue to be evaluated.

1. **(1)** The decision to implant an ICD should be individualized by taking into consideration patient risk factors as well as age. The frequency of annual ICD-related complications in patients with HCM is 4%. Patients who are younger at the time of implantation are at higher lifetime risk for complications (e.g., infection, inappropriate ICD discharge) because of the longer length of device implantation.

TABLE 10.7 Risk Factors for Sudden Cardiac Death

Established Risk Markers for Secondary Prevention
Previous cardiac arrest
Sustained ventricular tachycardia
Established Risk Markers for Primary Prevention
Prolonged or repetitive episodes of nonsustained ventricular tachycardia on Holter monitor
Left ventricular wall thickness >30 mm
Family history of SCD in first-degree relative
Failure to increase blood pressure by ≥20 mm Hg with exercise
Syncope without other attributable cause
Risk Modifiers
Late gadolinium enhancement on cardiac MRI
Left ventricular apical aneurysm

magnetic resonance imaging; SCD, sudden cardiac death.

3. **(2)** Patients with a history of cardiac arrest and sustained ventricular arrhythmias should be strongly considered for an ICD. In this group, the annual rate of appropriate ICD discharge is ~10%.
4. **(3)** Selection of patients for ICD implantation as primary prevention based on one or more risk factors for SCD is difficult and must be individualized. In the primary prevention group, the annual rate of appropriate ICD discharge is about 4%. Current guidelines state that it is reasonable to consider ICD implantation in patients with a family history of SCD or multiple risk factors. The HCM Risk-SCD calculator was recently developed to estimate risk for SCD and has been validated in small population studies, although a larger validation study is ongoing.

IX.SPECIAL CONSIDERATIONS

A.Athlete's heart

1. **Differentiating HCM from hypertrophy of athletes.** Failure to diagnose HCM places an athlete at undue risk for sudden death whereas incorrect labeling of HCM often leads to irrational treatments, unnecessary fears, and inappropriate recommendations concerning exercise. Diagnostic uncertainty is greatest when maximal diastolic LV wall thickness exceeds the upper limit of normal (12 mm) but is less than the defined lower limit of expected hypertrophy (15 mm) for HCM and in the absence of SAM and LV outflow obstruction.

a. Characteristics that **substantiate the diagnosis of HCM** include unusual patterns of hypertrophy, an LV end-diastolic diameter of <45 mm, septal thickening >15 mm, left atrial enlargement, abnormal diastolic function, family history of HCM, and abnormal LV filling.

b. Findings more consistent with physiologic LVH in **an athlete** are LV end-diastolic diameter >45 mm, septal thickening <15 mm, left atrial size <4 cm, and a decrease in LV thickness with deconditioning.

c. Cardiometabolic stress testing can be useful to distinguish between patients with physiologic LVH and HCM. A peak VO_2 >50 mL/kg/min or >120% predicted maximum VO_2 differentiates athlete's heart from HCM.

d. Should differentiation still not be possible, the patient should stop training and over several months ventricular hypertrophy will typically regress if physiologic, but persist in HCM.

2. Participation in sports. HCM is the most common cause of sudden death in young athletes. The American College of Cardiology Bethesda Conference and European Society of Cardiology recommend prohibiting athletes with HCM from participating in competitive high school and college sports because of increased risk of SCD during intense exercise. These recommendations remain in force after medical or surgical intervention.

a. Athletes with HCM with or without obstruction who are <30 years should **not** participate in competitive, aerobically demanding sports.

b. Participation in recreational sports should take into consideration the intensity of the activity (with the resulting fluctuations in hemodynamics) and the danger to the individual should impaired consciousness occur.

B. Infective endocarditis (IE)

1. Prophylaxis. Guidelines on the prevention of IE published by the American Heart Association in 2007 question the practice of treating patients with HCM with antibiotics prior to dental procedures and recommend against it except in the setting of prior endocarditis. Given the catastrophic consequences of endocarditis in patients with HCM, routine antimicrobial prophylaxis for IE should be weighed on an individual basis.

C. Yamaguchi or apical HCM

1. Clinical presentation. Patients experience chest pain, dyspnea, fatigue, and, in rare instances, sudden death.

2. Prevalence. Within Japan, apical HCM constitutes 25% of all cases of HCM. Outside Japan, only 1% to 2% of cases are associated with isolated apical hypertrophy.

3. Diagnostic testing

a. An **ECG** reveals giant negative T-waves in the precordial leads and LVH (Fig. 10.3).

b. Echocardiographic findings include the following:

1. **(1)** Localized hypertrophy in the distal left ventricle beyond the origin of the chordae tendineae
2. **(2)** Wall thickness in the apical region of at least 15 mm or a ratio of maximal apical to posterobasal thickness >1.5
3. **(3)** Exclusion of hypertrophy in other parts of the ventricular wall
4. **(4)** No LVOT obstruction or gradient

c. MRI demonstrates localized hypertrophy to the cardiac apex. MRI is useful in the care of patients with poor echocardiographic windows.

d. Cardiac catheterization reveals a spadelike configuration of the LV cavity at end diastole and apical end-systolic LV cavity obliteration.

4. Prognosis is favorable compared with that associated with other forms of HCM.

5. Management. Therapeutic efforts are limited to management of diastolic dysfunction with β-blockers and calcium channel antagonists.

D. HCM among the elderly

1. **Clinical presentation.** In addition to the signs and symptoms of other forms of HCM, hypertension is more common with HCM in the elderly population.
2. **Incidence.** Although the incidence is unknown, HCM among the elderly is probably more common than expected.
3. **Genetic aspects.** Reports have suggested that the delayed expression of mutations in the gene for cardiac myosin-binding protein C may play an important role in HCM in the elderly.
4. **Echocardiographic findings** for elderly patients (65 years or older) are compared to findings for young patients (40 years or younger) as follows:

a. Common findings

1. **(1)** LVOT gradient, both provocable and at rest
2. **(2)** Asymmetric hypertrophy
3. **(3)** SAM of the mitral valve

FIGURE 10.3 Electrocardiogram (ECG) in an apical hypertrophic cardiomyopathy (HCM, Yamaguchi). The classic ECG for apical HCM has deep anteroapical T-wave inversions.

b. Differences pertaining to the elderly

1. **(1)** Less hypertrophy
2. **(2)** Less RV involvement
3. **(3)** Ovoid versus crescentic left ventricle
4. **(4)** Prominent septal bulge (i.e., sigmoid septum)
5. **(5)** More acute angle between the aorta and septum as the aorta uncoils with age

5. **Prognosis.** Favorable compared with patients who present at a younger age
6. **Management.** Similar to that of other HCM patients

E. Screening of family members

1. Serial 12-lead ECG and transthoracic echocardiogram are recommended **every 12 to 18 months in first-degree relatives** of HCM patients starting at age 12 during adolescence because of the propensity of HCM to worsen during growth spurts.
2. Because of the possibility of late-onset phenotypic expression, **screening of first-degree relatives should continue into middle age**, but the frequency of screening can be scaled back to a minimum of every 5 years once full growth has been obtained.
3. If genetic testing reveals a mutant HCM gene in the offspring, the high penetrance of the mutation imparts a >95% lifetime risk of developing clinical and/or phenotypic evidence of disease. These gene-positive offspring should continue with serial examinations.
4. First-degree relatives that are mutation negative have no risk of developing HCM and do not need further screening.

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CHAPTER 11

Myocarditis

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I. INTRODUCTION. Myocarditis is defined as an inflammatory infiltration of the myocardium with associated necrosis or degeneration, or both. The disease is also known as **inflammatory cardiomyopathy** (or myocarditis with cardiac dysfunction in the World Health Organization 1995 classification for cardiomyopathy). The incidence and prevalence of myocarditis are unclear; the syndrome is underdiagnosed because of the large number of asymptomatic cases. Myocarditis usually affects younger individuals; the median age of patients with lymphocytic myocarditis is 42 years.

A. Clinicopathologic classification of myocarditis is clinically oriented but not widely used.

1. **Fulminant myocarditis** (17%) usually has a distinct onset. It can result in either complete, spontaneous resolution or rapid deterioration and death due to severe cardiac compromise. Usually, there are multiple active foci of inflammatory infiltrate on histology with complete resolution.
2. **Acute myocarditis** (65% of myocarditis cases) has an indistinct onset, with moderate cardiovascular compromise and incomplete recovery, often resulting in cardiac dysfunction or subsequent death. Histologically, there are active or borderline inflammatory infiltrates that resolve completely over time.
3. **Chronic active myocarditis** (11% of myocarditis cases) has a presentation similar to that of acute myocarditis, but the chronic form usually progresses to only mild or moderate cardiac dysfunction, occasionally with restrictive physiology. Histologic examination often shows ongoing fibrosis, suggesting chronic inflammatory changes.
4. **Chronic persistent myocarditis** (7% of myocarditis cases) has an indistinct onset, with nonresolving active or borderline inflammatory infiltrates seen on histologic examination. Usually, there is no cardiovascular compromise.

B. Histologic classification of myocarditis, also called the Dallas classification (1986)

1. Initial biopsy

a. Myocarditis: myocardial necrosis or degeneration, or both, in the absence of significant coronary artery disease with adjacent inflammatory infiltrates or fibrosis, or both
b. Borderline myocarditis: inflammatory infiltrates too sparse or myocyte damage not apparent
c. No myocarditis: no inflammatory infiltrates or myocyte damage

2. Subsequent biopsy

a. Ongoing (persistent) myocarditis or fibrosis, or both
b. Resolving (healing) myocarditis or fibrosis, or both

c. Resolved (healed) myocarditis or fibrosis, or both

C. **World Health Organization (Marburg Criteria, 1996).** A minimum of 14 infiltrating leukocytes per mm (1), preferably T lymphocytes, and up to four macrophages may be included.

II. CLINICAL PRESENTATION

A. Signs and symptoms

1. Myocarditis can be **totally asymptomatic** or can manifest with **chest pain syndromes** ranging from mild persistent chest pain of acute myopericarditis (35% of cases) to severe symptoms that mimic acute myocardial infarction. Chest pain associated with coronary artery vasospasm may rarely occur in patients with myocarditis. Alternatively, chest pain may be more typical for pericarditis, suggesting pericardial involvement.
2. About 60% of patients may have antecedent arthralgias, malaise, fever, sweats, or chills consistent with viral infections (e.g., pharyngitis, tonsillitis, and upper respiratory tract infection) 1 to 2 weeks before onset.
3. The hallmark symptoms are those of **heart failure** (e.g., dyspnea, fatigue, and edema). In many patients who develop heart failure, fatigue and decreased exercise capacity are the initial manifestations. However, diffuse, severe myocarditis can progress rapidly and result in acute myocardial failure and cardiogenic shock. The diagnosis is usually presumptive, based on patient demographics and the clinical course (i.e., spontaneous recovery after supportive care).
4. In some instances, patients may present with **arrhythmia** in the form of syncope, palpitations caused by heart block (i.e., Stokes–Adams attack), ventricular tachyarrhythmia, or even sudden cardiac death. Sinus tachycardia is more frequent than serious atrial or ventricular arrhythmias. Palpitations secondary to premature atrial or ventricular extrasystoles are common.

B. **Physical findings.** Patients often present with signs of **acute decompensated heart failure**, including an S_3 (third heart sound) gallop, central and peripheral edema, jugular venous distention, and tachycardia (see Chapter 8). An audible pericardial friction rub may accompany concomitant myopericarditis. Specific findings in special cases are as follows:

1. **Sarcoid myocarditis:** lymphadenopathy, also with arrhythmias, and sarcoid involvement in other organs (up to 70%)
2. **Acute rheumatic fever** (usually affects the heart in 50% to 90%): associated signs such as erythema marginatum, polyarthralgia, chorea, and subcutaneous nodules **(i.e., Jones criteria)**
3. **Hypersensitive or eosinophilic myocarditis:** pruritic maculopapular rash and history of onset temporally related to initiation of potential culprit medications
4. **Giant cell myocarditis (GCM):** sustained ventricular tachycardia in rapidly progressive heart failure
5. **Peripartum cardiomyopathy:** heart failure developing in the last month of pregnancy or within 5 months after delivery (see Chapter 38)

III. LABORATORY EVALUATION

A. Inflammatory markers of myocarditis

1. **Complete blood count.** Leukocytosis is common (often lymphocytic), although the presence of eosinophilia may suggest hypersensitive (eosinophilic) myocarditis.
2. **Elevated acute phase reactants** such as erythrocyte sedimentation rates or ultrasensitive C-reactive protein are good monitors of clinical progression or response to therapy, but they have **low specificity** for myocarditis. Novel inflammatory markers under investigation include

tumor necrosis factor-α, interleukins, interferon-γ, serum-soluble Fas, and soluble Fas ligand levels. Elevation of these markers portends a worse prognosis.

3. **Serum viral antibody titers** are usually increased fourfold or more acutely and gradually fall during convalescence. However, measurement of viral antibody titers is rarely indicated.

4. **Anticardiac antibody titers.** Because of their low specificity, measurement of anticardiac antibody titers (against sarcolemma, myosin, laminin, ADP/ATP translocator, or β-adrenergic receptors) is not indicated (only 62% of myocarditis cases have titers ≥1:40).

B. Rheumatologic screening. Screening of antinuclear antibodies and rheumatoid factor is often indicated. Disease-specific testing is indicated if the following conditions are suspected:

1. Systemic lupus erythematosus: anti-dsDNA (reported positive anti-Ro/SSA and anti-La/SSB in lupus carditis in children)
2. Polymyositis: anti-Jo_1
3. Wegener granulomatosis: c-ANCA (antineutrophil cytoplasmic antibody)
4. Scleroderma: anti-Scl_{70}

C. Serum cardiac enzymes (markers of myonecrosis): creatinine kinase (myoglobin subfraction) is elevated in only 7.5% of patients with biopsy-proven myocarditis, whereas the cardiac **troponin I or T is elevated in at least 50% of patients** with biopsy-proven myocarditis (89% to 94% specificity and 34% to 53% sensitivity).

IV. DIAGNOSTIC TESTING

A. Electrocardiogram. The electrocardiogram often reveals sinus tachycardia, although the presence of nonspecific ST-segment and T-wave abnormalities may represent focal or global ischemia. Occasionally, the changes in electrocardiogram are suggestive of an acute myocardial infarction and may include ST-segment elevation. Pericarditis can accompany myocarditis and is often manifested in pericarditis like changes seen on electrocardiography. The sensitivity of the electrocardiogram for myocarditis is low (47%). In some cases, fascicular block or atrioventricular conduction disturbances and ventricular tachyarrhythmia may be hemodynamically significant.

B. Echocardiogram. A complete echocardiogram is standard procedure for patients with suspected myocarditis in order to exclude alternative causes of heart failure, detect the presence of intracardiac thrombi and associated valvular disease, and quantify the degree of left ventricular (LV) dysfunction to monitor response to therapy.

1. Occasionally, focal wall motion abnormalities and presence of pericardial fluid may prompt further workup or intervention.
2. Fulminant myocarditis is often characterized by near-normal diastolic dimensions and increased septal wall thickness, whereas acute myocarditis often has increased diastolic dimensions but normal septal wall thickness.
3. In a series of 23 patients with biopsy-proven myocarditis, significant reduction in right ventricular function was a powerful predictor of death or the need for cardiac transplantation.

C. Other imaging modalities

1. **Antimyosin scintigraphy (indium III monoclonal antimyosin antibody)** provides identification of myocardial inflammation, with a high sensitivity (91% to 100%) and negative predictive value (93% to 100%) but low specificity (28% to 33%).
2. **Gallium scanning** identifies severe myocardial cellular infiltration with high specificity (98%) but low sensitivity (36%).

3.Gadolinium-enhanced magnetic resonance imaging (MRI) is being used more frequently for diagnosis based on several small observational studies that have found up to 100% sensitivity and specificity depending on the protocol. In one study, MRI was also used for guiding biopsy to areas of focal increased uptake of gadolinium in patients with clinically suspected myocarditis with significantly higher diagnostic yield compared with those who did not have enhancing areas with which to guide the bioptome.

D.Coronary angiography. Cardiac angiography is often indicated to rule out coronary artery disease as the cause of new-onset heart failure, because the clinical presentation of myocarditis may mimic myocardial infarction (i.e., pseudoinfarct pattern), especially if there are focal wall motion abnormalities and localizing electrocardiographic changes.

V.ETIOLOGY.

Up to 50% of all cases may not have a clear underlying cause (i.e., idiopathic cases).

A.Infective causes (Table 11.1)

1.Viral myocarditis. Cardiotropic viruses such as enteroviruses (specifically, the coxsackie group B and echoviruses) may cause direct cardiotoxic injuries, cytokine activation, cytoskeletal damage, and autoimmune responses. However, data suggest that the incidence of myocarditis after infection is lower than previously projected. Viral myocarditis is often considered when accompanied by a clinical picture of recent febrile illness, often with prominent myalgias, followed by rapid onset of cardiac symptoms. However, direct proof is lacking (and often unnecessary), and many cases of idiopathic dilated cardiomyopathies have been attributed to antecedent viral myocarditis. Antiviral therapies have not proved to be useful.

TABLE 11.1 Causes of Myocarditis

Cause	Examples
	Infectious Causes
Viruses	Enteroviruses, coxsackievirus A and B, echovirus, influenza virus, poliovirus, he rubella, rubeola, hepatitis B or C virus, human immunodeficiency virus, Epstein parvovirus B19
Rickettsia	Rocky Mountain spotted fever
Fungi	Cryptococcosis, aspergillosis, coccidioidomycosis, and histoplasmosis
Protozoa	*Trypanosoma cruzi* (Chagas disease) and *Toxoplasmosis gondii*
Helminths	Trichinosis and schistosomiasis
Bacteria	*Legionella, Clostridium*, streptococci, staphylococci, *Salmonella*, and *Shigella*
Spirochetes	*Borrelia burgdorferi* (Lyme disease)
	Noninfectious Causes

TABLE 11.1 Causes of Myocarditis

Hypersensitive reaction	Eosinophilic myocarditis
Cardiotoxic drugs	Catecholamines, amphetamines, cocaine, chemotherapeutic drugs (e.g., anthrac cyclophosphamide, interleukin-2, trastuzumab [Herceptin]), and smallpox vaccir
Collagen vascular diseases	Systemic lupus erythematosus (i.e., lupus carditis), Wegener granulomatos dermatomyositis or polymyositis, and scleroderma
Systemic illnesses	Sarcoidosis, giant cell myocarditis, Kawasaki disease, large-vessel vasculitis (e.g., arteritis), and inflammatory bowel diseases (e.g., ulcerative colitis and Crohn dis
Acute rheumatic fever	
Bites and stings	Venoms of scorpions, snakes, wasps, and black widow spiders
Chemicals	Hydrocarbons, carbon monoxide, thallium, lead, arsenic, and cobalt
Physical injury	Irradiation, heat stroke, and hypothermia
Childbirth	Peripartum cardiomyopathy
Alloantigens	Posttransplantation cellular rejection

2. Chagas disease. Cardiomyopathy caused by *Trypanosoma cruzi* in South and Central America, particularly in persons aged 30 to 50 years. It is estimated that 16 to 18 million persons are infected with *T. cruzi* in Latin America. Cardiac involvement usually appears decades after initial treatment and is the leading cause of death of persons aged 30 to 50 years in the endemic areas.

a. Diagnosis

1. **(1)** Serologic test results should be positive for at least two types of tests (i.e., indirect immunofluorescence, indirect hemagglutination, complement fixation, immunoenzymatic, and radioimmune assays).
2. **(2)** Cardiac lesions diagnosed by in situ polymerase chain reaction methods of analyzing biopsies
3. **(3)** Typical electrocardiographic changes include right bundle branch block with left anterior hemiblock, premature ventricular complexes, T-wave inversions, abnormal Q waves, variable atrioventricular blocks, low QRS voltage, and sick sinus syndrome.
4. **(4)** Echocardiographic findings include LV aneurysm with or without thrombi, posterior basal akinesis or hypokinesis with preserved septal contraction, and diastolic dysfunction.

b. Clinical presentation

1. **(1)** The acute and subacute phases (i.e., 4 to 8 weeks of acute inflammation) consist, for the most part, of local inflammation at the parasite entry site and flulike symptoms. Occasionally hepatosplenomegaly and lymphadenopathy occur, but concomitant meningoencephalitis is rare. These manifestations often result from pathogen-induced cytotoxicity and inflammatory responses. More than 90% of cases resolve in 4 to 8 weeks without therapy.

2. **(2)** The chronic phase (up to 10 to 30 years after acute infection) manifests with symptoms of palpitations, syncope, chest pain, and, subsequently, heart failure. Approximately 5% to 10% of affected patients may develop direct acute-to-chronic progression.

1. **(a)** Heart failure (predominantly right sided in advanced stages) may develop in 25% to 30% of those affected.
2. **(b)** Cerebral or pulmonary thromboembolism may occur in 10% to 15% of those affected.
3. **(c)** Concomitant megaesophagus or megacolon may develop.
4. **(d)** Apical LV aneurysm and apical fibrosis may develop.

3. **(3)** Chagas disease is highly arrhythmogenic.

1. **(a)** Frequent, complex ectopic beats and ventricular tachyarrhythmia occur in 40% to 90% of affected patients, with sudden cardiac death occurring in 55% to 65%.
2. **(b)** Bundle branch block occurs in 50% of affected patients, and bradyarrhythmia with high-grade atrioventricular block occurs in 7% to 8%.
3. **(c)** Atrial fibrillation develops in 7% to 10% of affected patients.

c. Antibiotic therapy aims to reduce parasitemia and prevent complications.

1. **(1)** Benznidazole (5 to 10 mg/kg/d q12h for 60 days) or
2. **(2)** Nifurtimox (8 to 10 mg/kg po q24h for 90 to 120 days)

3. Human immunodeficiency virus (HIV)–related cardiomyopathy. HIV disease has been recognized as an important cause of dilated cardiomyopathy, with an estimated incidence of 1.6%. HIV type 1 (HIV-1) virions appear to infect myocardial cells in patchy distributions, leading to cytokine activation and progressive tissue damage. Cardiac autoimmunity, nutritional deficiencies, and drug toxicities (i.e., mitochondrial damage from zidovudine and vasculitis or coronary artery disease associated with highly active antiretroviral therapy regimens) are possible contributing causes. In addition, other known viral pathogens, including cytomegalovirus, Epstein–Barr virus, and coxsackievirus B, have been isolated from endomyocardial biopsy (EMB) specimens of HIV-positive patients with myocarditis in conjunction with HIV nucleic acid sequences, suggesting that opportunistic viral infections may play an important role in the pathogenesis of this type of cardiomyopathy.

B. Peripartum cardiomyopathy (see Chapter 38)

C. GCM (i.e., pernicious myocarditis, Fiedler myocarditis, granulomatous myocarditis, or idiopathic interstitial myocarditis): This is a rare disorder with an unclear origin. The **hallmark feature is the presence of fused, multinucleated (>20 nuclei) epithelioid giant cells of histocytic origin within a diffuse, intramyocardial inflammatory infiltrate with lymphocytes**.

1. GCM often presents with an **aggressive clinical course**, with progression over days to weeks. Rapidly progressive heart failure is the presentation in 75% of affected patients. Sustained ventricular tachyarrhythmia occurs in 29% of patients with GCM and atrioventricular block occurs in 50%.

2. The prognosis is **dismal without therapy**, but the disease is often refractory to standard medical therapy, with a 1-year mortality rate of up to 80% (median survival of 3 to 5 months from symptom onset).

3. Small observational series have suggested potential benefits of immunosuppressive therapy, and a randomized, prospective multicenter study is ongoing. Consideration for **early cardiac transplantation** is appropriate (71% 5-year survival after successful transplantation). Often, mechanical support may be required as a temporary bridge to recovery or transplantation. A

20% to 25% rate of histologic recurrence in surveillance EMBs has been observed after transplantation.

D. Hypersensitive reaction (i.e., eosinophilic myocarditis). Eosinophilic endomyocardial disease (i.e., Loeffler endomyocardial fibrosis, see Chapter 9) occurs as a major complication of idiopathic hypereosinophilic syndrome as a result of direct toxic damage caused by eosinophil granule proteins within the heart. Drug-induced eosinophilic myocarditis is independent of cumulative dose and duration of therapy.

The absence of peripheral eosinophilia does not rule out eosinophilic myocarditis. Although observational series suggest potential clinical benefits of corticosteroid therapy, the best strategy is to remove the causative agent when known.

1. Medications that may cause eosinophilic myocarditis include the following:

a. Antibiotics (e.g., ampicillin, chloramphenicol, tetracycline, and sulfisoxazole)
b. Diuretics (e.g., hydrochlorothiazide and spironolactone)
c. Anticonvulsants (e.g., phenytoin and carbamazepine)
d. Other drugs (e.g., lithium, clozapine, and indomethacin)
e. Tetanus toxoid

2. Collagen vascular diseases such as Wegener granulomatosis or Churg–Strauss syndrome (i.e., allergic granulomatosis and vasculitis) may also lead to eosinophilic myocarditis.
3. Other causes include parasitic infection, drug hypersensitivity, and cellular rejection after cardiac transplantation, as well as postvaccinia myocarditis after smallpox vaccination.

E. Systemic autoimmune disorders with myocarditis. Although the histologic appearance of myocarditis occurring as part of sarcoidosis, systemic lupus erythematosus, or polymyositis is similar to that seen in isolated myocarditis, the natural history is different. **Systemic causes of myocarditis often respond poorly to medical therapy and cardiac transplantation**, and their prognoses are often unfavorable. However, small retrospective surveys and case series have identified a significant decrease in mortality and improved clinical course among cardiac sarcoid patients treated with corticosteroids and other immunosuppression strategies.

VI. PROGNOSIS.

On the basis of population studies, adults with myocarditis may present with few symptoms or with an acute toxic state of cardiogenic shock or frank heart failure (i.e., fulminant myocarditis). However, adults may present with heart failure years after the initial index event of myocarditis (up to 12.8% of patients with idiopathic dilated cardiomyopathy had presumed prior myocarditis in one case series).

A. Natural history and sequelae of myocarditis. The outlook is poor in the acute phase, regardless of clinicopathologic classification, but those surviving the acute phase have a more favorable prognosis (except for those with chronic active myocarditis).

1. Many patients may have **full spontaneous clinical recovery**, even after weeks of mechanical support (e.g., intra-aortic balloon counterpulsation and mechanical assist devices).
2. In the Myocarditis Treatment Trial, the 1-year mortality rate was 20%, and the 4-year mortality rate was 56%.
3. In-hospital case series point to an 11-year survival rate of 93% for patients with fulminant myocarditis and 45% for nonfulminant myocarditis.
4. Evolution to dilated cardiomyopathy

a. Up to one-half of patients with myocarditis develop subsequent cardiomyopathy over a range of 3 months to 13 years.

b. Histologic evidence of myocarditis is seen in 4% to 10% of EMBs of patients with idiopathic dilated cardiomyopathy.

5. Severe heart block requiring permanent pacemaker placement occurs in 1% of patients.

B. Predictors for morbidity and mortality

1. Unfavorable factors for survival include extremes of **age** (i.e., very old or very young), **electrocardiographic abnormalities** (e.g., QRS alterations, atrial fibrillation, and low voltages), **syncope**, and **specific diagnoses** (e.g., peripartum cardiomyopathy and GCM).
2. Favorable factors for survival include normal ventricular function, shorter clinical history, and fulminant presentation at onset.

VII. TREATMENT

A. Heart failure management

1. Patients who present with myocarditis with acute dilated cardiomyopathy should be treated according to the current American Heart Association, the American College of Cardiology, the European Society of Cardiology, and the Heart Failure Society of America (HFSA) guidelines. Standard heart failure therapy consists of diuretics, angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists. Studies have not been done to determine when and how to discontinue standard heart failure therapy in patients who recover LV function.
2. Because of its proarrhythmic properties in animal models, digoxin should be avoided.
3. Anticoagulation to prevent thromboembolic events is usually recommended in patients with apical aneurysm with thrombus (e.g., Chagas disease, atrial fibrillation, and prior embolic episodes).
4. Inotropic therapy is reserved for severe hemodynamic compromise, particularly in fulminant myocarditis.
5. Aggressive support with mechanical and surgical intervention is often indicated (see Chapters 8 and 12).

a. Intra-aortic balloon counterpulsation for hemodynamic support and afterload reduction

b. Mechanical assistive devices (LV assist device)

c. Extracorporeal membrane oxygenation

6. Early consideration for cardiac transplantation should be given, especially for patients with progressive, biopsy-proven GCM or peripartum cardiomyopathy. However, patients with myocarditis have increased rates of rejection and reduced survival after heart transplantation compared with those without myocarditis, and recurrent disease may affect the allograft.

B. Exercise restriction

1. There is a theoretical increased risk of myocardial inflammation and necrosis, cardiac remodeling, and death, as shown in animal models.
2. Patients are usually advised to abstain from vigorous exercise for up to 6 months or longer after the onset of symptoms. The length of activity restriction can be based on recovery of LV function.

C. Arrhythmia management

1. Antiarrhythmics provide first-line treatment using standard therapy such as β-blockers, amiodarone, and sotalol.
2. Implantable cardioverter–defibrillators are used for patients stabilized in the chronic phase with persistently low ejection fraction (EF) and for those with malignant arrhythmias that are refractory to medical therapy.
3. Permanent pacemakers are used for heart block or bradyarrhythmia.

D. Follow-up

1. Clinical follow-up should be close because persistent chronic inflammation may lead to dilated cardiomyopathy. Initially, 1- to 3-month intervals are used for drug and physical activity titration.
2. Serial echocardiographic assessment of ventricular structure and function is often performed, although there is no agreement regarding the frequency of echocardiographic assessment after myocarditis.

E. Immunosuppressive therapy is reserved for refractory disease or biopsy-proven GCM. No benefits have been established for antiviral regimens or nonsteroidal anti-inflammatory agents (see Section **VIII.B**). The most recent HFSA guidelines do not recommend routine use of immunosuppressive therapy in patients with myocarditis. More work is needed to identify patient cohorts who will benefit from tailored antiviral and immunosuppressive therapy.

VIII. CONTROVERSIES IN MYOCARDITIS

A. Endomyocardial biopsy

1. Routine EMB confirmation of myocarditis is unnecessary

a. EMB can be considered in those patients with a **rapid deterioration in cardiac function** of unknown etiology who do not respond to standard medical therapy.

b. Incidence of biopsy-proven myocarditis in recent-onset, unexplained heart failure can be as low as 8% to 10%. Concerns have emerged that this is caused by low sensitivity of the Dallas criteria, and several recent trials of immunosuppressive therapy have utilized supplemental pathologic criteria to assess myocarditis, including upregulation of human leukocyte antigen, presence of virus, and anticardiac antibodies.

c. **False-negative rates are high** (50% even in four or five biopsies) because of the small number of lymphocytes and difficulties in distinguishing cell types, with wide interobserver variability.

2. However, EMB may be considered in patients with the following conditions in which a diagnostic biopsy may provide information on prognosis and/or therapeutic possibilities (see Table 11.2):

a. Rapidly progressive heart failure symptoms despite conventional therapy or new-onset frequent ventricular tachyarrhythmia or conduction disturbances

b. Suspected specific causes of myocarditis (e.g., GCM, eosinophilic myocarditis, cardiac sarcoidosis, and vaccinia myocarditis)

3. Although specificity is high (98%), sensitivity has been found in some series to be as low as 10% to 22%. It increases with multiple biopsies, but postmortem examinations have found that more than 17 specimens were needed to make the diagnosis with 80% sensitivity in proven myocarditis cases.

TABLE 11.2 Relevant ACC/AHA Recommendations for the Role of Endomyocardial Biopsy Scena

New-onset heart failure of <2-wk duration associated with a normal-sized or dilated left ventri hemodynamic compromise

TABLE 11.2 Relevant ACC/AHA Recommendations for the Role of Endomyocardial Biopsy Scena

New-onset heart failure of 2-wk to 3-mo duration associated with a dilated left ventricle and new ve arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk
Heart failure of >3-mo duration associated with a dilated left ventricle and new ventricular arrhythmias, or third-degree heart block, or failure to respond to usual care within 1–2 wk
Heart failure associated with a dilated cardiomyopathy of any duration associated with suspected allergic and/or eosinophilia
New-onset heart failure of 2-wk to 3-mo duration associated with a dilated left ventricle, without new ve arrhythmias, or second- or third-degree heart block that responds to usual care within 1–2 wk
Heart failure of >3-mo duration associated with a dilated left ventricle, without new ventricular arrhyth second- or third-degree heart block that responds to usual care within 1–2 wk
Unexplained ventricular arrhythmias

4.Adapted from Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease. *Circulation*. 2007;116:2216–2233; American Heart Association, Inc.

TABLE 11.3 Treatment Regimens for Myocarditis in Clinical Trials

Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) Study[a]
Intravenous immune globulin (Gamimune N, 10%): 1 g/kg/d IV × 2 d
Giant Cell Myocarditis Study[b]
Cyclosporine: 25 mg po bid, increase by 25 mg increments to target level
Monoclonal whole-blood immunoassay: 200–300 ng/mL
High-performance liquid chromatography assay: 150–250 ng/mL
Fluorescence polarization immunoassay serum-based polyclonal assay: 100–150 ng/mL
Dose reduction if renal dysfunction develops
Muromonab-CD3 (OKT-3): 5 mg IV qd × 10 d
Dose reduction if hypotension develops
Corticosteroid: methylprednisolone, 10 mg/kg IV qd × 3 d, followed by prednisone, 1–1.25 mg/kg with e
Azathioprine: 200 mg po qd

TABLE 11.3 Treatment Regimens for Myocarditis in Clinical Trials

Myocarditis Treatment Trial[c]
Corticosteroid/cyclosporine versus corticosteroid/azathioprine versus placebo (biopsy-proven myocardit
Oral prednisone: 1.25 mg/kg/d in divided doses × 1 wk; reduce oral dose by 0.08 mg/kg/wk until dose is oral dose until week 20, and then reduce dose by 0.08 mg/kg/wk until week 24; then off
Oral cyclosporine: 5 mg/kg bid to achieve level of 200–300 ng/mL × 1 wk; adjust oral dose to achieve le 2 to 4; adjust oral dose to achieve level of 60–150 ng/mL from weeks 4 to 24
Immunosuppressive Therapy for Active Lymphocytic Myocarditis[d]
Prednisone 1 mg/kg/d for 4 wk; reduced to 0.33 mg/kg/d for 5 mo; azathioprine 2 mg/kg/d for 6 mo

5.LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

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10.Biopsy for staging of myocarditis

a. Cell types include lymphocytic, eosinophilic, neutrophilic, giant cell, granulomatous, and mixed.

b. Amount of cells: none (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3)

c. Distribution: focal (i.e., outside of vessel lumen), confluent, diffuse, and reparative (i.e., in fibrotic areas)

11. Other tests

a. Immunohistochemical staining to examine upregulation of major histocompatibility complex antigens and quantify inflammation, although rates of correlation with biopsy-proven myocarditis have not been consistent between studies.

b. Approximately 12% to 50% of patients with acute or chronic myocarditis have persistent viral mRNA detected in biopsy samples.

B.Immunosuppressive therapy in acute myocarditis

1. Routine immunosuppressive therapy is not recommended because of the neutral findings from multiple trials, including the Myocarditis Treatment Trial and the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) study. There is no Food and Drug Administration–approved regimen for the treatment of acute or chronic myocarditis.

2. Considerations are reserved for patients with new-onset, rapidly deteriorating, advanced heart failure with suspicion of the following conditions:

a. GCM is treated with combination therapy (Table 11.3).

b. Eosinophilic or sarcoid myocarditis is treated with high-dose steroids.

c. Specific therapy is used for underlying collagen vascular diseases, if present.

3. Studies are ongoing in an attempt to identify markers to predict favorable response to immunosuppressive regimens. A study of 112 patients with histopathologic acute lymphocytic myocarditis who failed to improve with conventional therapy and subsequently received prednisone and azathioprine found that one-half of the treated group improved, with EF rising from 26% to 47% and improvement in biopsy findings. Of those who failed conventional therapy, those patients who responded to immunosuppression were significantly more likely to have positive cardiac antibodies (90% vs. 0%) and less likely to have viral persistence when compared with nonresponders (14% vs. 85%).

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CHAPTER 12

Nontransplantation Surgical Treatment for Chronic Heart Failure and Durable Mechanical Circulatory Support

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I. INTRODUCTION. Heart failure carries a significant morbidity and mortality and requires tremendous medical resources and costs.

A. Over the past 20 years, there have been significant advances in medical therapy for systolic heart failure that have improved survival, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers (ARB), β-blockers, mineralocorticoid receptor antagonists, and, most recently, combination ARB/Neprilsyn inhibitors. In addition, the use of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) has improved survival, with CRT also leading to a better quality of life and reverse remodeling. Despite these advances, heart failure is progressive, and most patients, despite optimal medical therapy, will develop advanced stage D disease.

B. Although cardiac transplantation remains the most efficacious option for treatment of stage D heart failure, the increasing prevalence and the limited availability of donor organs prevent transplantation from being widely applicable. Similarly, for those patients with advanced age and comorbid conditions, cardiac transplantation is often not an option to address advanced heart failure.

C. Systolic heart failure is a continuous disease process with negative remodeling of the ventricles. In addition to optimal medical therapy, surgical interventions can prevent or reduce the impact of negative remodeling in the failing heart. It is crucial that patients with chronic systolic heart failure are managed by a multidisciplinary team consisting of heart failure cardiologists and cardiac surgeons for the best outcomes.

In this chapter, current and evolving surgical strategies for treating advanced heart failure will be reviewed, including surgical revascularization, valvular surgery, ventricular remodeling, and durable mechanical circulatory support.

II. SURGICAL REVASCULARIZATION FOR ISCHEMIC CARDIOMYOPATHY

A. Pathophysiology. Ischemic cardiomyopathy is defined as a left ventricular ejection fraction (LVEF) less than 40% caused by coronary artery disease (CAD). There are three major pathophysiologic mechanisms leading to ischemic cardiomyopathy, including:

1. **Myocardial hibernation.** Myocardial hibernation is defined as persistent contractile dysfunction at rest caused by chronically reduced coronary blood flow that can be partially or completely restored to normal by coronary revascularization. Hibernating myocardium may be a result of a shift in metabolic activity to match a reduction of coronary blood flow. Hibernating myocardium can be visualized with various imaging modalities.
2. **Myocardial stunning.** The viable myocardium may demonstrate transient, reversible, postischemic contractile dysfunction after revascularization caused by generation of reactive oxygen species and loss of myocardial filament calcium sensitivity.
3. **Myocyte loss.** Irreversible loss of the cardiac myocytes caused by myocardial infarction leading to fibrosis. Negative remodeling of the left ventricle leads to progressive ventricular dilatation, increased wall tension, and subsequent impairment of systolic and diastolic function.

B. Clinical significance and recommendations

1. In the United States, about 60% of systolic heart failure is due to ischemic cardiomyopathy.
2. Coronary angiography is indicated in patients with heart failure and angina in which the suspicion of obstructive CAD is high, and, additionally, may also be useful in assessing patients without angina but with left ventricular dysfunction.
3. Prior to completion of the Surgical Treatment of Ischemic Heart Failure (STICH) trial, there were no randomized clinical trials evaluating the outcome of revascularization in patients with ischemic cardiomyopathy, as the prior trials comparing coronary artery bypass grafting (CABG) versus medical management had excluded patients with LV dysfunction or heart failure. In the STICH trial, 1,212 patients with ischemic cardiomyopathy, LVEF ≤35%, and coronary anatomy suitable for CABG were randomized to medical therapy or medical therapy and CABG. At 56 months, there were no significant differences in the primary end point of all-cause mortality; however, CABG was associated with a 16% relative risk reduction of death or heart failure readmissions. Although this trial was well conducted, a limitation includes the 17% crossover rate from medical therapy to CABG, which may have resulted in dilution of the benefits of CABG.
4. Patient selection for surgical revascularization includes evaluation of the presence of angina, left ventricular dimension and ejection fraction, hemodynamic compromise, and suitability of targets for revascularization. LV dysfunction and heart failure remain important predictors of mortality after CABG and the Society of Thoracic Surgeons (STS) risk score can be assessed to risk stratify patients undergoing surgical revascularization.
5. The current guidelines of the American Heart Association/American College of Cardiology Foundation (AHA/ACCF) recommend coronary artery revascularization via CABG or percutaneous intervention as a class I indication for patients with systolic heart failure on goal-directed medical therapy with angina and suitable coronary anatomy, especially for a left main stenosis (>50%) or left main equivalent disease.
6. In the STICH trial, myocardial viability was tested in a subset of patients; however, the role of viability testing in the decision making for surgical revascularization requires additional clinical trials and studies to determine its need and value. Patients without viable myocardium on imaging studies should not be excluded from surgical revascularization.

III. VALVULAR SURGERY IN HEART FAILURE

A. Mitral valve. Primary mitral valve disorders are addressed elsewhere, and here functional mitral regurgitation secondary to systolic heart failure and left ventricular dilatation will be discussed.

1.Pathophysiology

a. The main pathogenic mechanism leading to functional mitral valve regurgitation in systolic heart failure is where changes in LV geometry and dilation cause apical and posterolateral tethering of the papillary muscles; this leads to apical tethering of one or both leaflets from the original coaptation point, causing posteriorly directed eccentric or central regurgitation. Other mechanisms include LV dyssynchrony, papillary muscle ischemia/infarction, and, lastly, annular dilation of the mitral valve, which is much less of a pathogenic factor.

b. The functional mitral regurgitation caused by systolic heart failure results in an increased hemodynamic load on the left ventricle, which subsequently leads to further dilatation and hypertrophy. This eventually leads to a vicious cycle of worsening mitral regurgitation and heart failure.

2.Management

a. Functional mitral valve regurgitation can be treated with neurohormonal therapy, which may improve the severity by effecting favorable reverse remodeling. In selected patients, CRT may also provide a hemodynamic benefit and reduction of regurgitation grade.

b. For patients with severe functional ischemic mitral regurgitation, isolated mitral valve surgery has a class 2B indication and should be considered for severely symptomatic patients with severe regurgitation who have proven refractory to medical therapy and resynchronization therapy if that is appropriate. However, for patients with more than moderate MR who are undergoing CABG or another valve procedure, mitral valve surgery is recommended. A recent study indicated similar outcomes in terms of survival for mitral valve (MV) replacement versus repair in this setting. MV replacement had lower need for reoperation, and thus chordal sparing MV replacement is now a class IIA indication in the 2017 ACC/AHA updated Valve Disease Guidelines. In patients with moderate ischemic MR undergoing CABG, no significant difference in outcome was shown in a recent trial for a strategy of CABG alone versus CABG + MV repair, and thus MV repair now carries a class IIB indication in this setting.

c. There can be hemodynamic and symptomatic benefit as well as improvement in left ventricular function and dimension with surgical correction of functional mitral regurgitation in heart failure; however, thus far no significant mortality benefit has been demonstrated.

d. Transcatheter therapies to address MV regurgitation are currently under investigation.

IV.LEFT VENTRICULAR RECONSTRUCTION

A.Pathophysiology

1. In systolic heart failure, in order to maintain stroke volume the left ventricle cavity size increases and becomes more spherical, thus increasing wall stress, as dictated by the Laplace law. Ultimately, this leads to increased myocardial oxygen consumption and adverse ventricular remodeling, which lead to progressive LV dysfunction and heart failure.
2. Left ventricular reconstruction surgeries were initially developed as an alternative to cardiac transplantation. The procedures were devised to restore normal left ventricular geometry to reduce wall stress and increase cardiac efficiency.

B.Surgical

1. **Endoventricular circular patch plasty (EVCPP).** EVCPP, classically named the “Dor” procedure, may be considered with anteroapical left ventricular aneurysm after anterior myocardial infarction. A ventriculotomy is created in the true aneurysm, and the opening is closed with a Dacron or pericardial patch. This restores normal long axis LV chamber geometry.

a. EVCPP is typically done concomitantly with CABG (90%) and additional valvular surgeries, including MV surgery (50%).

b. The STICH trial also evaluated surgical reconstruction, and despite a reduction in LV volume, there was no difference in symptoms, exercise tolerance, hospitalization, or death in patients who had CABG and surgical anterior ventricular restoration (SAVER) procedure (modified EVCPP) in comparison with those who underwent CABG alone.

c. Ventricular reconstruction does not have a demonstrated significant survival benefit in heart failure. It has a class IIB guideline indication in carefully selected patients with intractable heart failure and arrhythmias.

2. Partial left ventriculotomy. In the partial LV ventriculotomy or the Batista procedure, a section of the LV free wall, between the papillary muscles, is resected from the apex to mitral annulus and reapproximated.

a. A reduction in LV dimension was noted in several centers in the United States; however, there was also a high incidence of symptomatic heart failure and fatal arrhythmias. Heart Failure Society of America 2010 guidelines recommend against partial LV ventriculotomy in nonischemic heart failure, and the procedure has been largely abandoned.

3. Cardiomyoplasty. Cardiomyoplasty is also known as dynamic cardiomyoplasty, in which the latissimus dorsi is wrapped around the heart and paced. The rationale behind this procedure is that LV dilatation could be halted through the girdling effect of the muscle wrap and could also provide an auxiliary pump to the failing LV. This procedure has been abandoned in heart failure because there was high surgical mortality and no significant survival benefit. This procedure, however, led to the development of LV left ventricular constraint devices.

4. Left ventricular constraint devices

a. The concept of ventricular restraint with cardiomyoplasty was translated into using man-made materials in lieu of muscle to constrain the left ventricle to prevent left ventricular dilatation. Currently, there are no FDA-approved left ventricular constraint devices.

b. The Acorn CorCap is a knitted polyester sock–type device that is anchored over the ventricles to limit LV dilatation. It was tested in an unblinded trial in which there was a sustained reduction in LV diastolic volume but no difference in mortality.

c. The Paracor HeartNet device is an elastic metal mesh that surrounds the ventricles, which was tested in the PEERLESS-HF trial. The trial was stopped early because of no change in peak VO_2 at 6 months.

V. EMERGING THERAPIES

A. Stem cell transplantation. Currently, there is insufficient evidence regarding the role of various types of stem cells in cardiac regeneration and modifying systolic heart failure; however, further clinical trials may provide additional mechanistic insights and clinical evidence.

B. Nonsurgical LV chamber reduction. Currently, the PARACHUTE trials are testing the LV chamber reduction method through the percutaneous approach to deliver a polymer membrane on a nitinol skeleton. Essentially, it partitions the distal chamber of the infarcted ventricle from the ventricular chamber and thus reduces the left ventricular volume.

VI. MECHANICAL CIRCULATORY SUPPORT

A. Introduction. Despite advances in medical and surgical therapies for heart failure, even with optimal medical management, the prognosis of those patients with New York Heart

Association class III and IV symptoms and stage D heart failure with medical management is poor.

Patient with advanced heart failure have limited medical options, which include **inotropic agents; however, the long-term use of these medications is associated with a 50% mortality at 6 months**.

However, there is a discrepancy between the limited availability of donor organs and the ever-increasing number of patients with heart failure. In 2015, about 5,000 heart transplants were performed worldwide, with 2,600 in the United States.

Despite the increasing prevalence of heart failure and, resultantly, the number of patients who would benefit from heart transplantation, the donor volume has remained flat. Similarly, for those patients with advanced age and comorbid conditions, cardiac transplantation is often not an option to address advanced heart failure. Left Ventricular Assist Devices (LVADs) have evolved as a mechanism that unloads the left ventricle, provides increased cardiac output, improves quality of life, and improves mortality in patients with advanced systolic heart failure. In the past decade, LVAD therapy has rapidly gained widespread acceptance in the treatment of advanced heart failure. Here, we will focus on durable mechanical circulatory support. Devices for percutaneous mechanical circulatory are covered in Chapter 62.

B. Early LVAD experience

1. The **landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial** randomized patients with end-stage heart failure ineligible for transplant to optimal medical therapy or the HeartMate XVE, and demonstrated that at 1 year the survival with an LVAD was 52% versus 25% with optimal medical therapy. The REMATCH trial established the survival and quality of life advantages of implanted LVADs in end-stage heart failure. The HeartMate XVE LVAD (Thoratec, Pleasanton, CA) was an implantable pulsatile pump that was one of the most commonly used LVADs worldwide (Fig. 12.1). Although the REMATCH trial demonstrated a clear survival benefit with this device over optimal medical management, several limitations of this device exist. The applicability was limited to those patients with a body surface area (BSA) of 1.5 m^2 or greater. The durability of this device was also a critical limitation, with the valve and motor failure occurring after 12 months of support. Even with revisions to the design, the durability at 2 years was only 5%.

FIGURE 12.1 (**A**) Schematic of the pulsatile HeartMate XVE and (**B**) Chest radiograph demonstrating an implanted HeartMate XVE. (A, Reprinted with permission from Savage RM, Aronson S, Shernan SK. *Comprehensive Textbook of Perioperative Transesophageal Echocardiography*. 2nd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011. B, Image courtesy of HeartMate.)

2. **Development of continuous-flow LVADs.** The limitations of the first generation pulsatile pumps, led to the development of newer continuous-flow LVADs. These LVADs are smaller and more durable and allow for long-term mechanical circulatory support in a wider patient population. Since their inception, LVADs have evolved substantially and are now an accepted treatment modality for patients with end-stage heart failure. Improvement in device design and a better understanding of indications for device insertion have allowed for increased applicability and improved results with LVADs, revolutionizing the treatment options available for the patient with end-stage heart failure.

C. Implantation strategies for LVADs

1. The purpose of VADs is to reduce myocardial work by completely unloading the ventricle while maintaining its output. The classifications are many and can be based on site of support (either left ventricular, right ventricular, or biventricular support), duration of support (temporary versus permanent), or type of device (continuous versus pulsatile flow).
2. Clinically, VAD use can be categorized into groups for indication of VAD support, including bridge-to-decision, bridge-to-bridge, bridge-to-transplant, and destination therapy.

a. **Bridge-to-decision.** In those patients with acute cardiogenic shock and multisystem organ failure whose condition does not allow for evaluation of transplant eligibility because of unclear neurologic status and reversibility of myocardial and end-organ function. The outcomes of permanent LVAD implantation in this group are exceptionally poor. Placement of temporary circulatory support, such as extracorporeal membrane oxygenation, or short-term VAD (see Chapter 62) as a bridge-to-decision allows for establishment of hemodynamic stability and end-organ recovery to plan further definitive treatment such as a bridge-to-bridge for long-term device placement or, more rarely, bridge-to-recovery. Devices designed for this group of patients are those that are easily and quickly implantable and cost-efficient.

b. **Bridge-to-transplant.** The bridge-to-transplant (BTT) is the most traditional of LVAD clinical uses. These patients have irreversible ventricular failure and meet standard criteria for heart transplantation. Positive outcomes with this clinical application have been important for expanding the field of mechanical circulatory support.

c. **Destination therapy**

1. **(1)** Destination therapy (DT) exists for those patients with chronic heart failure who are transplant ineligible. DT evolved from encouraging results with VADs as bridge-to-transplant therapy.
2. **(2)** Currently, in the United States, based on the clinical trials, the Centers for Medicare and Medicaid Services (CMS) mandate the following requirements for DT implantation patients:

1. **(a)** LVEF less than 25%
2. **(b)** New York Heart Association (NYHA) IV symptoms
3. **(c)** Objective functional impairment with a maximal oxygen consumption less than 14 mL/kg/min (or <50% predicted)
4. **(d)** Optimal medical management for 45 of 60 days or inotropic therapy for 14 days or an intra-aortic balloon pump for 7 days

3. **(3)** As devices improve in the future, it is expected that the indications for DT and the demand will grow to help meet the growing number of patients with end-stage heart disease.

D. Patient evaluation and selection for LVAD

1. Successful therapy with LVADs critically hinges **on appropriate patient selection**, which requires patient evaluation with a multidisciplinary team.
2. Initial indications for LVAD therapy were derived from the inclusion criteria of clinical trials and include symptomatic advanced heart failure refractory to conventional therapy, including those that are inotrope dependent, LVEF less than 25%, peak oxygen consumption <14 mL/kg/min or <50% predicted.
3. Although it has been established that patients with NYHA class IV symptoms benefit from LVAD therapy, the Interagency for Mechanical Circulatory Support (INTERMACS) developed a new nomenclature for classification of advanced heart failure undergoing LVAD therapy. **The INTERMACS profiles capture the severity of disease** and divide patients into seven categories ranging from profile 1 (Critical Cardiogenic shock) to profile 7 (ambulatory NYHA class III) (Table 12.1).

4. The latest INTERMACS registry data demonstrated that approximately 15% of patients were implanted as INTERMACS profile 1, 37.6% as INTERMACS profile 2, 28.4% as INTERMACS profile 3, 13.5% as INTERMACS profile 4, and very few as INTERMACS profiles 5, 6, or 7.
5. Patients undergoing LVAD with a higher severity of illness (INTERMACS 1) have worse short- and long-term survival than those undergoing LVAD with a lower severity of illness.

TABLE 12.1 INTERMACS Profiles

Adult Profiles	IV Inotropes	Official Parlance
INTERMACS Level 1	Yes	"Crash and burn"
INTERMACS Level 2	Yes	"Sliding fast" on inotropes
INTERMACS Level 3	Yes	"Stable" on inotropes
INTERMACS Level 4	No	Resting symptoms on oral therapy at home
INTERMACS Level 5	No	"Housebound," comfortable at rest, symptoms with minima
INTERMACS Level 6	No	"Walking wounded," ADLs possible but meaningful activity
INTERMACS Level 7	No	Advanced class III

6. ADLs, activities of daily living.

7. The optimal timing of LVAD implantation remains to be determined. There are currently ongoing studies to further investigate the outcomes of LVAD implantation in less ill heart-failure patients.

8. Transplant candidacy

a. In patients being considered for LVAD implantation, a determination should be made if the patient is a transplant candidate.
b. The contraindications to transplantation, including recent malignancy, severe irreversible pulmonary hypertension, obesity, and advanced age, should be evaluated in all patients being considered for LVAD therapy.

9. Right ventricular function

a. Although severe pulmonary hypertension in patients with end-stage dilated cardiomyopathy is not a contraindication to LVAD implantation, there must be rigorous evaluation of right ventricular function during the evaluation process.
b. Right heart function is a critical limiting factor in LVAD therapy, because development of right-sided heart failure after LVAD implantation is associated with multisystem organ failure, increased morbidity and mortality, as well as prolonged hospitalization.
c. Unfortunately, prediction of post-LVAD right ventricular failure is challenging.
d. Many risk factors, including patient characteristics and hemodynamic parameters, have been identified, including CVP/PCWP >0.63, right ventricular stroke work index <300 mm Hg/mL/m^2, and composite risk scores that include renal and hepatic dysfunction.

10. Renal function

a. Although many patients with end-stage heart failure have abnormal renal function, if cardiorenal dysfunction is the primary cause, the renal function will very likely improve after LVAD implantation.

b. However, intrinsic renal dysfunction that requires renal replacement therapy, although not an absolute contraindication for LVAD implantation, can be challenging.

11. Nutrition

a. Assessment of nutrition is important in patients being evaluated for LVAD, because malnutrition is a risk factor for infection and mortality after LVAD implantation. If malnutrition is noted, patients should have their nutrition optimized prior to LVAD implantation.

12. Psychosocial factors

a. Psychosocial factors also play a pivotal role in VAD outcomes because the care and maintenance of the LVAD requires patient compliance and caregiver support. Thus, it is critical for patients to undergo neuropsychiatric evaluation for assessment of compliance, substance use, social support, and health literacy.

E. Continuous-flow LVADs

1. Introduction

a. A significant advance in LVAD therapy has been the development of continuous-flow LVADs. The continuous-flow LVADs draw blood from the LV apex into the pump and return the blood to the circulation via the outflow graft attached to the ascending aorta.

b. These pumps have a subcutaneous driveline that exits the body, and the device can be powered using AC power or an external battery system.

c. The rotor in these devices rotates at a set constant speed and acts to unload the left ventricle.

d. Given that there is continuous flow, the main contribution of pulsatility is from the native left ventricle.

e. A major advantage of the continuous-flow LVADs is their smaller size and increased durability, which has allowed for a wider application. Two main continuous-flow LVADs include the HeartMate II (Abbott) and the HVAD (HeartWare, Medtronic). Recently, the newest pump on the market, HeartMate III (Abbott), has been approved for bridge to BTT.

2. HeartMate II

a. The HeartMate II is an axial continuous-flow LVAD (Fig. 12.2).

b. It has an electromagnetically powered impeller that spins on a blood-lubricated ruby bearing. The pump itself weighs about 10 oz, has an implant volume of 63 mL, and generates up to 10 L of flow per minute. The inflow cannula is implanted in the LV apex, with the pump placed in the preperitoneal space. The HeartMate II is one-seventh the size and one-fourth the weight of the previous HeartMate XVE.

FIGURE 12.2 HeartMate II left ventricular assist device (LVAD) and radiograph demonstrating an implanted HeartMate II LVAD. Image courtesy of HeartMate.

c. The axial flow design and the absence of blood sac eliminate the need for venting, which was required for the first generation of implantable pumps, thus reducing the size of the percutaneous driveline and also eliminating the need for internal one-way valves.

d. The FDA approved the HeartMate II LVAD for BTT in 2008 and subsequently for DT in 2010. The initial HeartMate II LVAD BTT clinical trial enrolled 133 patients from 2005 to 2007 with a 1 year survival of 68%.

e. Importantly, over time the 1-year survival has improved. In 2011, the FDA postapproval HeartMate II study demonstrated a 1-year survival of 85%.

3. HeartWare

a. The HeartWare HVAD (HVAD) is a miniaturized centrifugal pump without bearings (Fig. 12.3).

b. It is unique in that its small size allows for implantation within the pericardial space, obviating the need for the creation of a peritoneal pocket. This allows for ease of implantation and shorter operative times.

FIGURE 12.3 HeartWare left ventricular assist device (LVAD) and chest radiograph demonstrating the intrapericardial implantation. Image courtesy of HeartWare.

c. The pump weighs only 5 oz (1/2 the weight of HeartMate II) and has a volume of 45 mL and yet supports flows up to 10 L/min.

d. It has a wide-blade impeller design, which is suspended via a passive magnetic and hydrodynamic bearing system.

e. The HVAD was evaluated as a BTT in the ADVANCE trial, a multicenter noninferiority trial. The HVAD ADVANCE trial participants were compared to a comparable, contemporary group of patients receiving continuous-flow LVADs who were entered into the INTERMACS registry. The primary outcome in ADVANCE was survival on the originally implanted device, transplantation, or explantation for recovery. A total of 140 patients received the HVAD, and this was compared to 499 patients who received a commercially available continuous-flow LVAD. The primary end point was achieved in 90.7% in the HVAD arm and 90.1% in the control arm (noninferiority, $p < 0.001$). On the basis of these data, the HVAD was approved for BTT by the FDA in 2012.

f. The HVAD was evaluated as DT in the ENDURANCE trial, a multicenter noninferiority trial comparing it to the HeartMate II. The results showed no difference in survival but a higher rate of stroke in the HVAD arm, which prompted the ENDURANCE supplemental trial that mandated BP control aimed at a mean arterial blood pressure (MAP) of <85 mm Hg. This subsequent trial showed no statistically significant difference in survival or stroke, leading to its FDA approval for DT in 2017.

4. HeartMate III

a. The HeartMate III is a continuous-flow LVAD with a centrifugal, magnetically levitated, bearing-less design. It is a small device that can be implanted in the intrapericardial space, comparable to the HVAD (Fig. 12.4).

b. In the MOMENTUM 3 trial, the survival without disabling stroke was lower than HeartMate II, and based on this study it received FDA approval as BTT in 2017.

F. Total artificial heart

1. While LVADs are effective for left ventricular systolic failure, biventricular heart failure, as well as other infiltrative cardiomyopathies, are challenging to deal with only left ventricular support. In view of right ventricular failure and small cavity sizes, LVAD alone is not always an ideal option.

2. A strategy for durable treatment of biventricular heart failure can include the total artificial heart (TAH) as a BTT (Fig. 12.5). Currently, the SynCardia TAH (Syncardia Systems, Tucson, AZ) is approved for the bridge-to-transplantation indication.

3. The Syncardia TAH has two artificial ventricles made from a semi-rigid polyurethane with flexible diaphragms with mechanical valves in the inflow and outflow ports of each ventricle.

4. During implantation of the TAH, the ventricles are resected, and the TAH is attached to the atrial cuffs and great vessels. Pneumatic drivelines are tunneled outside of the body.
5. The Syncardia TAH is available in a 50- and 70-mL ventricle to allow for implantation in different body sizes.
6. The TAH was compared to optimal medical therapy and intra-aortic balloon counterpulsation in a clinical trial. The TAH had improved survival to transplantation in comparison to the control group (79% vs. 46%).
7. The Syncardia TAH also has a smaller version of the driver, allowing patients to potentially be discharged from the hospital.

G. Investigational devices

1. HeartWare Miniaturized Ventricular Assist Device (MVAD)

a. The MVAD is a small, implantable continuous-flow LVAD with an axial flow design that is also magnetically levitated and bearing-less (Fig. 12.6). The significantly smaller size of the device may facilitate minimally invasive implantation.

H. Complications. Recent studies of patients who have been supported by continuous-flow LVADs have indicated that there is a decreasing incidence of complications and that outcomes have improved. However, LVAD complications, including pump thrombosis, bleeding, infections, stroke, and right ventricular failure, remain an issue for long-term LVAD use.

FIGURE 12.4 Syncardia total artificial heart device. (Image courtesy of syncardia.com.)

FIGURE 12.5 HeartMate III left ventricular assist device (LVAD). Image courtesy of HeartMate.

1. Pump thrombosis

a. As with most other implanted devices, LVADs activate the coagulation system, resulting in device-related thrombus. Thus, the continuous-flow LVADs require both antiplatelet and warfarin anticoagulation.

FIGURE 12.6 Miniature ventricular assist device left ventricular assist device (LVAD). Image courtesy of HeartWare.

b. Pump thrombosis is preceded by hemolysis, which can be clinically evaluated by following serum lactate dehydrogenase and plasma-free hemoglobin levels.
c. Clinical signs of pump thrombosis include hemoglobinuria, increased power spikes, and increasing heart failure. Patients with suspected pump thrombosis may require intensified anticoagulation, thrombolytics, or pump exchange.

2. Bleeding

a. The standard strategy to reduce the risk of thromboembolism has been systemic anticoagulation. Furthermore, the risk of bleeding after LVAD implantation is exacerbated with anticoagulation.
b. Gastrointestinal (GI) bleeding is a complication of continuous-flow pump support that may be severe and require that anticoagulation therapy be reduced or discontinued. Two hypotheses of the cause of GI bleeding during LVAD support that are being studied are acquired von Willebrand syndrome caused by increased shear stress and reduced pulsatility of the continuous-flow device.
c. In critical aortic stenosis associated with gastrointestinal bleeding, it has been shown that high shear stress induces a structural change in the von Willebrand molecule, which leads to lysis of

the high-molecular-weight multimers. The loss of these multimers, which are the most effective in platelet-mediated hemostasis, leads to an acquired von Willebrand syndrome. Aortic valve replacement reverses this hematologic problem. A similar phenomenon is seen in patients receiving LVADs.

3.Infection

a. The range of LVAD-related infections, which includes driveline infections, LVAD-related bloodstream infection, and pump pocket infection in more recent clinical trials of the HeartMate II, has shown a range from 15% (DT) to 35% (BTT).
b. Preoperative factors such as obesity and malnutrition have been identified as risk factors for LVAD-related infections.
c. The most common presentation of LVAD-related infection is driveline exit site infection. Local inflammatory changes and purulent drainage are frequently seen.
d. *Staphylococcus aureus* and coagulase-negative staphylococci account for more than 50% of cases of LVAD-related infections. Enterococci, *Enterobacter* spp., and *Pseudomonas aeruginosa* are other commonly isolated bacterial pathogens in LVAD-related infections.
e. Strategies to treat LVAD-related infections include long-term suppressive antibiotics, localized debridement, and device exchange or removal. Preventive measures such as perioperative antibiotics, vancomycin beads, and meticulous driveline care are important in reducing the risk of infection.
f. Infectious complications, including driveline infections and bacteremia, are a major morbidity of LVAD therapy and increase the duration of support in patients awaiting transplantation.

4.Stroke

a. Both ischemic and hemorrhage stroke are known complications after VAD therapy.
b. When amalgamating the data from clinical trials and the INTERMACS registry, the yearly rate is up to 10% to 15%, half of which is hemorrhagic in nature.
c. Adequate anticoagulation to prevent thrombus in the pump and adequate blood pressure management (target MAP < 85 mm Hg) are the main strategies to reduce the rate of ischemic and hemorrhagic stroke, respectively.

5.Right ventricular failure

a. RV failure is a leading cause of morbidity and death after LVAD implant because of the inability of the RV to pump sufficient blood through the pulmonary circuit to adequately fill the left heart. It is a major contributing factor to other serious adverse events such as bleeding, renal failure, and prolonged hospitalization. RV function is a major consideration for both volume-displacement and continuous-flow devices.
b. There has been a large range of reported RV failure requiring RVAD in prior studies. In the HeartMate II BTT trial, the incidence of postoperative RV failure, defined as need for RVAD support or inotropic support for 14 days, the incidence was 20%.
c. These observations indicate the need for better patient selection for those who are at high risk for right ventricular failure or potentially providing preoperative RVAD support.

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CHAPTER 13

Cardiac Transplantation

Julie L. Rosenthal

I.INTRODUCTION. The year 1967 marks the historic, first heart transplant performed by Christiaan Barnard in Cape Town, South Africa. Since then, cardiac transplantation has evolved into a well-established therapeutic intervention for a select group of patients living with end-stage heart disease. It offers these patients a chance for improved survival and quality of life. However, cardiac transplantation should not be perceived as a curative procedure. Following transplant a new set of potential, long-term complications may arise primarily owing to the secondary effects of chronic immunosuppression.

Approximately 100,000 adult heart transplants have been reported according to the International Society for Heart and Lung Transplantation (ISHLT) registry from 1982 through June 2012. The majority of the transplants come from reporting centers within North America followed by Europe. Despite a growing population and heart failure cohort, the number of reported cardiac transplants over the last decade remains static, hovering around 4,000 annually.

Within the United States, the Scientific Registry of Transplant Recipients (SRTR) notes a 17.1% increase in annual cardiac transplants since 2004 with 2,407 US transplants in 2012 compared with 2,188 in 2002. This subtle increase may be reflective of changes within donor allocation criteria as outlined by the Organ Procurement and Transplantation Network. According to the United Network of Organ Sharing (UNOS), which is the national organization that maintains organ transplantation waiting lists, initiates the evaluation of potential organ donors, allocates organs when a donor is identified, and compiles annual statistics on all aspects of the transplant process, the median wait time to transplant remains problematic and is dependent on both candidate status and transplant center in addition to blood type and body size. Status 2 candidates, the least urgent, had a median wait time of approximately 20 months versus 2.4 months for status 1A (most urgent) in 2012. Despite long wait times and an increasing number of transplants occurring within patients of highest medical urgency (58.5% of transplants were performed in 1A candidates compared with 34.8% in 2002), pretransplant mortality rates continue to decline with a reported 15.8 deaths per 100 wait-list year in 2002 compared with 12.4 in 2012. This may be attributed to the growing use of both permanent and temporary mechanical circulatory support devices and increased use of an implantable cardioverter defibrillator.

Global and national characteristics of transplant patients have evolved over the last decade demonstrating similar trends with a growing, nonischemic cardiomyopathy cohort (54%) followed by ischemic cardiomyopathy (37%); other primary diagnosis conditions

include retransplant, congenital, and valvular heart disease. According to the annual SRTR report from 2012, US recipient demographics demonstrate the median age range is 50 to 64 years of age, 72% are male, and 37.1% are blood type O compared with 42.2% type A versus 6.3% type AB, and 14.5% type B. As alluded to above, ISHLT data demonstrate the percent of patients requiring additional mechanical support as a bridge to transplantation has risen from approximately 20% in 2000 to almost 40% in 2011. The mainstay of this support remains left ventricular (LV) assist devices (LVAD) but includes right ventricular assist device (RVAD) and biventricular support (total artificial heart or LVAD + RVAD). Again, these numbers remain consistent with US data, with SRTR reporting that 41.3% of transplant recipients had a VAD at time of transplant in 2012 compared with 23% in 2002. Whereas mechanical circulatory support remains on the rise, the role of inotropes as a bridge to transplant has decreased from 43.4% in 2007 to 36% in 2012. The global shift in management is also reflected by the decline in patients hospitalized at time of transplant (44.3% in 2006 to 2012 compared with 60.8% in 1992 to 2000).

Survival rates post cardiac transplantation have improved over the years with the advancements of medical care and immunosuppression. The 1-year survival is 84% with a median survival of 13 years assuming the recipient survives the first year. Outcomes are influenced by multiple factors including etiology, age, and multiple comorbidities. The risk of death remains highest in the first 6 months posttransplantation predominately secondary to infection and graft failure. Examples of pretransplant multivariable factors associated with higher risk of mortality in the first posttransplant year include requiring temporary mechanical circulatory support and congenital heart disease. Historically, VAD use has been associated with increased mortality; however, SRTR survival curves from 2005 to 2007 demonstrate increased 1-year survival. Additional variables that may impact 1-year mortality include history of renal replacement therapy, mechanical ventilation, prior blood transfusion, and infection as well as recipient age, weight, and height, donor gender mismatch, pretransplant bilirubin and creatinine, ischemic time, and center volume.

The issue of supply and demand remains problematic and demonstrates why it is imperative for transplant programs to adequately screen and responsibly select potential transplant recipients.

II. INDICATIONS FOR CARDIAC TRANSPLANTATION

A. Patients failing optimal medical and device therapy for congestive heart failure, as recommended by the American College of Cardiology/American Heart Association guidelines, including but not limited to an angiotensin-converting enzyme inhibitor (ACEI) or alternative, aldosterone antagonist, β-blocker, and digoxin. When indicated, select patients should have received cardiac resynchronization therapy.

B. Medically reversible causes of decompensated congestive heart failure should be excluded, including thyroid disease, tachycardia-mediated cardiomyopathy, alcohol abuse, obstructive sleep apnea, hypertension, and medical noncompliance.

C. Surgically reversible causes of decompensated congestive heart failure should be excluded, including valvular heart disease, un-revascularized coronary artery disease, hypertrophic obstructive cardiomyopathy, and LV aneurysm for which resection would improve overall cardiac hemodynamics.

D. If the previous criteria are met, indications for a cardiac transplant evaluation are as follows:

1. **Progressively worsening or refractory congestive heart failure** symptoms, New York Heart Association class IIIb or IV
2. **Cardiogenic shock** requiring continuous intravenous (IV) inotropic therapy for hemodynamic stabilization
3. Cardiogenic shock requiring **mechanical circulatory support** (i.e., LVAD or intra-aortic balloon pump counterpulsation)
4. **Recurrent life-threatening ventricular arrhythmias** despite an implantable cardiac defibrillator, antiarrhythmic medications, and/or when appropriate an attempt at catheter-based ablation
5. **Refractory angina** without therapeutic options
6. **End-stage complex congenital heart disease** without pulmonary hypertension

III. COMPONENTS OF A CARDIAC TRANSPLANT EVALUATION AND CONTRAINDICATIONS. The purpose of a cardiac transplant evaluation is to exclude patients with medical and psychosocial comorbidities and to quantify the severity of a patient's cardiac impairment. Recommended investigations prior to a transplantation are summarized in Table 13.1 and exclusion criteria for cardiac transplantation are summarized in Table 13.2.

A. Blood work. A standard blood workup includes a complete blood cell count with differential, complete metabolic panel, thyroid function tests, and blood type. Human leukocyte antigen (HLA) typing, panel reactive antibody (PRA), and antibody screening are also collected. A serologic assessment should also be performed to determine the recipient's exposure to cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus, toxoplasmosis, syphilis (rapid plasma reagin), hepatitis B and C viruses, tuberculosis, and human immunodeficiency virus (HIV). In addition, vaccine-preventable infections should be screened to allow time for intervention pretransplant: hepatitis A and B; pneumococcus; tetanus; mumps, measles, rubella, and varicella.

1. Patients who are **anemic** should have a thorough evaluation, including iron studies and colonoscopy. When indicated, an esophagogastroduodenoscopy and/or a hematologic evaluation, including a bone marrow biopsy, should be considered. Some patients may benefit from erythropoietin treatment to increase red blood cell counts without the need for transfusions that may expose the patient to further antigens.
2. Patients found to have an **elevated serum creatinine** level should undergo further evaluation to determine its relationship with low renal perfusion. A normal urinalysis result suggests the absence of renal parenchymal disease. This should include an assessment of cardiac hemodynamics and a renal ultrasound to assess renal parenchymal size and the presence of two kidneys without evidence of obstruction.
3. Patients found to have **elevated hepatic enzymes** should undergo further evaluation with hepatic ultrasound scan and right heart catheterization to further delineate potential etiologies of hepatic insult.
4. The patient's serum should be **screened for antibodies** against HLA, both classes I (all nucleated cells) and II (antigen-presenting cells: B-cells, dendritic cells, and macrophages). These antibodies are collectively referred to as PRAs and are often elevated in multiparous women and patients with multiple transfusions (often perioperatively in the past).

Elevated PRA levels may increase the likelihood of a positive crossmatch, making it more difficult to find an ideal match. In addition, sensitized patients have associated

increased posttransplant morbidity: rejection and cardiac allograft vasculopathy (CAV). Although controversial, some centers have highly sensitized patients (PRA > 80%) undergo desensitization protocols as an attempt to facilitate a negative crossmatch. The following agents have been tried: IV immunoglobulin, plasmapheresis, rituximab, and combination therapies.

TABLE 13.1 Recommended Evaluation prior to Transplantation

Complete history and physical examination

Laboratory investigations

- Complete blood count with differential and complete metabolic panel
- Thyroid function studies (thyroid-stimulating hormone)
- Liver function panel, creatinine clearance
- Lipid profile, hemoglobin A1c, and urinalysis

Immunologic data

- Blood type and antibody screen
- Human leukocyte antigen typing
- Panel reactive antibodies' screen

Serology for infectious diseases

- Hepatitis (HBsAg, HBsAb, HBcAb, and HepCAb)
- Herpes group virus
- Human immunodeficiency virus
- Cytomegalovirus IgG antibody
- Toxoplasmosis
- Varicella and rubella titers
- Epstein-Barr virus IgG and IgM antibodies
- Venereal Disease Research Laboratory or rapid plasma reagin

Cardiovascular investigations

- Electrocardiogram, chest x-ray, and echocardiogram
- Exercise test with oxygen consumption
- Right and left heart catheterization
- Myocardial biopsy (if indicated, e.g., to rule out infiltrative process such as amyloidosis)

Vascular assessment

TABLE 13.1 Recommended Evaluation prior to Transplantation

- Carotid Doppler
- Peripheral vascular assessment (ankle–brachial index and/or duplex ultrasound)
- Abdominal ultrasound
- Ophthalmology examination (if indicated, e.g., to rule out diabetic retinopathy)

Cancer screening

- Prostate-specific antigen (in men if indicated)
- Papanicolaou smear and mammography (in women if indicated)
- Colonoscopy (if indicated)

Psychosocial evaluation

- Support system
- Substance abuse history (alcohol, tobacco, and drug use)
- Psychiatric history

Baseline investigations

- Dental examination
- Bone density scan
- Pulmonary function tests

IgG, immunoglobulin G; IgM, immunoglobulin M.

TABLE 13.2 Exclusion Criteria for Cardiac Transplantation

Irreversible pulmonary parenchymal disease
Renal dysfunction with Cr >2.0–2.5 or CrCl <30–50 mL/min (unless for combined heart–kidney transpla
Irreversible hepatic dysfunction
Severe peripheral and cerebrovascular disease
Insulin-dependent diabetes with end-organ damage
Acute pulmonary embolism
Irreversible pulmonary hypertension (PVR >4.0 Wood units after vasodilators)
Psychosocial instability or substance abuse
History of active malignancy or recent with probability of recurrence
Active infection

TABLE 13.2 Exclusion Criteria for Cardiac Transplantation
Severe osteoporosis

PVR, pulmonary vascular resistance.

Traditionally, each potential recipient undergoes **a thorough HLA tissue typing analysis**, via a complement-dependent cytotoxicity assay or molecular typing for assistance in finding an ideal donor. Once a possible donor is identified, random donor lymphocytes are incubated with recipient sera and evaluated by flow cytometry to determine the presence of potential donor-specific antibodies, also known as the crossmatch (see later). Currently, most programs use solid-phase assay, such as flow cytometry, to assess for preformed antibodies. This allows for the detection of weaker interactions and provides a more efficient and sensitive screening process.

B.Imaging

1. All patients should undergo **coronary angiography** or a functional assessment for ischemia and viability. If ischemia or viability can be demonstrated, consideration should be given to percutaneous or surgical revascularization.
2. Peripheral vascular studies may be obtained to exclude patients with significant disease including carotid and lower extremities.
3. Occasionally, an abdominal aortic ultrasound is obtained to rule out an aneurysm, particularly in patients being considered for mechanical support.

C.Functional assessment

1. **Metabolic stress testing** is performed to assess the severity of cardiac functional impairment. Patients with compensated congestive heart failure and a peak oxygen consumption **(Vo2)** of <14 mL/kg/min in patients intolerant to β-blocker or <12 mL/kg/min in the presence of a β-blocker, or <50% predicted are considered sufficiently impaired for transplantation. Adequate patient effort during the stress test can be assessed by the respiratory exchange ratio (RER). RER >1.05 denotes adequate aerobic achievement; RER <1.05 denotes a suboptimal test. The minute ventilation–carbon dioxide production relationship **(VE/Vco2 slope)** serves as an additional marker, >35 portends a worse prognosis.
2. Generally, a **right heart catheterization** is performed to assess cardiac hemodynamics and to optimize a patient's medical therapy prior to listing for transplant and again at 3- to 6-month intervals once listed for continued assessment. An attempt should be made to medically decrease the pulmonary hypertension with inotropic agents, nitrates, or nitroprusside. Sometimes an LVAD is required to sufficiently decompress the left ventricle to reverse the pulmonary hypertension. Endomyocardial biopsy (EMB) is rarely performed, except when an infiltrative cardiomyopathy is suspected. **Fixed, severe pulmonary hypertension, defined as a pulmonary vascular resistance (PVR) >4 Wood units, is a contraindication to cardiac transplantation.** In this setting, the donor right ventricle will likely immediately fail after implantation because it is not accustomed to high pulmonary pressures.
3. Pulmonary function tests are performed to exclude patients with significant chronic obstructive or restrictive pulmonary disease.

D. Comorbidities and implications of heart transplant listing. Advanced age, cancer, and obesity are the three common comorbidities that remain somewhat controversial regarding their impact on whether an individual program will list a patient for heart transplantation.

1. Age criteria for eligibility were initially quite rigorous; however, it has become apparent that **chronologic and physiologic age are often discrepant.** Most centers do not have a fixed upper age limit, but generally patients >70 years of age are very carefully screened to rule out comorbidities. ISHLT recommends considering patients for cardiac transplantation if they are ≤70 years of age. Patients >70 years of age may be considered for cardiac transplantation at the discretion of the transplant program and should theoretically be in excellent health except for heart disease. An alternate type of program has been proposed for these patients, whereby older donor hearts would be utilized in this population.
2. Active **malignancy** other than skin cancer is an absolute contraindication to cardiac transplantation because of limited survival rates. Chronic immunosuppression is associated with a higher-than-average incidence of malignancy and with increased recurrence of prior malignancy. Patients with cancers that have been in remission for ≥5 years and patients with low-grade cancers such as prostate cancer are generally accepted for transplant evaluation. Preexisting malignancies are heterogeneous in nature and some are readily treatable with chemotherapy. Thus an individualized approach to these patients is required, and consultation with an oncologist regarding prognosis is often very helpful.
3. Traditionally, centers have been cautious when considering **obese** patients for transplantation. Most currently available data indicate that patients with a pretransplant body mass index (BMI) >35 kg/m^2 have poor outcomes following cardiac transplantation. Current ISHLT recommendations are that patients achieve a BMI <35 kg/m^2 prior to being listed for cardiac transplantation. This cutoff will vary from center to center, but generally a BMI >35 kg/m^2 will preclude listing for cardiac transplantation.
4. **Assessment of frailty** should be considered during the evaluation process including >10 lb of unintentional weight loss over a 1-year period, muscle loss, fatigue, slow gait speed, and change in activity level.

E. Consultations

1. A **psychosocial assessment** is a crucial component of every cardiac transplant evaluation. Accepted psychosocial contraindications for cardiac transplantations include active smoking; active substance abuse, including alcohol; medical noncompliance; and significant untreated psychological or psychiatric diagnoses. Relative psychosocial contraindications to cardiac transplantation include posttraumatic stress disorder and lack of an adequate support structure.
2. For **diabetic patients, an ophthalmology consultation** is obtained for an assessment of retinal end-organ damage related to the diabetes.

IV. UNOS AND THE RECIPIENT LIST. After a patient is accepted as a potential cardiac transplant recipient by a UNOS-certified transplant program, the patient's name is entered on a national list compiled by UNOS. The patient is given a status level based on predefined clinical criteria (Table 13.3), which can be adjusted as the patient's clinical situation evolves. A patient's priority on the UNOS list depends on his or her status level and the duration of time on the list. **Highest priority is given to patients with status 1A and those who have been waiting the longest.** A critical patient initially listed as status 1A immediately has a higher priority than a patient with a status 1B, regardless of the duration

of time spent as status 1B. Whether a patient is hospitalized or not does not affect priority on the list, other than the fact that hospitalized patients are more likely to be receiving hemodynamic support (mechanical or inotropic) and are at a higher status level. A hospitalized patient on continuous inotropic therapy without invasive hemodynamic monitoring has the same status as a similar patient on home continuous inotropic therapy.

TABLE 13.3 Description of Status Levels in the United Network of Organ Sharing List

Status	Description
1A	Inpatient receiving high-dose inotropic support (i.e., dobutamine > 7.5 μg/kg/min or milrinor regardless of dose) with invasive hemodynamic monitoring
	Inpatient receiving mechanical support: VAD, TAH, IABP, or ECMO
	LVAD and/or RVAD for 30 d following implantation
	VAD-related complication: thromboembolism, infection, mechanical failure, life-threatening
	Life-threatening refractory arrhythmias with or without a VAD
	Mechanical ventilation
1B	Inotrope dependent
	VAD not meeting criteria for 1A status
2	All patients who do not meet status 1A or 1B criteria
7	Inactive on list because of improved clinical status or short-term contraindications to cardia

V.ECMO, extracorporeal membrane oxygenator; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart; VAD, ventricular assist device.

VI. WORKUP OF A POTENTIAL CARDIAC DONOR. Potential cardiac donors are patients who are declared brain dead but otherwise have viable internal organs. Generally, these are patients with lethal head injuries or catastrophic central nervous system events (i.e., intracranial hemorrhage, stroke, or cerebral anoxia).

A. Declaration of brain death. A neurologist or a neurosurgeon usually declares the brain death of a potential organ donor. Usually, this declaration is made after a period of observation (about 12 hours) during which no neurologic improvement is seen. Physicians involved in the care of potential transplant recipients are not involved in this decision to avoid conflicts of interest. Criteria for the determination of brain death are very specific. Absence of any one of the following criteria makes the patient ineligible for organ donation:

1. A known cause of death
2. Absence of hypotension, hypothermia, hypoxemia, and metabolic perturbations
3. Absence of medical or recreational drugs known to depress the central nervous system
4. Absence of cerebral cortical function
5. No response to painful stimuli
6. Absence of brainstem reflexes
   a. Pupillary constriction to light

b. Corneal reflex
c. Vestibular ocular reflexes (i.e., doll's eyes or cold caloric testing)
d. Gag reflex
e. Cough reflex

7. Positive apnea test: no spontaneous respiration despite arterial P_{CO_2} >60 mm Hg for at least 10 minutes after disconnection from the ventilator
8. An electroencephalogram (EEG) is not required but may be performed at the discretion of the examining physician. The EEG should demonstrate electrical silence.

B. Potential donor screening. After a patient is declared brain dead, a local organ procurement organization (OPO), under the auspices of UNOS, performs the initial evaluation of a potential donor. This evaluation includes a thorough patient and family history, focusing specifically on cardiac risk factors and potentially transmittable diseases (i.e., malignancy and infection). Preliminary blood tests are done, including comprehensive metabolic panel, complete blood count, cardiac enzymes, hepatitis B and C serologies, HIV, toxoplasmosis, CMV, and EBV. In addition, ABO blood group typing and HLA typing are performed. An echocardiogram is routinely obtained to assess cardiac function and rule out congenital anomalies, valvular disease, and other anomalies. At the request of the potential recipient's physician, a coronary angiogram may be acquired if the donor has significant cardiac risk factors, has positive cardiac enzymes, or is relatively advanced in age. Cardiac donor selection criteria are summarized in Table 13.4.

Potential recipients undergo both a virtual and a prospective crossmatch, in which the recipient's serum is incubated with donor lymphocytes to identify potential donor–recipient HLA incompatibility. If the HLA tissue typing of the potential donor does not include the antigens against which the recipient is sensitized, it is assumed that the actual crossmatch will be negative (i.e., a "virtual" negative crossmatch). If a prospective crossmatch is not performed, a retrospective crossmatch (typically by flow cytometry) is performed using donor lymphocytes obtained from donor aortic lymph nodes retrieved at the time of harvest.

C. Donor–recipient matching. UNOS maintains a computerized list of all patients listed and waiting for cardiac transplantation. A list of potential recipients with compatible blood types is generated for each potential donor organ and is made available to the OPO. In this list, priority is given to local patients (defined as within the OPO's territory) with the highest status level that has been waiting the longest. Allocation guidelines can be found within the organ procurement and transplantation network policy manual; see UNOS website for current guidelines.

Transplant physicians of the potential recipient may also reject a potential organ because of a positive prospective crossmatch, donor–recipient size mismatch, or a prolonged projected ischemic time (usually related to long-distance travel). Matching donor and recipient size is important, because an oversized donor organ may not allow closure of the chest without compression of the organ and an undersized donor organ may not be able to pump a sufficient quantity of blood. Current recommendations suggest a donor weight should ideally be within approximately 30% of a potential recipient' (20% if female donor to male recipient) to avoid size mismatch.

TABLE 13.4 Cardiac Donor Selection Criteria
Must meet legal requirements for brain death
No history of chest trauma or cardiac disease
No prolonged hypotension or hypoxemia
Normal ECG
Absence of significant coronary artery disease, if catheterization is performed
Negative HBsAg+, human immunodeficiency virus serologies, fungal infections, and active tuberculos
Infections with special consideration: HCV, donor bacterial infections, HBsAg–, HBcAb+ ("core-pos nonliver; or liver with intensive prophylaxis; preferably to vaccinated recipient)
Systolic blood pressure > 100 mm Hg or mean arterial pressure > 60 mm Hg
Central venous pressure 8–12 mm Hg
Minimal inotropic support, that is, <10 μg/kg/min dopamine to maintain blood pressure
Age < 55 y preferred
No history of active malignancy with exception of confined brain tumor

ECG, electrocardiogram; HB, hepatitis B; HCV, hepatitis C virus.

VII. SURGICAL ISSUES RELATED TO CARDIAC TRANSPLANTATION. Most surgical issues related to cardiac transplantation are beyond the scope of this chapter and are mainly of interest to the cardiac surgeon. The main surgical issue of interest to the transplant cardiologist is related to the anastomosis of the right atrium. The surgeon may suture the donor atrium to the recipient atrium (i.e., **biatrial anastomosis**) or suture the donor superior vena cava to the recipient superior vena cava and the donor inferior vena cava to the recipient inferior vena cava (i.e., **bicaval anastomosis**). The bicaval anastomosis approach is more time consuming but reduces the incidence of atrial arrhythmias (including sinus node dysfunction), reduces the incidence of posttransplant tricuspid regurgitation, and improves right atrial hemodynamics. The bicaval anastomosis approach does, however, provide some potential difficulties to the cardiologist trying to perform surveillance EMBs, because these anastomoses have a tendency to scar and narrow the central lumen over time. Currently, most centers employ the bicaval anastomosis approach, although no survival advantage has been conclusively demonstrated with this approach.

VIII. POSTOPERATIVE COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

A. Surgical complications. The most common surgical complication is the development of a **pericardial effusion** with or without tamponade. Pericardial effusions are very common because of the large potential space left behind as the dilated and dysfunctional recipient left ventricle is replaced with a more appropriately sized donor left ventricle. Rarely, pericardial tamponade develops, necessitating percutaneous or surgical evacuation of the pericardium.

Other surgical complications are much less common but can be catastrophic and usually result from a problem either at a site of anastomosis or at a site of cannulation.

B. Early graft dysfunction

1. **LV systolic dysfunction.** It is common for transplant recipients to require inotropic support as they come off cardiopulmonary bypass. The most commonly used inotropic agents in this setting are dobutamine, milrinone, and isoproterenol, used alone or in combination. It is also common for transplant recipients to require peripheral vasoconstrictors such as epinephrine, norepinephrine, and dopamine in the early postoperative period. Most patients can be weaned off inotropic therapy and peripheral vasoconstrictors within the first few days.
2. **LV diastolic dysfunction** is very common soon after cardiac transplantation. It usually results from reversible ischemia or reperfusion injury to the donor organ and normally resolves over a period of days to weeks. If the ischemia or reperfusion injury is sufficiently severe to induce significant contraction band necrosis or myocardial fibrosis, as seen on EMB, chronic diastolic dysfunction can ensue. Another potential cause of diastolic dysfunction is donor–recipient mismatch, particularly with a small donor organ or acute rejection.
3. **Right ventricular dysfunction** is much more common than LV dysfunction after cardiac transplantation, especially in patients with preexisting pulmonary hypertension. The right ventricle is subjected to similar ischemic or reperfusion injury risks as the left ventricle. Right ventricular dysfunction is usually accompanied by right ventricular dilation and the failure of coaptation of the tricuspid valve leaflets, leading to severe tricuspid regurgitation. The treatment for perioperative right ventricular dysfunction is usually IV milrinone, dobutamine, dopamine, or pressors for those who are persistently hypotensive. In patients with persistent RV dysfunction confounded by pulmonary hypertension, prostanoids or inhaled nitric oxide should be considered.

C. Cardiac arrhythmias. Most transplant recipients require perioperative temporary atrioventricular pacing. Sinus node dysfunction is very common, probably because of a combination of surgical trauma, ischemia, or reperfusion injury, and denervation. The incidence of sinus node dysfunction is believed to be reduced with bicaval anastomosis. With time, the sinus node typically recovers and a permanent pacemaker is not necessary. Preoperative use of amiodarone increases the likelihood of bradycardia posttransplantation. Other cardiac arrhythmias are rare and may signify rejection.

D. Renal dysfunction. Preoperatively, many transplant recipients have some degree of impaired renal function. There is a risk of worsening renal function perioperatively. This risk is compounded by the fact that the major immunosuppressive agents (i.e., calcineurin inhibitors) are nephrotoxic. Induction therapy should be considered for patients who are at increased risk for perioperative renal dysfunction as a means to delay calcineurin therapy. Interleukin-2 (IL-2) receptor blocker (i.e., basiliximab or Simulect) or Thymoglobulin (rabbit—antithymocyte globulin) remains the mainstay for induction therapy, as OKT 3 and Campath have fallen out of vogue secondary to risk profile.

IX. SYSTEMIC IMMUNOSUPPRESSION.

Much of the success in cardiac transplantation today is attributed to advances in immunosuppression. However, **balancing the risk of allograft rejection against the inherent risk of immunosuppression (i.e., infection, malignancy) remains a challenge**. Immunosuppressant protocols during and after cardiac transplantation vary greatly from program to program and even from patient to patient within a specific center. **Triple therapy**, which constitutes the cornerstone of modern

immunosuppressive regimens in cardiac transplantation, includes a **calcineurin inhibitor** (such as cyclosporine or tacrolimus), **a cell cycle–modulating or antiproliferative agent**(such as mycophenolate mofetil [MMF] or azathioprine), and a **corticosteroid**. The ideal regimen and dosage remains in question. For example, the tacrolimus in combination, tacrolimus alone compared trial prospectively randomized 150 cardiac transplant patients in an open fashion to receive either tacrolimus monotherapy or tacrolimus and MMF. Corticosteroids were used in all patients but were successfully discontinued over 8 to 9 weeks. The addition of MMF to tacrolimus did not provide an advantage over tacrolimus alone in terms of primary end point of rejection over the first 6 months, the secondary end points of allograft vasculopathy, and 3-year survival. The trial has, however, been criticized for being underpowered to demonstrate true differences in the primary and secondary end points, its use of an unvalidated biopsy grading scale, inconsistent timing of intravascular ultrasound (IVUS), use of higher and potentially nephrotoxic levels of tacrolimus, and the lack of a control arm of routine triple-drug immunosuppression for comparison with the two study arms. Controversy remains about the advisability of using induction therapy in the nonsensitized recipient without renal failure (Table 13.5).

A. **Steroids**. The mechanism by which steroids serve as immunosuppressants is complex and not completely understood. Steroids bind to nuclear receptors, thereby preventing gene expression of various cytokines important for B-cell and T-cell activation and proliferation, the most important of which is IL-2. Steroids also have important anti-inflammatory properties and suppress macrophage activity. Important side effects of steroids include **diabetes**, hypertension, weight gain, **osteoporosis**, and avascular necrosis of the femoral head.

Steroid-dosing protocols also vary from one institution to another. A dose of 500 to 1,000 mg of IV Solu-Medrol is usually given to the patient intraop and then 125 to 150 mg is usually repeated every 8 hours for a total of three additional doses. Some centers then start a dose of 1 mg/kg/d and wean by 5 mg daily, whereas others start 20 mg oral daily or the equivalent of 16 mg IV methylprednisone until patient is able to tolerate an oral regimen. The dose of steroid is typically slowly tapered, provided the patient remains free of rejection. The trend in clinical practice is to wean most patients completely off steroids by the end of the first year if not sooner. Some centers continue to advocate the indefinite use of low-dose prednisone (2.5 to 5 mg daily). If a decision is made to withdraw steroids completely, it should be done approximately 1 month before the next scheduled biopsy to ensure continued lack of rejection.

Steroids are also given in “pulses” to treat episodes of acute rejection. If a patient has acute rejection associated with hemodynamic compromise, he or she is admitted for 1 g of IV Solu-Medrol daily for 3 days and may be given cytolytic therapy or plasmapheresis, or both. If no hemodynamic compromise is associated with the episode of rejection, a daily dose of 100 mg oral prednisone for 3 days is usually sufficient, followed by repeat biopsy at most 2 weeks later to ensure resolution—again this is center specific.

B. **Calcineurin inhibitors.** Calcineurin is a phosphatase enzyme that triggers transcription of new messenger RNA after activation of the T-cell receptor by an appropriate antigen, leading to increased gene expression of IL-2 and other important cytokines. Calcineurin

antagonists inhibit this phosphatase activity, thereby preventing the synthesis of these cytokines, which prevent B-cell and T-cell proliferation.

TABLE 13.5 Common Immunosuppressants

	Steroids	Calcineurin Inhibitors	MMF	AZA	T
Drugs	Prednisone (P) (po)	Neoral (N)	-	-	R
	Solu-Medrol (S) (IV)	Tacrolimus (T)	-	-	E
Indication	Chronic IM, acute rejection	Chronic IM	Chronic IM, skin cancer with AZA	Chronic IM	C
Dosing					
Initial	IV 125-150 mg q8h	N: 100 mg bid T: 2 mg bid	1.5 g bid	1-2 mg/kg/d	R E
Induction	-	-	-	-	-
Maintenance	Weaned off	Adjusted to levels	1.5 g bid	1-2 mg/kg/d	A
Acute rejection	P: 100 mg qd × 3 S: 1 g IV qd × 3	Consider change from CsA to tacrolimus	-	-	-
Target levels	-	See Tables 12.3 and 12.4	2-4 ng/mL, 12-h trough, WBC > 4.0	WBC > 3.0	R
Common side effects	Diabetes, osteoporosis, weight gain, hypertension, and adrenal insufficiency	Nephrotoxicity, hypertension, tremors, and gingival hyperplasia	Diarrhea, nausea, and myelosuppression	Myelosuppression, skin cancer	H
Common drug interactions	-	Erythromycin, diltiazem, verapamil, rapamycin, anticonvulsants, rifampin, and statins	Cholestyramine and probenecid	Allopurinol	C

C.AZA, azathioprine; CMV, cytomegalovirus; CsA, cyclosporine A; IL, interleukin; IM, immunosuppression; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; TOR, target of rapamycin; WBC, white blood cell.

1. **Cyclosporine** (Neoral, Gengraf, and Sandimmune) is a calcineurin antagonist with a highly variable pattern of bioavailability, depending on the oral formulation taken. Bioavailability of the original soft gelatin capsule (Sandimmune) was low and depended on emulsification by bile salts. The newer microemulsion formulation (Neoral) does not depend on bile salts for emulsification and has a more consistent bioavailability. Nevertheless, there remain tremendous interpatient differences in bioavailability, and dosing of Neoral is primarily based on serum drug trough levels. Because of the narrow therapeutic range of cyclosporine, drug trough levels are also important to prevent toxicity. **Nephrotoxicity** is the most important side effect of cyclosporine therapy and is related to renal afferent arteriolar vasoconstriction and the resultant reduced renal perfusion. Other side effects include systemic hypertension, gingival hyperplasia, and tremors. Calcium channel blockers (CCBs), particularly diltiazem, reduce hepatic metabolism of cyclosporine, thereby increasing serum drug levels. This drug interaction is frequently used clinically to reduce the oral dose of cyclosporine required to achieve a given serum drug concentration, thereby minimizing the cost of immunosuppression.
   Postoperatively, once the patient is hemodynamically stable with good urine output, cyclosporine is initiated via continuous infusion at 1 mg/h. When the patient is able to take oral medicines, Neoral is begun at a dose of 100 mg twice daily, with adjustments in the dose based on serum trough levels (Table 13.6). The dose of Neoral is gradually reduced over a period of 1 year if the patient has a clean biopsy record.
2. **Tacrolimus** (Prograf), previously known as FK506, is another calcineurin inhibitor that has low oral bioavailability. Tacrolimus-based regimens have demonstrated lower rates of rejection compared with cyclosporine but there is no evidence to suggest a survival benefit. It has become standard of practice to change a patient's immunosuppressive regimen from cyclosporine to tacrolimus when recurrent or persistent acute cellular rejection occurs in the setting of adequate cyclosporine levels. The major side effects of tacrolimus are **nephrotoxicity and neurotoxicity** (most commonly tremor).
   Like cyclosporine, tacrolimus is initiated postoperatively once the patient is hemodynamically and renally stable. A dose of 0.01 mg/kg/d of tacrolimus is administered by continuous infusion. Unfortunately, IV tacrolimus is seemingly more nephrotoxic than cyclosporine. Tacrolimus can be given sublingually using an oral to sublingual dose ratio of 1:1 with dose adjustment based on serum drug levels (Table 13.7).

D. Mycophenolate mofetil (CellCept). MMF inhibits DNA synthesis by inhibiting de novo purine synthesis. Because human lymphocytes depend on the de novo synthesis of purines for DNA replication, MMF has the unique ability to inhibit B-lymphocyte and T-lymphocyte proliferation without affecting DNA synthesis in other cell lines, which can obtain purines through the parallel and unaffected purine salvage pathway. MMF has become the preferred immunosuppressant over azathioprine at most transplant centers because of a reduced mortality rate at 1 year (6.2% vs. 11.4%; $p = 0.03$). The main disadvantage of MMF over azathioprine is the increased cost (approximately 20-fold) and the potential **increased risk of opportunistic viral infections.** Toxicities of MMF include **gastrointestinal**

symptoms (nausea, vomiting, and diarrhea) and **myelosuppression**. Some patients on MMF develop clinically significant leukopenia, necessitating dose reduction or discontinuation of the drug. Most symptoms will resolve with the reduction of dose.

TABLE 13.6 Target Serum Cyclosporine A Levels

Time (mo)	Target Level (12-h Trough) (ng/mL)
0–3	250–350
3–12	200–250
>12	150–175

TABLE 13.7 Target Serum Tacrolimus (FK506 or Prograf) Levels

Time	Target Level (12-h Trough) (ng/mL)
0–30 d	12–20
1–6 mo	8–15
6–18 mo	5–15
>18 mo	5–10

E. MMF is given intravenously or orally. Because of the high bioavailability (>90%), the initial dose of MMF is 1 g taken twice daily, regardless of the route of administration. The initial dose is given within the first 12 hours after transplantation. Routine monitoring of **mycophenolic acid (MPA)**, the active metabolite of MMF, is not recommended; however, an MPA level <1.5 mg/L is considered subtherapeutic. Serum levels of MPA are higher when MMF is administered with tacrolimus compared with cyclosporine; therefore, it may be advisable to empirically reduce the dosage of MMF when switching from cyclosporine to tacrolimus.

F. Azathioprine (Imuran) is a purine analog that impairs DNA synthesis, thereby preventing B-lymphocyte and T-lymphocyte proliferation in response to antigen stimulation. Azathioprine has largely been replaced by MMF as the antiproliferative agent of choice in the triple immunosuppressant cocktail of today. Because there is no drug level assay available, azathioprine dosing is usually fixed between 1 and 2 mg/kg/d. The major side effect of azathioprine is **myelosuppression**, and the dose of azathioprine is usually adjusted to maintain a white blood cell count of >3,000/mL. Azathioprine is metabolized by xanthine oxidase, and xanthine oxidase inhibitors, such as allopurinol, can lead to toxic levels of azathioprine and profound, prolonged myelosuppression.

G. Inhibitors of the target of rapamycin (TOR) enzyme. Sirolimus (Rapamune) and everolimus (Certican, also known as RAD). TOR is activated after IL-2 stimulation of the T-cell IL-2 receptor and is critical for lymphocyte growth and proliferation. In contrast to calcineurin inhibitors, TOR inhibitors do not block cytokine production (e.g., IL-2) but rather block the cellular response to these cytokines. TOR inhibitors also inhibit vascular smooth muscle cell growth and proliferation in response to various growth factors. It is hoped that this property of TOR inhibitors will help reduce the rate of progression of CAV. Unlike calcineurin inhibitors, TOR inhibitors are not nephrotoxic. When used in combination with

cyclosporine, TOR inhibitors appear to act synergistically with regard to immunosuppression. However, worsening of renal function is common but can be prevented by lowering the cyclosporine dose without worsening of immunosuppression. The main side effects of this class of compounds are significant **hypertriglyceridemia, thrombocytopenia, and poor wound healing**.

Sirolimus and everolimus are both TOR inhibitors. They are structurally similar, but everolimus has a much higher bioavailability than sirolimus. The appropriate dosing of these agents remains unclear, but for sirolimus, it is probably 1 to 5 mg/d, and for everolimus, it is probably 1.5 to 3 mg/d. Sirolimus appears to lower the incidence of acute cellular rejection in humans and slow the progression of transplant vasculopathy. Preliminary human studies using intravascular coronary ultrasonography (IVUS) have also shown a reduction in neointimal proliferation with both sirolimus and everolimus. It remains unclear where TOR inhibitors will fit in with current immunosuppressive protocols. The most likely scenario is their use in combination with a calcineurin inhibitor and prednisone, in place of MMF or azathioprine. One-year posttransplant IVUS data demonstrated significantly lower increase in maximal intimal thickness in patients receiving everolimus compared with MMF. Alternatively, they could be used in place of calcineurin inhibitors and in combination with MMF or azathioprine and prednisone, particularly in patients with either preexisting or worsening renal dysfunction.

H. **Induction therapy and therapy for steroid-resistant acute rejection.** The purpose of induction therapy is to deplete T-lymphocytes or to prevent lymphocyte proliferation during the most immunoreactive phase, which occurs immediately after transplantation. Induction therapy remains controversial, and practice patterns across centers continue to vary. According to recent SRTR data approximately 50% of centers utilize induction therapy at the time of transplant. A recent retrospective review of over 17,000 patients from UNOS registry demonstrated that the use of induction therapy did not impact overall survival. Three indications to use induction therapy are as follows: in patients with renal dysfunction, which would preclude the early introduction of calcineurin inhibitors; in the highly sensitized patient at time of transplant; and in patients with compromised graft function secondary to rejection.

1. **Polyclonal antilymphocyte antibodies** are produced by injecting animals with human lymphocytes or thymocytes and then collecting the animal's serum. Two commercially available formulations are antithymocyte globulin (Atgam), which is horse based, and Thymoglobulin, which is rabbit based. The antibodies produced in this manner are directed against a variety of targets on the surface of B- and T-cells and induce complement-mediated lymphocytolysis. The recommended doses of Atgam and Thymoglobulin are 15 and 1.5 mg/kg/d, respectively; the total dose depends on the course of action: induction versus rejection. Adequate lymphocyte depletion can be ensured and dose adjustments made by quantifying the CD3 or CD2 counts. Immunity may develop to the animal component of these antibodies, rendering them ineffective if further courses of therapy are necessary. An increased incidence of posttransplant lymphoproliferative disorder (PTLD), lymphoma, and opportunistic viral infections has also been observed. Patients receiving either formulation are often prophylactically treated with ganciclovir or valganciclovir to prevent CMV infection.
2. **IL-2 receptor blockers: basiliximab (Simulect) and daclizumab (Zenapax)**. IL-2 receptor antagonists target the IL-2R-α chain (CD25) on activated T-lymphocytes and inhibit IL-2–mediated activation of subsequent lymphocytes. Prior daclizumab studies demonstrated a

reduced risk of rejection; however, one large, multicenter randomized control trial demonstrated excess risk of death. Subsequently, daclizumab was removed from the market in 2009. Basiliximab is predominately used at the time of induction; cytolitic agents like Thymoglobulin are reserved for episodes of rejection and induction.

X.REJECTION. According to the ISHLT registry, rates of rejection within the first year of transplant continue to decline and were 25% in 2010 compared with 32% in 2004. Females and young patients were at higher risk than males and older patients, respectively. Allograft rejection involves both the cellular and humoral arms of the adaptive response. An ideal immune monitoring strategy has been described as the one that would be noninvasive, would reliably distinguish between the presence and absence of rejection, and would detect over-immunosuppression. Such an ideal strategy does not exist; however, surrogate markers are available through gene expression profiling (GEP) tests and immune function assays. The immunologic status of a transplant recipient is currently monitored by immunosuppressant drug levels, echocardiographic assessment of allograft function, and EMB. Noninvasive monitoring therapies have been tested in the hope of overcoming these limitations. The GEP test, also known as AlloMap, is an example of a promising alternative when used in the appropriate substrate (see below for additional description).

A.Endomyocardial biopsy. The current gold standard of rejection surveillance after cardiac transplantation is EMB. Rejection of the cardiac allograft is usually clinically silent unless it is accompanied by significant hemodynamic compromise (i.e., congestive heart failure). As a result, EMBs are routinely performed for rejection surveillance. However, EMB is invasive, inconvenient, expensive, and subject to sampling and interpretation error. To mitigate interobserver variability, the ISHLT revised and simplified the grading criteria for acute cellular and antibody-mediated rejection (AMR) (Table 13.8). Because the likelihood of acute rejection is highest early posttransplant, the frequency of biopsies remains high during this period and then gradually tapers off, depending on the results (Table 13.9).

TABLE 13.8 Rejection Grading Scale for Endomyocardial Biopsies

Grade	Severity of Cellular Rejection	Histologic Findings
1R[a]	Mild	Interstitial and/or perivascular infiltrate with up to 1 focus
2R	Moderate	≥2 foci of infiltrate with associated necrosis
3R	Severe	Diffuse infiltrate with multifocal necrosis ± edema ± hemo
Grade		**Histologic findings**
pAMR 0		Negative for pathologic AMR. Both histologic and immun
pAMR 1 (H+)		Histopathologic AMR alone. Histologic findings are prese negative
pAMR 1 (I+)		Immunopathologic AMR alone. Histologic findings are neg are positive
pAMR 2		Pathologic AMR. Both histologic and immunopathologic f

TABLE 13.8 Rejection Grading Scale for Endomyocardial Biopsies	
pAMR 3	Severe pathologic AMR

B.[a]R = revised.

C.AMR, antibody-mediated rejection.

TABLE 13.9 Example of Endomyocardial Biopsy Schedule—Center Dependent	
Weeks After Transplantation	**Biopsy Frequency**
1–4	Weekly
5–12	Every 2 wk
13–24	Monthly
25–52	Every 2 mo
Year 2	Every 3–4 mo
Years 3–4	Every 6 mo
>4 y	Only if clinically indicate
After biopsy with acute rejection	2 wk after initial biopsy

D.Surrogate markers of rejection

1. **Peripheral biomarkers.** Although high levels of circulating pretransplant, **donor-specific antibodies to HLAs have been demonstrated to predict greater risk of severe rejection**, no peripheral markers have been shown to reliably correlate with allograft rejection posttransplantation among those evaluated, including cytokine levels, markers of myocardial necrosis (creatine kinase-muscle/brain and troponin), complement fragments, prothrombin, P-selectin fragments, CD69 membrane protein, soluble CD30, endothelin, serum nitrate, thromboxane A_2, matrix metalloproteinase-1 in brain, vascular endothelial growth factor, natriuretic peptide, and C-reactive protein.
2. **Echocardiography.** Echocardiography is ubiquitous in cardiac transplant centers, drawing investigative attention to it as a noninvasive surveillance alternative to EMB for cardiac allograft rejection. For it to be a useful screening tool, however, echocardiography must identify graft rejection before global LV systolic dysfunction ensues. The challenge has been to identify such sentinel markers. Myocardial performance index, pressure halftime, intraventricular relaxation time, and acoustic quantification of cardiac filling volumes have not shown consistency. Changes >10% in serial measurements of pulsed wave tissue Doppler measurements of early diastolic basal posterior wall motion velocity were able to exclude clinically relevant rejection with positive predictive value and negative predictive value of 92% and 95%, respectively. Technical limitations with this technique in the cardiac transplant population together with inconsistent observer interpretation have meant that echocardiography is neither sufficiently sensitive nor specific to supplant routine EMB.

3. **Gene expression profiling.** GEP is a new modality for surveillance of cardiac allograft rejection. **This test uses microarray and quantitative polymerase chain reaction (PCR) of peripheral blood mononuclear cells to measure the expression of 20 genes** (11 informative and 9 control and normalization). A score ranging from 0 to 40 is generated by a multigene algorithm. It has been shown to correlate strongly with histologically diagnosed cellular allograft rejection. In the Cardiac Allograft Rejection Gene Expression Observational study**, a score of <34 was associated with a negative predictive value of >99% for grade ≥3A/2R rejection**. Several factors influence AlloMap score, including time posttransplantation, peripheral alloimmune activity, corticosteroid dose, and CMV. Transplant vasculopathy has been shown to be associated with increased AlloMap GEP score. GEP testing can be used in clinically stable cardiac transplant recipients who are >15 years of age and 6 months or more posttransplantation. It is used to identify patients at low risk for moderate/severe (≥3A original ISHLT grade or ≥2R revised ISHLT grade) cellular rejection. In the Invasive Monitoring Attenuation through Gene Expression (**IMAGE**) trial, 602 patients who had undergone cardiac transplantation at least 6 months previously were randomly assigned to the AlloMap test or EMB. The composite primary outcome of the study was allograft dysfunction, death, or retransplantation. At 2 years, the cumulative rate of this composite end point was 14.5% with GEP and 15.3% with EMB. The AlloMap test was thus not inferior to EMB in detecting allograft cellular rejection. However, wholesale embrace of the IMAGE trial is tempered by the limitations of the trial, including the enrolment of only 20% of potentially eligible patients and of patients at lower risk for rejection. The noninferiority margin chosen was wide and included events that would not be associated with rejection because not all cases of graft dysfunction, death, or retransplantation are due to rejection.

   The frequency of rejection surveillance using the GEP or AlloMap testing should be individualized to the patient's rejection history, immunosuppression regimen, time posttransplantation, and transplant center protocol. GEP is a cost-effective and less expensive alternative to EMB for monitoring allograft cellular rejection in cardiac transplant patients.

E. Types of rejection

1. **Hyperacute rejection** is usually fatal and is the result of allograft rejection by preformed antibodies. It can occur immediately on surgical reperfusion. The incidence of hyperacute rejection is rare in the era of PRAs and virtual and prospective crossmatch.
2. **Cell-mediated rejection is characterized by infiltration of mononuclear inflammatory cells that are predominantly T-cells directed against the allograft.** Variability in the interpretation of histologic grading of cellular rejection of EMB by pathologists led to the revision of the grading system in 2004. Biopsy grades of ≥2R warrant accentuation of immunosuppression. If there is no hemodynamic compromise, then patients are routinely treated as outpatients with 100 mg of prednisone taken orally for 3 days; again this varies from center to center. If there is a hemodynamic compromise or persistent or recurrent severe rejection (at least grade 2R), then many therapeutic options are available: methylprednisolone, cytolytic therapy with Atgam or Thymoglobulin, plasmapheresis, photopheresis, and in severe cases total lymphoid irradiation combined with optimization of maintenance immunosuppression.
3. **Antibody-mediated rejection** occurs because of preformed or de novo alloantibody (immunoglobulin G or M) against donor antigens. Such antibodies and complements are deposited in the donor coronary microvasculature and are demonstrable by immunofluorescence or by immunohistochemistry staining against CD68, C4d, or C3d complement fragments that

mediate vascular injury and, ultimately, allograft failure. The ISHLT proposed a framework for reporting pathologic AMR which includes any combination of histopathologic and immunopathologic findings. Treatment regimens for patients with AMR include IV or oral steroids, plasmapheresis, or immunoadsorption and are determined by degree of rejection defined by presence of graft dysfunction, pathologic, and serologic assessment.

XI. INFECTIOUS DISEASE AFTER TRANSPLANTATION. The risk of infection is highest in the first year post cardiac transplantation, accounting for 29% of deaths. Thereafter, the risk falls but remains >10%. In the first month posttransplantation, nosocomial infections predominate. The therapeutic immunosuppression consequent upon transplantation leaves cardiac allograft recipients vulnerable to **opportunistic infections** or **reactivation of latent infection**, particularly between 1 and 6 months. Infections after 6 months are usually **community acquired**. An infectious disease specialist with an interest in transplantation is an invaluable resource to any transplant program. The two pathogens of particular interest in the transplant patient are CMV and *Pneumocystis jiroveci* pneumonia (PJP), formerly called pneumocystis carinii pneumonia, but there are several potential pathogens including *Mycobacterium*, *Nocardia*, *Listeria*, *Candida*, *Aspergillus*, and *Strongyloides*.

A. Cytomegalovirus. Primary CMV infection occurs when a CMV-negative recipient receives a CMV-positive donor organ or is infected de novo from another source. **Secondary CMV** infection occurs when a CMV-positive recipient has reactivation of quiescent CMV infection with viremia after immunosuppression, particularly with induction therapy or bolus immunosuppression prescribed for a rejection episode. Active CMV disease may manifest as fevers, myalgias, gastritis, colitis, pneumonitis, retinitis, or leukopenia and thrombocytopenia. The most **sensitive and specific test for diagnosing CMV is quantitative PCR**. PCR detects CMV deoxyribonucleic acid (DNA) in plasma and quantifies the CMV viral load. Although CMV DNA replication may be detected by PCR, most patients do not have the clinical syndrome of CMV disease. The issues of whether a detectable CMV viral load will progress to the clinical syndrome and whether to treat patients with CMV detection in the absence of symptoms remain controversial.

Prophylaxis against CMV disease is considered to be the standard of care for CMV-positive recipients (regardless of the CMV status of the donor) and CMV-negative patients with a CMV-positive donor. There is no consensus on the duration of ganciclovir therapy in these patients. Most patients are initially treated with IV ganciclovir, followed by a variable course of oral valganciclovir or acyclovir. Periodic monitoring of the CMV viral load may assist in guiding the duration of therapy in these patients.

Passive immunization with CMV immunoglobulin (CytoGam) may be considered in patients deemed at risk for CMV disease, particularly if they have low levels of serum immunoglobulins (<500 mg/dL). Patients undergoing induction therapy, polyclonal or monoclonal antibody therapy for steroid-resistant rejection, or increased immunosuppressive therapy for acute rejection should be deemed at risk for reactivation of CMV disease.

The duration of therapy with valganciclovir for active CMV disease is usually 3 to 6 weeks. An undetectable CMV viral load should be demonstrated in such patients before consideration is given for antiviral therapy discontinuation.

B. *P. jiroveci* pneumonia. Transplant recipients are at increased risk for the development of PJP because of their immunocompromised state. **PJP is rare if appropriate prophylaxis with**

trimethoprim–sulfamethoxazole (TMP–SMX) is provided. Patients intolerant to TMP–SMX may be treated with inhaled pentamidine or dapsone. PJP is rarely seen at maintenance immunosuppressant doses in transplant patients. TMP–SMX may be discontinued 6 to 12 months after transplantation in most patients.

XII. CARDIAC ALLOGRAFT VASCULOPATHY. CAV is a progressive, neointimal proliferative process in the epicardial coronary arteries and microcirculation. It is common, with an incidence of 30% and >50% at 5 and 10 years, respectively, and greater posttransplant. CAV is a significant cause of mortality beyond the first year after transplantation, accounting approximately 15% after 5 years posttransplant. The pathophysiology of CAV is not completely understood. **Initially CAV was thought to be an accelerated form of atherosclerosis; however, it is now clear that both immunologic and nonimmunologic factors are involved in the process.** Chronic, subclinical, and immune-mediated injury at the level of the donor coronary endothelium creates a chronic inflammatory milieu. The exact mediator of the endothelial injury remains controversial, but it is probably multifactorial, including chronic humoral and cellular rejection, ischemic and reperfusion injury at the time of transplantation, and chronic CMV infection of endothelial cells. Table 13.10 lists risk factors for the development of CAV, of which older donor age and hyperlipidemia are well-established risk factors, whereas the others are potential risk factors.

Because donor hearts are denervated at explantation, **the transplant recipient typically will not experience cardiac angina from advanced CAV.** The clinical presentation of CAV previously unrecognized in a patient may include symptomatic or asymptomatic LV dysfunction, myocardial infarction, or cardiac arrhythmia, including ventricular arrhythmias, heart block, syncope, or sudden cardiac death. Owing to the usually asymptomatic nature of CAV, **transplant recipients require frequent surveillance studies to detect significant vasculopathy**, including coronary angiography with or without IVUS, cardiac perfusion magnetic resonance imaging, and dobutamine echocardiography. The frequency and method of surveillance remain center specific. Although coronary angiography is useful for the diagnosis of nontransplant coronary artery disease, its sensitivity is considerably less in CAV because of the diffuse nature of this disease. Coronary IVUS imaging provides useful tomographic perspective to study the development and progression of CAV and is now considered by many to be the gold standard modality for diagnosing CAV. However, not all centers have access to routine IVUS imaging and thus its use will vary greatly from center to center. The recommended nomenclature for CAV is as follows:

A. **CAV0 (not significant).** No detectable angiographic lesion

B. **ISHLT CAV1 (mild).** Angiographic left main (LM) <50%, primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction

C. **ISHLT CAV2 (moderate).** Angiographic LM <50%, a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of two systems, without allograft dysfunction

D. **ISHLT CAV3 (severe).** Angiographic LM ≥50%, two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all three systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤45% usually in the presence of regional

wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific).

TABLE 13.10 Risk Factors for the Development of Cardiac Allograft Vasculopathy

Advanced donor age
Hyperlipidemia
Donor brain death secondary to spontaneous intracranial hemorrhage
Cytomegalovirus infection
Increased C-reactive protein levels
Recurrent cellular rejection
Humoral (vascular) rejection
HLA mismatch
Donor hepatitis B and C
Female donor
Prolonged ischemic time
Pretransplant coronary atherosclerotic disease
Conventional atherosclerosis risk factors (diabetes, hypertension, and smoking)

E.HLA, human leukocyte antigen.

F. The detection of significant CAV should prompt aggressive percutaneous or more rarely surgical revascularization. Because of its relationship with chronic rejection, advancement of the immunosuppressant regimen has also been advocated. **Statins have been shown prospectively to decrease the incidence of transplant vasculopathy and improve survival**, regardless of the patient's lipid profile. Preliminary studies investigating the antiproliferative effects of TOR inhibitors suggest a significant reduction in coronary neointimal proliferation and, therefore, transplant coronary vasculopathy but larger, prospective clinical trials are needed. In severe, advanced CAV, frequently the only viable option is retransplant. Despite diagnosis of CAV the management dilemma remains.

XIII. MALIGNANCY. Malignancy is a common and devastating complication of cardiac transplantation. In immunocompetent people, the cellular arm of the immune system actively defends against a variety of neoplastic processes. With the initiation of immunosuppression after transplantation, this defense mechanism is rendered feeble and previously undeclared neoplastic foci may proliferate. Because up to 37% of patients undergo cardiac transplantation for ischemic cardiomyopathy, a significant proportion of which is smoking related, lung cancers can occur. Other common tumors include skin cancers, lymphomas, colon cancers, and breast cancers. Posttransplant malignancies are particularly common in patients who have received cytolytic or induction therapy with OKT3 (no longer used), Atgam, or Thymoglobulin, and the risk correlates with cumulative dosing of immunosuppression. The risk of developing a malignancy as a result of

immunosuppression is enhanced by the inability to adequately assess for over-immunosuppression. Under-immunosuppression is readily detected because of the development of acute rejection, whereas there is no clinical finding to suggest over-immunosuppression.

PTLD is an EBV-related clonal expansion of B-lymphocytes. PTLD may develop in any location but most commonly affects the gastrointestinal tract, lungs, and central nervous system. The primary treatment for PTLD is a reduction in immunosuppression (by about 50%), which can frequently be curative. Surgical debulking, systemic chemotherapy, and antiviral therapy may also be indicated in selected patients.

XIV. HYPERTENSION. Arterial hypertension commonly develops after cardiac transplantation secondary to the untoward effects of immunosuppression. **Hypertension developing after cardiac transplantation occurs in most cyclosporine-treated and tacrolimus-treated patients.** Three mechanisms proposed are as follows: direct sympathetic activation, increased responsiveness to direct circulating neurohormones, and direct vascular effects. A common end point of these proposed mechanisms is vasoconstriction of the renal vasculature, leading to sodium retention, and an elevated plasma volume. Corticosteroids play a minor role in the pathogenesis of cardiac transplant hypertension, which is described as a salt-sensitive type. Abnormal cardiorenal reflexes secondary to cardiac denervation may also contribute to salt-sensitive hypertension and fluid retention.

Patients with blood pressure consistently >140/90 mm Hg should be treated like the general population. Titrated monotherapy with either CCBs or ACEI/angiotensin receptor blocker (ARB) should be considered in diabetic patients; combination therapy with CCB and ACEI/ARB is most commonly employed. The use of diltiazem, verapamil, or amlodipine necessitates the use of lower doses of cyclosporine and initially more frequent cyclosporine level monitoring because these drugs are competitive antagonists of cyclosporine at the cytochrome P450 level. Problematic hypertensives requiring multiple agents often require diuretics as part of their regimen. Hypertension in some patients is inadequately controlled despite maximally tolerated doses of both CCBs and ACEIs. The final tier of management would be to add an α-blocker such as clonidine, doxazosin, or methyldopa, or a vasodilator such as hydralazine in refractory cases. β-blockers have traditionally been avoided because of their known tendency to reduce exercise performance and because of concerns about excessive bradycardia. Some transplant cardiologists, however, routinely use β-blockers to manage hypertension in their transplant patients. Thus, β-blockers are not contraindicated but rather may be used with caution.

XV. OUTCOMES AFTER CARDIAC TRANSPLANTATION. Survival outcomes after cardiac transplantation continue to improve on a yearly basis despite what is generally accepted as a population of transplant recipients at greater risk, primarily because of advancing recipient age and increasing severity of heart failure. **The 1-year survival rate after cardiac transplantation is 84% nationwide,** but it is frequently >90% at large transplant centers. The mortality in the first year after transplantation primarily results from postoperative complications, including multiorgan failure, primary graft failure, and systemic infection. Those surviving the first year posttransplantation have a median survival of 13 years. It is unlikely that any major improvements in early posttransplant survival will occur in light of these excellent results. However, a 10-year survival rate after

cardiac transplantation is only 50%. Mortality in the long term primarily results from transplant coronary vasculopathy, malignancy, and renal failure. It is hoped that a major impact can be made on long-term survival with newer immunosuppressive drug regimens that may be less nephrotoxic and more effective at preventing transplant coronary vasculopathy.

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RELEVANT WEB SITES

International Society for Heart and Lung Transplantation (ISHLT): www.ishlt.org
Scientific Registry of Transplant Recipients: http://www.srtr.org
United Network for Organ Sh

CHAPTER 14

Pulmonary Hypertension

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I. INTRODUCTION. Pulmonary hypertension (PH) is a routinely made diagnosis in contemporary cardiology and pulmonary clinics. Substantial advances are being made in the management of pulmonary arterial hypertension (PAH), which is more rapidly available at centers specializing in PH.

A. Terminology/definitions. PH is defined as mean pulmonary artery pressure (mPAP) >25 mm Hg. PH encompasses a heterogeneous group of diseases with a common clinical manifestation. The terms PH, which is a hemodynamic and pathophysiologic condition, and PAH, a clinical condition, are different terminologies that should not be used interchangeably. The clinical classification of PH is based on hemodynamic data derived from right heart catheterization (RHC). Some terminologies that are commonly employed in PH include the following:

1. **Transpulmonary gradient (TPG)** is defined as the pressure difference between mean left atrial pressure (LAP) (more commonly, pulmonary capillary wedge pressure [PCWP] is used as a surrogate) and mPAP.
2. **Pulmonary vascular resistance (PVR)** is defined as TPG divided by the cardiac output (CO) (PVR = TPG/CO in Wood units).
3. **PAH** is hemodynamically defined as PH (i.e., mPAP ≥ 25 mm Hg) with increased PVR (more than 3 Wood units) and normal wedge pressure (<15 mm Hg). It is a clinical condition characterized by precapillary PH and pathologic changes in the lung microcirculation.
4. **Pulmonary venous hypertension is characterized by mPAP ≥ 25 mm Hg, PVR > 3** Wood units, **and elevated wedge pressure (PCWP ≥ 15 mm Hg).**

B. Classification. The World Health Organization has endorsed the clinical classification of PH based upon pathologic, pathophysiologic, and therapeutic characteristics. This classification from 2008 is listed in Table 14.1.

C. Epidemiology. The total PH burden of the disease is substantial as it represents an end stage of multiple disease processes such as left-sided heart disease, chronic lung diseases, and PAH, which is very rare. Most of the patients who are diagnosed with PH on routine testing (echocardiogram with pulmonary arterial systolic pressure [PASP] >40 mm Hg) will end up having left heart disease (nearly 80%), some will have lung disease and hypoxia (10%), and only a small minority (4%) will have PAH.

Data from registries estimate the prevalence of PAH at around 15 to 50 cases per million adults and its incidence at around 2.4 cases per million adults per year. Idiopathic PAH (IPAH) and familial PAH (previously known as "primary PH") are rare diseases with a prevalence of around 6 cases per million. Familial cases account for 5% to 10% of all PAH cases. Mutations in the *bone morphogenetic protein receptor-II* (*BMPR2*) gene have been identified in about 70% of patients with familial PAH and 10% to 40% of patients with sporadic IPAH. Genetic testing and screening echocardiograms may be recommended for family members.

PAH has been associated with environmental factors such as the use of drugs and toxins. **Anorexigens** (appetite suppressant drugs that increase serotonin release and block serotonin reuptake) have been associated with PAH, with agents such as aminorex fumarate and (dex)fenfluramine. Select patient populations at an increased risk of developing PAH are discussed below.

TABLE 14.1 Dana Point Classification of Pulmonary Hypertension (Simplified)

	Type	Subtype
1	Pulmonary arterial hypertension	Idiopathic Heritable Drugs and toxins induced Associated with CTD, HIV, portal hype schistosomiasis, and chronic hemolytic Persistent PH of newborn
1′	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis	
2	PH because of left heart disease	Systolic Diastolic Valvular
3	PH because of lung disease and/or hypoxia	COPD ILD Mixed obstructive and restrictive lung dis Sleep-disordered breathing Alveolar hypoventilation syndromes, etc.
4	Chronic thromboembolic PH	
5	PH with unclear and/or multifactorial mechanisms	Hematologic Systemic such as sarcoid and vasculitis

COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; HIV, human immunodeficiency virus; ILD, interstitial lung disease; PH, pulmonary hypertension.

1. **Patients with connective tissue diseases** (CTDs), especially the **limited cutaneous form of systemic sclerosis**. The prevalence of hemodynamically proven PAH in systemic sclerosis is around 10%. In other CTDs, such as systemic lupus erythematosus, mixed CTD, rheumatoid arthritis, dermatomyositis, and Sjögren syndrome, PAH is observed less frequently.

2. **Human immunodeficiency virus (HIV) infection** is associated with approximately 0.5% incidence of PAH. However, because of this low incidence, routine screening is not recommended.
3. Patients with **cirrhosis and portal hypertension** are at an increased incidence of PH (5% of patients were referred for liver transplantation).
4. **Congenital heart disease** may lead to PAH when the underlying systemic-to-pulmonary shunt is not corrected. Most commonly, it occurs with conditions where blood flow is high and the pulmonary vasculature is exposed to systemic level pressures (e.g., ventricular septal defect and patent ductus arteriosus). However, high blood flow alone, as in atrial septal defect, may be sufficient. Once PVR approaches or exceeds the systemic vascular resistance, the shunt is reversed, leading to desaturation and cyanosis (Eisenmenger syndrome).

II. SIGNS AND SYMPTOMS

A. Symptoms. The symptoms of PH are nonspecific and are gradual in onset; therefore, there is a lag time of about 2 years (from symptom onset to diagnosis) in 90% of patients with PAH. These symptoms may include dyspnea on exertion, fatigue, weakness, chest pain, palpitations, syncope, abdominal distention, and pedal edema. Symptoms at rest occur only at late stages of the disease and portend poor prognosis.

Some patient populations are at an increased risk for developing PH and should be carefully screened by clinicians by careful history taking, examination, and laboratory tests. These populations include patients with known, or relatives of those with, BMPR2 mutations, CTD, HIV infection, portal hypertension, prior appetite suppressant use, congenital heart disease with shunt, recent acute pulmonary embolism, left heart disease, chronic obstructive pulmonary disease, interstitial lung disease, or sleep apnea.

It is advisable to perform annual screening with echocardiography in select high-risk groups, such as

1. Those with known BMPR2 mutation or those with first-degree relatives of a patient with the BMPR2 mutation;
2. Those with systemic sclerosis;
3. Those with sickle cell disease.

B. Physical examination. Physical examination may provide clues as to the cause of PH. Physical findings specific to systemic sclerosis, interstitial lung disease, or stigmata of liver disease can be helpful. Cardiovascular examination of patients with PH may reveal a left parasternal lift, a loud P_2 at the apex, a pansystolic murmur of tricuspid regurgitation that increases with inspiration, a diastolic murmur of pulmonary insufficiency, and a right ventricular (RV) S_3. Lung sounds are usually normal (except for those with class 3 PH). Jugular vein distension, hepatomegaly with a pulsatile liver, peripheral edema, and ascites are ominous signs suggestive of advanced stages with right-sided heart failure.

III. LABORATORY EVALUATION

A. Blood work

1. Routine biochemistry, hematology, and thyroid function tests should be sent.
2. **Serologic testing** is important to detect the underlying CTDs, HIV (mandatory screening), thrombophilia (in chronic thromboembolic pulmonary hypertension [CTEPH]), and hepatitis (in patients with suspected liver disease). Specific laboratory tests for the diseases in question should be sent.

3. **Biomarkers.** Several circulating biomarkers have prognostic implications in patients with PAH, but their value in everyday clinical practice is still not established. Uric acid levels are shown to be increased in patients with IPAH. Elevated plasma troponin T levels (>150 pg/mg) have been associated with worse outcomes in patients with CTEPH and PAH. Brain natriuretic peptide (BNP) levels have also been used to monitor response to therapy or clinical course, as those with persistently elevated levels have worse outcomes. Similarly, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) below cutoff levels <1,400 pg/mL has been associated with better outcomes. BNP/NT-proBNP plasma levels should be checked for the initial risk stratification and may be considered for monitoring the effects of treatment, in view of their prognostic implications. Low and stable or decreasing BNP/NT-proBNP may be a marker of successful disease control in PAH.

B. The electrocardiogram (ECG). In typical cases of PH, the ECG shows right atrial (RA) dilatation, RV hypertrophy with strain, and a right axis deviation. In advanced stages of the disease, atrial flutter or atrial fibrillation often occurs.

C. Chest radiograph. Initial chest x-rays are abnormal in majority (90%) of patients with IPAH at the time of diagnosis. There is often central pulmonary arterial (PA) dilatation with "pruning" (loss) of the peripheral blood vessels, clear lung fields, and a prominent RV border. The chest x-ray may also point to lung abnormalities and show features suggestive of left heart disease.

D. Echocardiography. If PH is suspected based on history, risk factor assessment, and physical examination, an echocardiogram is the next appropriate study. By using the Doppler technique, peak velocity of the tricuspid regurgitation jet can be measured. From this measured velocity, the pressure difference between right ventricle and right atrium can be estimated by employing the simplified Bernoulli equation ($\Delta P = 4v^2$). On condition that there is no pulmonic valve stenosis, PASP = 4 × (tricuspid regurgitant jet velocity)^2 + right atrial pressure (RAP), which can vary significantly.

Other echocardiographic characteristics may raise the suspicion of PH, such as RA or RV dilatation, flattening of the interventricular septum with D-shaped left ventricle, increased RV wall thickness, dilatation of the pulmonary artery, and presence of pericardial effusion. These features tend to occur later in the course of the disease.

Although echocardiography is a useful screening tool, Doppler-derived pressure estimation can both underestimate PASP in patients with severe tricuspid regurgitation and overestimate PASP in non-PH patients. Ultimate confirmation requires RHC.

E. Right heart catheterization. RHC is required to **confirm the diagnosis of PH, to assess the etiology and severity, and to test for vasoreactivity of the pulmonary circulation**. Consecutively, RAP, right ventricular pressure, PAP, and PCWP are recorded using a balloon-tipped fluid-filled catheter (Table 14.2). CO can be determined using the thermodilution method and/or the Fick method (measurement of mixed venous saturation SvO_2 needed). PCWP is taken as a surrogate measure of LAP and, in the absence of mitral stenosis, left ventricular (LV) end-diastolic pressure. This measurement is very important because it helps differentiate PH associated with left heart disease from other conditions.

Temporal evolution of the hemodynamic variables with progression of PAH is depicted in Figure 14.1. As the disease progresses, the right ventricle starts to fail, leading to reduction in CO. As a result, PAP may decrease again. This decrease may give a false impression of

hemodynamic improvement or suggest that there is mild to moderate disease. Therefore, it is imperative to measure PVR, which will be high in this situation. Usually, the RAP and PCWP also increase, implying RV failure and LV diastolic dysfunction, respectively. The latter is the consequence of ventricular interdependence and abnormal compliance of the left ventricle produced by an enlarged right ventricle.

Vasoreactivity testing in PAH: In PAH, vasoreactivity testing should be performed to identify patients who may benefit from long-term therapy with calcium channel blockers (CCBs). The agent most often used to test this is inhaled NO, with (intravenous [IV]) epoprostenol and (IV) adenosine as alternatives.

A positive acute response is defined as a >10 mm Hg decrease in mPAP to reach an absolute value of mPAP <40 mm Hg with an increased or unchanged CO and without significant drop in systemic blood pressure.

TABLE 14.2 Normal Values of Pressures and Measurements Derived from a Right Heart Cathet

Measured Characteristic	Normal Value
RAP	Mean 1–10 mm Hg
RVSP/RVDP	15–30/1–10 mm Hg
PASP/PADP	15–30/5–10 mm Hg (mean < 20 mm Hg)
PCWP	Mean 5–12 mm Hg
LVEDP	5–12 mm Hg
CO	5–7.5 L/min
Cardiac index	2.5–4.0 L/min/m^2
PVR	0.25–1.6 Wood units
TPG	4–6 mm Hg

CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; PASP/PADP, pulmonary artery systolic and diastolic pressures; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSP/RVDP, right ventricular systolic and diastolic pressures; TPG, transpulmonary gradient.

FIGURE 14.1 Evolution of hemodynamic variables in function of disease severity. CO, cardiac output; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance. (From Galie N, Manes A, Palazzi M, et al. Pharmacological impact on right ventricular remodelling in pulmonary arterial hypertension. *Eur Heart J*. 2007;9(H Suppl):H68–H74. Reproduced by permission of The European Society of Cardiology.)

In patients with IPAH, about 10% to 15% are acute responders and nearly half of these will prove to be long-term responders with a more favorable prognosis. This concept is less clear in other forms of PAH, although vasoreactivity testing is still recommended but controversial in congenital heart disease. It is not useful in other forms of PH (groups 1′, 2, 3, 4, and 5). In veno-occlusive disease and left heart disease, it can even provoke pulmonary

edema. However, in patients considered for heart transplantation, pulmonary vasoreactivity testing may be used to assess reversibility and operability.

It is important to understand the difference between PAH vasoreactivity testing and the assessment of PH reversibility in left-sided heart failure. In PAH, vasodilator response testing is performed to select patients who may respond favorably to CCBs as the first agent versus those who will likely not. In left-sided heart failure and PH, vasodilatory drugs that affect the LV afterload, such as sodium nitroprusside, are given with an intention to reduce LV filling pressure and evaluate for reversible PH. Those who have persistent elevation in TPG and PVR to high levels (such as when TPG remains elevated to >15 mm Hg and/or PVR is >3 Wood units despite the reduction of PCWP to <15 mm Hg) are at high risk for transplant failure, as the transplanted heart may not withstand persistently elevated PAPs, which results in right heart failure.

F. **Pulmonary testing and arterial blood gas (ABG).** Pulmonary function tests and ABGs are used to identify underlying airway or parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (typically in the range of 40% to 80% predicted) and mild to moderate reduction in lung volumes. Arterial oxygen partial pressure is normal or only slightly lower than normal at rest and arterial carbon dioxide partial pressure is decreased because of alveolar hyperventilation.

G. **Six-minute walk distance.** The 6-minute walk test (6MWT) is the most commonly employed measure of exercise capacity in patients with PH, both in clinical assessment and in research settings. In addition to the distance walked, the degree of dyspnea (Borg score) and oxygen saturation are also measured. **A 6-minute walk distance of <332 m and a drop in oxygen saturation by >10% are suggestive of poor prognosis**. It is also measured on routine follow-ups and can be indicative of clinical deterioration. It may also be used to assess the response to therapy.

H. **Other tests.** Chest computed tomography and ventilation–perfusion (V/Q) scans are indicated to exclude primary parenchymal or thromboembolic diseases as a cause of PH. For excluding thromboembolic disease, V/Q scan is the preferred screening test. A normal or low-probability V/Q scan effectively excludes CTEPH with a sensitivity of 90% to 100% and a specificity of 94% to 100%, whereas a high-probability scan warrants further evaluation with a pulmonary angiogram.

IV. PATHOGENESIS

A. **Hemodynamically, PH is a disease state with increased pulmonary pressures.** Elevation in mPAP may be a consequence of ***elevation in PCWP, increase in flow, or increase in PVR***. However, pulmonary vessels are highly compliant and capable of recruitment with progressive reduction in PVR for the increment in flow. These low-pressure, low-resistance, and high-compliance characteristics of the pulmonary vascular bed are regulated by a balance between vasodilators and vasoconstrictors and between cell proliferation and apoptosis. Genetic and environmental factors may disturb this balance, resulting in excessive vasoconstriction, vascular remodeling, and micro-thrombosis, which leads to pulmonary (arterial) hypertension. This leads to elevated PVR and an increase in RV afterload, ultimately resulting in RV dilatation and hypertrophy.

B. **Histologically, PAH is a panvasculopathy predominantly affecting the small pulmonary arteries.** The initial lesions seem to be intimal hyperplasia and medial hypertrophy followed by more irreversible lesions such as intimal fibrosis, thrombosis in situ, inflammation, and

plexiform arteriopathy. These lesions may be present in various distributions, local or diffuse, in a patient.

C. Molecular and endothelial abnormalities. Various vasoactive molecules play an important role in the pathologic evolution of PAH. Our understanding of these factors and various pathologic forces is limited, but some pathways have been elucidated mainly because of their therapeutic potential (Fig. 14.2).

FIGURE 14.2 Therapeutic targets in pulmonary hypertension. ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; cAMP, cyclin adenosine monophosphate; cGMP, cyclin guanosine monophosphate; ET, endothelin; GC, guanylate cyclase; PDE, phosphodiesterase; PGI_2, prostacyclin; PGH_2, prostaglandin H_2; NO, nitric oxide. (Reprinted from Benza RL, Park MH, Keogh A, et al. Management of pulmonary arterial hypertension with a focus on combination therapies. *J Heart Lung Transplant*. 2007;26(5):437–446. Copyright © 2007 International Society for Heart and Lung Transplantation. With permission.)

1. **Prostacyclin/thromboxane A_2.** Prostacyclin and thromboxane A_2 are arachidonic acid metabolites in vascular cells. Prostacyclin has potent vasodilating, antiproliferative, and platelet-inhibiting properties, whereas thromboxane A_2 has the opposite effect. In PAH, the balance is shifted toward thromboxane A_2 in small and medium-sized pulmonary arteries.
2. **Endothelin-1 (ET-1).** ET-1 is produced by endothelial cells and exerts its effect on the smooth muscle cells through two receptors: endothelin receptor A (ET_A), expressed on vascular smooth muscle cells, and endothelin receptor B (ET_B), expressed on both vascular endothelial cells and smooth muscle cells. Stimulation of both receptors on the vascular smooth muscle cells causes vasoconstriction and has a mitogenic effect, whereas stimulation of ET_B on the endothelial cells causes vasodilatation via increased production of prostacyclin and nitric oxide (NO). In patients with PH, ET-1 levels are increased and ET_A receptors are abundant.
3. **Nitric oxide.** NO is produced in endothelial and epithelial cells in the lung from L-arginine by three isoforms of NO synthases (NOSs). It is a potent vasodilator and an inhibitor of platelet activation and of vascular smooth muscle cell proliferation. Once formed, the effects of NO are mediated by cyclic guanosine monophosphate (cGMP), which is rapidly inactivated by the phosphodiesterase enzymes, especially type 5 (PDE-5). Decreased endothelial NOS (NOS 3) has been observed in patients with PAH.

V. TREATMENT. The treatment of group 1 PH (or PAH) is primarily in the form of pulmonary-specific vasodilator therapy, whereas treatment in groups 2, 3, and 4 PH is mainly oriented toward treating the underlying condition (such as left heart disease and chronic lung disease).

A. General measures. A few general measures apply to all the PH groups:

1. Mild physical activity, possibly via exercise rehabilitation, is beneficial.
2. Routine influenza and pneumococcal vaccinations are recommended.
3. Contraception should be discussed with females of child-bearing age, as pregnancy carries a 30% to 50% mortality risk and is contraindicated.
4. Oxygen supplementation is advised to maintain saturation above 90%.
5. Exposure to high altitude should be avoided. If flying, supplemental oxygen should be used if the patient's preflight saturation is less than 92%.
6. Diuretic therapy is indicated to manage RV failure with volume overload.

7. Digoxin may be considered in the case of atrial tachyarrhythmias.
8. Oral anticoagulation is recommended in CTEPH, in IPAH, and in advanced diseases (e.g., continuous IV therapy). In PAH, a low therapeutic value of international normalized ratio (between 1.5 and 2) is generally targeted; however, this has not been evaluated in a randomized controlled trial (RCT).

B. Pulmonary vasodilators. The initial treatment choice in PAH is guided by vasoreactivity testing. For the responders (about 10% to 15% of the IPAH population), CCBs are the first line of treatment. Careful reassessment for safety and efficacy is mandatory, because only half of these patients will prove to be long-term responders and many will need additional vasodilators. The current treatment algorithm for PAH as suggested by the 2009 American College of Cardiology Foundation/American Heart Association expert consensus document is shown in Figure 14.3.

1. **Prostacyclin analogs.** Prostacyclin is a potent endogenous vasodilator and an inhibitor of platelet aggregation and also appears to have antiproliferative activity. This may explain why *epoprostenol* (Flolan) can be used to acutely lower PAPs (as used in vasoreactivity testing) as well as to achieve long-term hemodynamic improvement in patients with PH who are nonresponders. In RCTs, epoprostenol has been shown to improve the functional class, exercise tolerance, hemodynamics, and survival in patients with IPAH. Epoprostenol has to be administered in a continuous IV infusion. *Treprostinil* (Remodulin) is another prostacyclin analog that can be administered by inhalation, orally, or via continuous subcutaneous pump. It has been shown to improve the exercise capacity, hemodynamics, and symptoms. Infusion site pain is the most common side effect. *Iloprost* (Ventavis) is available as an aerosol administration and has a proven beneficial effect in patients with PAH and CTEPH.

FIGURE 14.3 PAH treatment algorithm. CCB, calcium channel blocker; ER_A, endothelin receptor antagonist; IV, intravenous; PDE-5 Is, phosphodiesterase type 5 inhibitors; SC, subcutaneous. (Reprinted from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension. *J Am Coll Cardiol*. 2009;53(17):1573–619. Copyright © 2009 American College of Cardiology Foundation and the American Heart Association, Inc. With permission.)

2. **Endothelin receptor antagonists (ERAs).** *Bosentan* (Tracleer) is an oral active dual ET_A/ET_B receptor antagonist that has been shown to improve the exercise capacity, functional class, hemodynamics, and cardiac performance as measured by echocardiography and clinical outcomes. *Sitaxsentan* and *ambrisentan* are more selective ET_A receptor antagonists with similar benefits as bosentan. Liver injury and teratogenicity are major concerns and require monthly monitoring.
3. **PDE-5 inhibitors.** Orally active PDE-5 inhibitors prevent the degradation of cGMP, causing vasorelaxation. *Sildenafil* (Revatio) has favorable effects on exercise capacity, symptoms, and hemodynamics. Tadalafil (Adcirca) has the same effects, although it also delays the time to clinical worsening. Headache, flushing, dyspepsia, and epistaxis are the usual side effects.

In low-risk patients, oral therapy with ET receptor antagonists or PDE-5 inhibitors is the first choice, whereas IV epoprostenol is reserved for the high-risk population. Combination therapy is being routinely employed if treatment goals are not achieved with one compound ("goal-directed therapy"). The rationale is based on attacking different pathologic processes with different agents.

4. **Soluble guanylate cyclase (sGC) stimulators.** The sGC stimulators are a new class of medication for PH that act by stimulating sGC directly and by increasing its sensitivity to NO. This in turn causes vasodilation and inhibits smooth muscle proliferation. It is approved for treatment of both primary PH and CTEPH on the basis of improvements in 6-minute walk distance which were comparable to other oral agents.

C. **Treatment of non–group 1 PAH.** Many pulmonary vasodilators have been evaluated for various non-PAH groups such as left-sided heart disease and lung disease. The following recommendations are based on current evidence:

1. **Group 2 PH (left-sided heart disease).** Prostanoids and ERAs are associated with an increased event rate in patients with LV dysfunction and are contraindicated. There is some evidence of improvement in the quality of life, exercise performance, and hemodynamics with sildenafil in patients with left heart disease and in patients bridged to transplantation with an LV assist device.
2. **Group 3 PH (lung disease of hypoxia).** Pulmonary vasodilators are not recommended.
3. **Group 4 PH (CTEPH).** Prostanoids, ERAs, PDE-5 inhibitors, and sGC stimulators may be used prior to surgery to improve hemodynamics. They may be used in patients with predominant peripheral disease or in those with persistent PH after surgery.

D. **Surgical therapies.** In CTEPH, surgery (pulmonary endarterectomy) is potentially curative in patients with accessible (proximal) disease. It is recommended that surgical evaluation and procedure be performed at high-volume centers. Balloon atrial septostomy is rarely performed for palliation in patients with advanced PAH with recurrent syncope and/or right heart failure who have failed all available medical treatments. RV assist devices have emerged as a therapy in postoperative RV failure in the presence of PH. Heart–lung transplantation should be considered in a subset of eligible patients who remain in New York Heart Association functional class III or IV or in those who cannot achieve a significant exercise and hemodynamic improvement after 3 months of epoprostenol therapy.

VI. Controversies.

Several controversies exist in the clinical and research arenas regarding PH, leading to frequent difference of opinions among referring internists, pulmonologists, and cardiologists. It is therefore important to identify such areas of concern. This may help target future research and identify those patients who would benefit from management at a specialized center where a multidisciplinary approach may be provided.

A. Most therapies (except epoprostenol) in PAH have not shown mortality benefits. Most therapeutic trials are small randomized clinical trials with soft end points such as 6MWT, exercise tolerance, and improvement in dyspnea scoring. Although this raises valid concerns regarding the long-term benefit of many expensive drugs, it is interesting that the overall survival in this patient population is improving.

B. Pulmonary vasodilators have generally been ineffective or harmful in patients with left-sided heart failure. However, PDE-5 inhibitors are an exception, as there have been multiple small studies that suggest improvement in exercise parameters and hemodynamics. One study, PhosphodiesterasE-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure Study, is currently enrolling participants to study the effect of sildenafil in patients with diastolic heart failure.

C. In “out-of-proportion” PH, many patients with left-sided heart failure may have only modest increase in PCWP (<22 to 25 mm Hg) but very high PAP (systolic PAP > 60 mm Hg) with

high TPG (>18 mm Hg). This usually happens in patients who have developed a "fixed" PH, as opposed to a very few who have both left-sided heart failure and PAH.

TABLE 14.3 Prognostic Variables in Pulmonary Hypertension

Lower	Determinants of Risk	Hig
No	Clinical evidence of RV failure	Ye
Gradual	Progression	Ra
II, III	WHO class	IV
Longer (>400 m)	6-Min walk distance	Sh
Minimally elevated	BNP	Ve
Minimal RV dysfunction	Echocardiographic findings	Pe Sig
Normal/near-normal RAP and CI	Hemodynamics	Hig

D.BNP, brain natriuretic peptide; CI, cardiac index; PH, pulmonary hypertension; RAP, right atrial pressure; RV, right ventricular; WHO, World Health Organization.

E.Adapted from McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126:78s–92s.

F. Pulmonary vasoreactivity is often used in heart transplant candidates with "out-of-proportion" PH by administering sodium nitroprusside or nitroglycerin in the cardiac catheterization laboratory and assessing hemodynamics with reduction in PCWP. Those who have reduction in PAP and TPG may be able to undergo transplantation without right heart failure.

G. The treatment for "out-of-proportion" PH is primarily focused on treating the underlying left-sided failure.

VII. PROGNOSIS AND FOLLOW-UP

A. Prognosis. Survival in patients with PH differs between PH groups and also within each group depending on the etiology. Best data regarding prognosis are available for the IPAH subset population. The natural history of this group shows survival rates of 68%, 48%, and 34% after 1, 3, and 5 years, respectively. There is registry level evidence that prognosis has improved with pulmonary vasodilator therapies. Table 14.3 outlines clinical, echocardiographic, and hemodynamic features that may predict the prognosis in patients with PAH. Again, these data are mainly derived from the IPAH population, and it is unknown whether these data are transferable to other P(A)H populations.

B. Follow-up

1. Routine evaluation. Assessment at each visit should include physical examination, assessment of functional class, 6MWT at each visit, and echocardiogram at 6 to 12 months. Blood work including biomarkers are usually performed at each visit or with change in clinical status or therapy; RHC is performed every 6 to 12 months in unstable patients, whereas in stable patients it is performed when there is clinical deterioration or change in therapy.

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CHAPTER 15

Aortic Valve Disease

James Gentry III

I. AORTIC STENOSIS

A. Introduction. Aortic stenosis (AS) causes progressive obstruction of the left ventricular outflow tract (LVOT), resulting in pressure hypertrophy of the left ventricle and the classic symptoms of heart failure, syncope, and angina pectoris. Stenosis most commonly occurs at the level of the valve; however, subaortic stenosis and supravalvular stenosis are also well-defined entities. Untreated AS is associated with significant morbidity and mortality. As prompt recognition and treatment are associated with improved life expectancy in those patients with symptomatic severe AS, careful evaluation and management can have a significant impact on survival.

B. Etiology

1. Valvular AS has several causes, including congenital, rheumatic, bicuspid, and most commonly inflammation with resultant calcification.

a. The most common cause of AS in the United States is calcific degeneration. Although initially thought to be the result of normal "wear and tear" of the valve leaflets, there is now ample evidence that suggests that the progression of stenosis is related to an **active**process of inflammation involving the renin–angiotensin system, lipid accumulation, and resultant calcification. Several inflammatory pathways are implicated, including those that utilize osteopontin, bone morphogenic proteins, and receptor activator of nuclear factor-κB ligand. Recent studies suggest that those with excess lipoprotein (a) are at greater risk of aortic valve calcification and progression to stenosis.

Aortic sclerosis is caused by calcification and thickening of the aortic valve without the increased gradients seen in AS. Both aortic sclerosis and calcific AS have been associated with traditional risk factors for atherosclerosis, such as smoking, hypertension, and hyperlipidemia. Aortic sclerosis is associated with increased risk of cardiovascular death and myocardial infarction and can progress to AS. Other conditions associated with calcific AS include Paget disease and end-stage renal disease.

b. Bicuspid aortic valve (BAV) is the most common congenital heart defect with a prevalence estimated between 0.5% and 2% with a 3:1 male predominance. It is present in ~10% of first-degree relatives; thus, all first-degree relative of patients with BAV should undergo echocardiographic screening for BAV. The most common abnormality seen in bicuspid valves is fusion of the right and left coronary cusps (79.3%); whereas right and noncoronary cusps (19.4%) are less common, and least common is left and noncoronary cusp fusion (0.5%; Fig. 15.1). Concurrent dilation of the thoracic aorta occurs in as many as 50% of

patients, while coarctation, aortic dissection, and coronary anomalies are seen in a minority of patients. BAV may be associated with Shone syndrome (in which multiple left-sided lesions of inflow/outflow obstruction occur), Williams syndrome with supravalvular stenosis, and Turner syndrome with coarctation. Severe AS usually develops by the fifth or sixth decade; however, earlier and later presentations are common.

FIGURE 15.1 A schematic representation of parasternal short axis of a congenitally abnormal aortic valve.

1. **(1) Diagnosis.** The mainstay of diagnosis is echocardiography (transthoracic or transesophageal if transthoracic imaging is suboptimal; 92% sensitivity and 96% specificity if adequate images are obtained). The diagnosis is made during systole in the short-axis view and classically the valve opens as an oval rather than as a triangle in normal people. In situations when echocardiography is nondiagnostic, cardiac magnetic resonance imaging (MRI) and computed tomography (CT) can be used to improve the diagnostic accuracy (ACC/AHA class I indication).
2. **(2) Complications**

1. **(a) Infective endocarditis.** The lifetime risk of infective endocarditis (IE) in the current era is 3%. On the basis of these data, prophylactic antibiotic therapy for dental procedures in isolated BAV is no longer recommended except in patients with prior IE. Unfortunately, when IE does occur in BAVs, it is associated with a higher incidence of perivalvular abscess and worse outcomes compared with tricuspid aortic valves.
2. **(b) Aortopathy** is present in ~50% of individuals with BAV and typically involves the aortic annulus, sinus, and proximal ascending aorta. In patients undergoing aortic valve replacement (AVR), 30% will require concomitant aortic root surgery. Per the 2014 ACC/AHA valve guidelines, aortic surgery is indicated when the aorta is ≥5.5 cm (class I) and there is no indication for valve surgery. However, if the patient is undergoing concurrent AVR and aorta is ≥4.5 cm concomitant aortic replacement is a class IIa indication. When the aorta is ≥5.0 cm and the rate of increase in diameter is ≥0.5 cm/y, this is considered a class IIa indication for aortic replacement. In addition, if the surgery is to be performed by an experienced aortic surgical team and the patient has a low surgical risk, it is reasonable to perform aortic surgery once the aorta is ≥5.0 cm. Increasingly, the impact of patient size on aorta size is being appreciated and therefore when the maximal ascending/aortic root area in square centimeter divided by patient's height in meters exceeds 10, this is considered an indication for surgical intervention by some authorities. In addition, serial evaluation of the aortic sinuses and ascending aorta by echocardiography, cardiac MRI, or CT angiography is recommended in all patients with BAV and should be performed annually in patients with aortic diameter >4.0 cm (ACC/AHA class I).

c. **Unicuspid aortic valve (UAV)** is a rare valvular anomaly and is described as being either pinhole-shaped acommissural UAV (typically presents at birth) or slit-shaped unicommissural UAV (Fig. 15.1). Patients typically present for cardiac surgery in their 30s and UAV shares many of the features of BAV including risk of aortopathy, aortic dissection, IE, coronary artery anomalies, PDA, and coarctation.

d. **Rheumatic AS** often coexists with aortic regurgitation (AR) and mitral valve lesions, especially mitral stenosis. It is a rare cause of isolated severe AS in the industrialized world. Fusion of the commissures occurs, leaving a small central orifice.

2. **Subvalvular AS** is a congenital condition, although it may not be apparent at birth. Typically, a circumferential **fibromuscular membrane involving the anterior**

mitral valve leaflet is present in the LVOT below the aortic valve. In more extreme cases, a tunnel-like obstruction may be present, rather than a discrete membrane. The pathogenesis of this condition is not perfectly understood but is thought to represent a maladaptive response to abnormal flow dynamics in the LVOT. It may exist with other left-sided obstruction lesions, such as coarctation or as part of Shone syndrome. The condition may recur even after successful membrane resection. Subvalvular AS may be difficult to distinguish from hypertrophic cardiomyopathy, especially when secondary left ventricular hypertrophy (LVH) is pronounced.

3. **Supravalvular AS** is uncommon and may occur as part of a congenital syndrome such as Williams syndrome in which a mutation in the elastin gene occurs. Characteristic features of Williams syndrome include hypercalcemia, elfin facies, developmental delay, small stature, and multiple stenoses in the aortic and peripheral arteries. Lipid deposits in severe forms of familial hypercholesterolemia may also cause obstruction above the valve in the ascending aorta.

C. Pathophysiology

1. **Pressure overload**. All forms of AS are characterized by progressive narrowing of the LVOT. To maintain cardiac output in the face of increased afterload, the left ventricle must generate higher systolic pressures, which increases LV wall stress. In response to the pressure overload and increased wall stress, the left ventricle undergoes compensatory concentric hypertrophy. The increase in LV wall thickness allows the wall stress to normalize according to Laplace's law: wall stress = (pressure × radius)/(2 × thickness). Eventually, the LV is unable to adequately compensate for the pressure overload and LV dilatation and systolic dysfunction ensue (Fig. 15.2).

2. **Diastolic dysfunction**. LV diastolic function is determined by LV relaxation properties and LV compliance (i.e., change in volume with change in pressure [dV/dP]). Increased afterload and LVH lead to a reduction in LV compliance. Furthermore, there are changes in strain and torsion characteristics of the left ventricle in AS. Passive early diastolic filling is reduced, and maintenance of an adequate LV preload becomes more dependent on active left atrial contraction.

3. **Supply–demand mismatch**. Myocardial oxygen is determined by heart rate, contractility, and myocardial wall stress imposed on the left ventricle by progressive pressure overload. As the AS becomes more severe, wall stress and myocardial oxygen demand increase in parallel. Concurrently, AS is associated with a decrease in myocardial oxygen supply. Progressive LVH and diastolic dysfunction lead to an elevation in left ventricular end-diastolic pressure (LVEDP). Elevated LVEDP leads to decreased perfusion pressure across the coronary bed and causes endocardial compression of small intramyocardial arteries, impairing coronary flow reserve. The imbalance between myocardial oxygen supply and demand can precipitate ischemia during exertion even in the absence of significant obstructive coronary disease.

FIGURE 15.2 Aortic stenosis: left ventricular compensatory response. LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

D. Natural history.

The classic survival curve for patients with untreated AS, as described by Ross and Braunwald, is shown in Figure 15.3.

1. **Asymptomatic patients**

a. The disease process of AS is characterized by a long latent phase, during which the patient has no symptoms. This period is associated with near-normal survival. The risk of sudden cardiac death in asymptomatic patients with critical AS is <2% per year.

b. Although the underlying cause helps predict the age of symptom onset, there is marked individual variability in the length of the latent period and the subsequent rate of progression of disease. In general, among asymptomatic valvular AS patients, the mean aortic valve gradient rises by 7 mm Hg/y, peak transvalvular velocity increases by 0.1 to 0.3 m/s/y, and aortic valve area (AVA) decreases by 0.1 cm^2/y.

FIGURE 15.3 Patient survival in aortic stenosis.

c. Because of the variable rate of disease progression, all patients with AS should be advised to report the onset of any symptoms to their physician and should be followed clinically and with Doppler echocardiography with increasing frequency as the lesion progresses.

1. **(1) Frequency of echocardiograms per 2014 ACC/AHA guidelines**

1. **(a)** Mild—Every 3 to 5 years
2. **(b)** Moderate—Every 1 to 2 years
3. **(c)** Severe—Every 6 to 12 months

d. Once the **valve becomes severely stenotic, as evidenced by a peak Doppler velocity of 4 m/s, the likelihood of development of symptoms or requiring surgical intervention over the following 2 years is very high.** This likelihood is increased if the valve is heavily calcified.

2. **Symptomatic patients.** When symptoms of AS develop, the survival rate decreases markedly, unless AVR is performed.

a. Patients with **angina** have a 50%, 5-year survival rate without surgical intervention. Those with **syncope** have a 50%, 3-year survival rate without surgical intervention. Patients with **heart failure** have a mean survival time of <2 years if treated medically.

b. In patients with severe, symptomatic AS, sudden cardiac death can occur in the setting of hypotension or arrhythmia due to ischemia, LVH, or impaired LV function. Resuscitation in this situation is difficult because of the difficulty of obtaining adequate transmural LV perfusion and cardiac output.

c. Signs and symptoms of severe AS may be subtle in some patients. Since AS is a slowly progressive disease, patients may subconsciously adapt their activities and thus remain "asymptomatic." Information concerning activity levels from family members may be useful in this situation, as may a symptom-limited stress echocardiogram to quantify the patient's functional capacity. **Exercise stress testing is absolutely contraindicated in the setting of definite symptoms (class III).**

E. Clinical manifestations

1. **Signs and symptoms.** The onset of symptoms usually indicates progression to severe AS and heralds the need for surgical evaluation.

a. **Angina.** Patients with severe AS can experience ischemia from myocardial supply–demand mismatch due to high LV diastolic pressures, decreased myocardial perfusion, and increased wall stress. Angina can also result from underlying coronary artery

disease (CAD). CAD is common among patients with severe AS and occurs in 40% to 80% of patients with angina and 25% of patients without angina.

b. **Syncope.** Because of a fixed LVOT obstruction, patients with severe AS are unable to augment their cardiac output under conditions of low systemic vascular resistance (SVR) (i.e., induced by certain medications or vasovagal reactions). The ensuing hypotension can cause presyncope, syncope, or even cardiovascular collapse and death. Syncope can also result from atrial or ventricular arrhythmias, abnormal baroreceptor function, or abnormal vasodepressor responses induced by LV pressure overload.

c. **Heart failure** symptoms, such as exertional dyspnea, orthopnea, or paroxysmal nocturnal dyspnea, and fatigue, may result from LV systolic or diastolic dysfunction.

2. Physical findings

a. **Arterial examination.** A hallmark finding in AS is a diminished and delayed carotid upstroke, pulsus parvus et tardus. However, elderly patients with noncompliant vessels or patients with concomitant AR may often maintain a normal carotid pulsation, despite severe AS. These findings are rare with obstruction above or below the valve. It is classically thought that severe AS is not associated with hypertension, as the narrowed valve limits the flow into the arterial system and thus gives rise to a narrowed pulse pressure and relative hypotension. In fact, in the elderly, hypertension and severe AS may often coexist, likely as a result of impaired elasticity of the aortic walls, and the finding of arterial hypertension does not preclude significant associated AS.

b. **Palpation.** With LVH and normal LV cavity dimensions, the apical impulse is usually nondisplaced, diffuse, and sustained. However, the apical impulse may later be displaced when there is LV systolic dysfunction. A double apical impulse represents a palpable *a*wave or S_4, caused by a noncompliant left ventricle. A systolic thrill may be palpable in the second right intercostal space.

c. **Auscultation.** The main auscultatory findings are shown in Figure 15.4.

1. **(1)** The typical murmur of AS is a systolic ejection murmur heard at the right upper sternal border that radiates to the neck. With a mobile bicuspid valve, an aortic opening sound or **click** may precede the murmur. As the severity of the stenosis increases, the murmur becomes longer and peaks later in systole. The intensity of the murmur does not necessarily correspond to the severity of AS. S_1 is usually normal in AS. As the AS becomes more severe, the aortic component of S_2 diminishes and eventually disappears, resulting in a soft, single S_2. Often, with severe AS, S_2 is paradoxically split because of the prolonged ejection duration through the severely narrowed valve. S_3 is indicative of poor LV systolic function. An S_4 is common because of reduced LV compliance.
2. **(2)** Careful examination for other murmurs should be performed. AS is often accompanied by AR. Maneuvers performed during the physical examination can help differentiate different types of LV outflow obstruction, whether this is at, below, or above the valve. These are summarized in Table 15.1.

3. Diagnostic testing

a. The typical **electrocardiogram (ECG)** of a patient with isolated severe AS usually demonstrates left atrial abnormality (80% of cases) and LVH (85% of cases) but a normal electrocardiogram does not exclude severe AS.

b. **Chest radiography** can be entirely normal, even in patients with critical LVH. The cardiac silhouette may become boot-shaped because of the concentric LVH.

Cardiomegaly may be identified if there is LV dysfunction or coexisting AR. Aortic valve and root calcification can be seen in adults with severe calcific, degenerative AS. Poststenotic dilation of the ascending aorta may also be evident.

c. **Natriuretic peptides** are released in response to pressure overload of the LV. There is increasing evidence that supranormal levels of these peptides may indicate early decompensation of the LV even in the presence of normal left ventricular ejection fraction (LVEF). Anemia commonly coexists with AS in the elderly who appear to be at increased risk of dysplastic vascular lesions in the bowel, which may bleed. Increased risk of bleeding may also occur because of disruption of Von Willebrand molecules with turbulent flow at the stenotic aortic valve (Heyde disease). Rarely, AS is so severe and turbulent to lead to intravascular hemolysis in a native valve.

FIGURE 15.4 Auscultatory findings in aortic stenosis. LVH, left ventricular hypertrophy; LV, left ventricle.

TABLE 15.1 Physical Findings and Maneuvers Useful in Distinguishing Various Forms of Obstruction

Maneuver Finding	Valvular	Supravalvular	Subvalvular
Pulse volume after PVC	Increases	Increases	Increases
Valsalva effect on systolic murmur	Decreases	Decreases	Decreases
AR	Common	Rare	Common
S_4	Common	Uncommon	Uncommon
Carotid pulse	Normal to anacrotic (parvus et tardus)	Unequal	Normal to anacrotic

Abbreviations: AR, aortic regurgitation; PVC, premature ventricular contraction.

4. **Severity of AS**. The severity of AS as defined by the 2014 ACC/AHA valve guidelines is summarized in Table 15.2. A normal aortic valve opens 3 to 4 cm^2.

TABLE 15.2 Aortic Stenosis Severity Parameters

Valve Severity	AVA (cm^2)	Mean Gradient (mm Hg)	Jet Velocity (Vmax) (m/s)	Miscellaneous
Mild	>1.5	<20	2.0–2.9	
Moderate	1.0–1.5	20–30	3.0–3.9	
Severe	0.6–1.0	≥40	≥4.0	
Very severe	<0.6	≥60	≥5	
LFLG severe	<1.0	<40	<4	LVEF < 50%; DSE

TABLE 15.2 Aortic Stenosis Severity Parameters

				cm^2
Pseudosevere	<1.0	<40	<4	LVEF < 50%; DSE
Paradoxical LFLG	<1.0	<40	<4	LVEF ≥ 50%; stroke DSE increases AVA

[a] Dependent on the presence of contractile reserve (20% increase in stroke volume with DSE).

Abbreviations: AVA, aortic valve area; DSE, dobutamine stress echocardiography; LFLG, low-flow/low-gradient; LVEF, left ventricular ejection fraction; Vmax, aortic valve maximum velocity.

7. Echocardiography

a. Transthoracic Doppler echocardiography is the test of choice to establish the diagnosis of AS, to determine the cause and location, and to assess its severity. It should be performed when the diagnosis of AS is first suspected and information such as LV wall thickness, size, and function should also be obtained. After the diagnosis is established, patients should have frequent regular clinical follow-up examinations to look for the development of symptoms. Development of new symptoms and signs should quickly prompt a repeat evaluation.

1. (1) The parasternal long-axis views, two-dimensional and M-mode, provide valuable information for determining the mechanism and severity of AS. In this view, the coaptation line of the aortic valve is normally centered within the LVOT in a trileaflet valve. The leaflets of a bicuspid valve often have an eccentric closure line, typically posterior to the midline. Systolic leaflet doming can be seen in congenital AS and rheumatic AS. The degree of LVH, chamber enlargement, or left atrial enlargement can be quantitated using two-dimensional and M-mode imaging. The LVOT diameter used in the continuity equation is measured in the two-dimensional, parasternal long-axis view.

Subaortic stenosis and supravalvular AS may also be detected in this view. **Subaortic stenosis** may be evident as a membrane below the aortic valve with normal opening of the valve. Pulsed Doppler may indicate that the obstruction is occurring below the valve, and two-dimensional echocardiogram often shows AR because of the turbulent jet hitting the aortic valve leaflets and causing leaflet scarring and impaired coaptation. In **supravalvular AS**, narrowing above the valve is evident on imaging.

2. (2) The parasternal short-axis view is the most useful view for establishing the cause of congenital AS. The number of commissures and the shape of the valve orifice should be assessed (Fig. 15.1). In diastole, the valve appears as three commissures and three cusps of equal size creating an inverted Y configuration or "Mercedes-Benz sign." However, this view alone should not be used to determine the anatomic morphology of the valve because in "functionally" bicuspid valves from commissural fusion, a raphe is present creating the appearance of a trileaflet valve. Thus a systolic image should be used to evaluate whether there is a triangular opening (trileaflet) or ellipsoid appearance (bicuspid valve). In UAV, the opening is elliptical but occurs across a radius rather than the diameter of the valve.

3. **(3)** The apical five-chamber and three-chamber views are well aligned with flow through the aortic valve. Continuous wave Doppler recordings across the aortic valve and pulsed wave Doppler flow in the LVOT proximal to the aortic valve are recorded in these views for the continuity equation.
4. **(4)** Continuous wave Doppler should be performed at multiple sites, including the suprasternal notch and the right sternal border, to ensure that the maximal velocity across the aortic valve is recorded. **Failure to obtain the maximum velocities will result in underestimation of the severity of AS**. The dimensions of the ascending aorta should be sought, especially in those with BAV.
5. **(5)** Newer technologies such as strain imaging are increasingly being employed in the assessment of ventricular function especially in those with normal LVEF. There is an increasing body of evidence that global myocardial strain may be abnormal before the LVEF deteriorates and may of itself be an indicator of higher long-term risk.

b. Transesophageal echocardiography (TEE). Planimetry of the aortic valve orifice is often possible with TEE and relates well to that measured by cardiac catheterization. Planimetry is difficult when the valve is extremely calcified. In a bicuspid valve, the smallest area should be sought carefully, as the valve opening in not planar but rather forms a cone because of the doming of the valve as it opens. TEE is particularly useful for determining the morphologic features of the valve in congenital AS. TEE is often necessary to confirm the diagnosis of subaortic membrane and to differentiate it from hypertrophic cardiomyopathy or valvular AS.

c. Dobutamine stress echocardiography (DSE) and exercise stress echocardiography (ESE). When discrepancy exists in regard to the severity of valve disease and symptoms, exercise stress testing can be helpful in objectively quantifying their functional capacity and appropriate classification of their valve disease. In patients with asymptomatic severe AS, two-thirds of ESEs are abnormal including one-third being attributed to development of symptoms alone. In addition, a normal test provides reassurance with an excellent 1-year prognosis with continued medical management and monitoring for the development of symptoms.

Low-dose DSE is also helpful in appropriately classifying the low-flow, low-gradient AS patients into true severe AS, pseudosevere AS, or paradoxical severe AS.

d. Other imaging modalities. CT scanning is increasingly used in the assessment of AS patients particularly those in whom transcatheter aortic valve replacement (TAVR) is a consideration to determine appropriate valve and peripheral vessel sizing and to avoid complications such as coronary impingement, aortic size and calcification, and other comorbidities. When there is doubt about severity of AS, the degree of calcification of the aortic valve by CT imaging may provide useful information. MRI is helpful in patients with congenital forms of AS associated with other anomalies and in assessment of the aorta or concomitant AR.

8. Hemodynamic calculations

a. Doppler echocardiography is the standard modality used for the assessment of transvalvular pressure gradients and AVA.

1. **(1) Simplified Bernoulli equation ($\Delta P = 4\,v^2$)**, in which P is pressure and v is peak velocity of flow across the aortic valve, is used to estimate the peak instantaneous gradient. The mean gradient across the valve can be determined by measuring the area under the Doppler envelope. The peak velocity of flow across the aortic valve should be measured in three areas: the LV apex, the right sternal border, and the suprasternal notch. The highest measured velocity is used to calculate the

peak transvalvular gradient. When stenosis is present at two levels (i.e., in LVOT and at the valve), the gradient across the LVOT reflects the integrated effects of the obstruction at both levels. It is usually impossible with Doppler to precisely differentiate the contribution of each level of obstruction to the total. This may be inferred by analysis of the images, by TEE, or by direct measurement by cardiac catheterization.

2. **(2)** Calculation of AVA based on the **continuity principle**, which states that flow of an incompressible fluid in a closed system must remain constant. Flow in a vessel is the product of the cross-sectional area (A) of the vessel and the velocity (V). Area is calculated as πR^2 or $\pi D^2/4 = 0.785D^2$, where R is the radius of the vessel and D is the diameter. A schematic representation of the variables for calculating AVA is shown in Figure 15.5. The continuity equation for the aortic valve is as follows:

$$\text{Area}_{\text{aortic valve}} = \text{diameter}_{\text{LVOT}}^2 \times 0.785 \times \text{VTI}_{\text{LVOT}}/\text{VTI}_{\text{aortic valve}}$$

In the above equation, VTI is the time–velocity integral. The continuity equation is valid only for valvular AS. It cannot be used to assess valve area when there are stenoses in series such as valvular and subvalvular narrowing occurring simultaneously.

3. **(3)** Care should be taken to avoid measuring post-extrasystolic beats. If the patient is in atrial fibrillation, ideally 10 consecutive beats should be measured and averaged for both velocity measurements.

4. **(4)** During evaluation of an aortic valve prosthesis, the standard continuity equation cannot be used. Instead, the velocity ratio or dimensionless index is used to estimate the severity of prosthetic stenosis. It is calculated by dividing the peak velocity in the LVOT by the peak velocity through the aortic valve. **A dimensionless index of <0.25 is generally accepted to represent severe stenosis**. This is also useful if the LVOT diameter is difficult to ascertain.

b. **Cardiac catheterization** was once considered the gold standard for the quantification of AS but is now only indicated in symptomatic patients when there is discrepancy between physical examination and noninvasive testing or when noninvasive tests are inconclusive in regard to the severity of the valve lesion (ACC/AHA class I indication).

FIGURE 15.5 A schematic representation of parasternal long-axis view and the continuity principle. LA, left atrium; LV, left ventricle.

1. **(1)** Preoperative left heart catheterization is indicated before valve intervention in patients with symptoms of angina, objective evidence of ischemia, decreased LV systolic function, history of CAD, or coronary risk factors (including men >40 years old and postmenopausal women) (ACC/AHA class I indication).

2. **(2)** Catheter-derived hemodynamics often differ from those of echocardiography and thus it is important to understand the differences in what is being measured. The mean gradients obtained during catheterization should be equivalent to the mean gradients obtained by echocardiography. These correlate well when performed expertly and simultaneously. The peak gradient measured during catheterization is the peak-to-peak gradient, which is lower than the peak instantaneous gradient obtained with echocardiography (Fig. 15.6). **In the setting of reduced cardiac output of any cause, the aortic gradient may be lower and may be <20 mm Hg in severe LV dysfunction despite critical AS.**

3. **(3)** The most precise measurement of transaortic valvular gradient is made with two different catheters (one in the LV cavity and the other in the ascending aorta or with a double lumen pigtail

catheter). A less optimal method is measuring the peak-to-peak gradient by catheter pullback from the left ventricle to the ascending aorta. A typical pressure tracing of simultaneous LV and aortic pressures is shown in Figure 15.6.

4. **(4)** Catheterization of the patient with severe AS should be performed with low-osmolar, nonionic contrast agents. These cause less hypotension because of peripheral arterial vasodilation, less bradycardia, less transient myocardial dysfunction, and less osmotic diuresis after the procedure. Left ventriculography should be avoided.

5. **(5)** The **Gorlin formula** is used to estimate the AVA:

$$\text{AVA (cm}^2\text{)} = \text{cardiac output}/(44.3 \times \text{heart rate} \times \text{SEP} \times \sqrt{\text{MVG}})$$

In the above equation, SEP is the systolic ejection period, defined as the time from aortic valve opening to closing (in seconds), and MVG is the mean valvular gradient (mm Hg). The **Gorlin formula** measures the **true anatomic area** of the aortic valve, as it has a correction factor (the discharge coefficient) to account for the difference of flow across the true anatomic valve versus the flow at the level of the vena contracta. The continuity equation measures the physiologic area (vena contracta) and as such is smaller than that measured by Gorlin.

FIGURE 15.6 Simultaneous recording of LV and aortic pressures. AO, aorta; LV, left ventricle.

An alternative measurement can be made by the Hakki equation, which is a simplification of the Gorlin formula, where the observation of heart rate × SEP approximates 1,000. This then simplifies the estimation of AVA:

$$\text{AVA (cm}^2\text{)} = \text{cardiac output}/\sqrt{\text{MVG}}$$

F. Therapy

1. **Medical therapy.** The mainstay of therapy for AS is replacement of the aortic valve. Onset of symptoms in patients with severe AS is associated with a marked reduction in lifespan when treated medically, rather than replacement. Medical therapy alone is ineffective for severe symptomatic valvular AS.

a. **Antibiotic prophylaxis.** The 2007 AHA guidelines for the Prevention of Infective Endocarditis do not recommend antibiotic prophylaxis before dental procedures with valvular pathology including BAVs unless the patient has a valve prosthesis or prior history of IE.

b. **Medical therapy in patient at risk for developing AS and asymptomatic AS.** Therapy should be directed at primary prevention of CAD, maintenance of sinus rhythm, and blood pressure control. Patient with hypertension should be treated according to guideline-directed medical therapy and started at a low dose, and slowly titrated upward as needed with appropriate clinical monitoring (ACC/AHA class I). ACE-inhibitors are no longer contraindicated and are potentially advantageous through a reduction in LV fibrosis. Alternatively, diuretics should be avoided solely for the use as an anti-hypertensive if the LV size is small as this can result in a decrease in cardiac output.

c. **Medical therapy in symptomatic patients.** Medical therapies may be necessary in patients with symptomatic severe AS who are awaiting surgery or who are considered inoperable and require palliation. Therapy for heart failure is directed at relief of

pulmonary congestion. This is usually achieved with cautious use of diuretics. Overly aggressive diuresis may cause hypotension if hypovolemia significant impairs cardiac output by diminishing preload. Nitrates may also cause hypotension and syncope by reducing preload and should be avoided or used with extreme caution. Thus, the management of symptomatic patients with AS and CAD is difficult, and urgent surgery is the optimal treatment where feasible. Digoxin is used for symptom relief in the setting of impaired LV systolic function and volume overload, particularly if atrial fibrillation develops.

d. **Vasodilator therapy** has been formerly relatively contraindicated in patients with AS because of the concern about lowering SVR in the setting of a fixed cardiac output causing syncope, especially in the ambulatory setting. However, patients with severe heart failure and LV dysfunction with severe AS may benefit from the careful titration of intravenous nitroprusside in the intensive care unit with concomitant invasive arterial and pulmonary artery catheter monitoring (ACC/AHA class IIb). One study suggests an improvement in hemodynamic indices with this approach. Intra-aortic balloon counterpulsation is another strategy that can be used while patients with LV dysfunction and severe AS in cardiogenic shock are worked up toward urgent surgery. Asymptomatic patients who have been successfully treated with vasodilator therapy for hypertension over a period of years do not necessarily need to have this adjusted on diagnosis of AS unless there is evidence of significant hypotension.

e. **Treatment of hyperlipidemia.** The association between AS and risk factors for atherosclerosis has prompted trials with statins to retard the progression of AS. Several studies suggested that when statin therapy is indicated on the basis of current guidelines for hyperlipidemia, it is associated with a modest effect in slowing the rate of progression of AS. However, in more recent randomized controlled trials of patients with calcific AS, where statin therapy was not otherwise mandated, statins had little effect on AS progression or need for AVR. As such, statin therapy is not indicated for prevention of progression of calcific AS in patients with mild-to-moderate disease (ACC/AHA class III). However, aggressive low-density lipoprotein (LDL) lowering with statins appears warranted in patients who have an indication for statin therapy. In patients with supravalvular AS due to severe familial hyperlipidemia, improvement in the obstruction may occur after LDL apheresis or aggressive lipid lowering by other means.

2. **Percutaneous aortic balloon valvuloplasty (PABV)** is a procedure involving inflation of a balloon across a stenotic aortic valve resulting in an increase in the AVA and cardiac output. Because of the risk of worsening AR, this procedure is contraindicated in patient with concomitant moderate or severe AR. With the advancement in percutaneous AVR, the usage of PABV has increased significantly as a bridge to valve replacement.

a. In pediatric congenital, noncalcific AS, PABV is a safe and effective therapy comparable to surgical repair or replacement. The goal of PABV in congenital AS is to achieve a 60% to 70% reduction in measured peak-to-peak transvalvular gradient. Redilatation or AVR becomes necessary within 10 years of the initial PABV in >50% of children. AR is well recognized as a potential early or late complication of PABV, although moderate-to-severe AR only occurs in a minority of cases.

b. In adults, PABV has limited utility and long-term effectiveness while also being associated with substantial risks. On average, the effective orifice area is

increased by 0.44 cm^2 with a decrease in mean aortic gradient of 24 mm Hg. However, the procedures effects are short lived with an ~50% restenosis rate at 5 months and 80% at 15 months. **No survival benefit with PABV has been reported even in those with the largest increment in valve area.** Complication rates are diminishing with improvements in technology and techniques, but there are still considerable risks of vascular complications (6.8%), respiratory failure (6.5%), and strokes (2.9%).

The general indications for PABV are (1) as a bridge to definite replacement with either TAVR or surgical AVR (SAVR; ACC/AHA class IIb); (2) to assess degree to symptomatology due to AS when the patient has other comorbidities (i.e., severe COPD) which may mimic the symptoms of AS; and (3) as a means of palliation for patients who are not candidates for TAVR/SVR. PABV is generally not recommended before moderate-risk elective noncardiac surgery in patients with asymptomatic severe AS. Such patients are better served with appropriate intraoperative and postoperative hemodynamic monitoring to avoid significant periprocedural hypotension (ACC/AHA class IIa).

3. **TAVR.** An exciting and evolving strategy is the placement of a stented bioprosthetic valve over the native aortic valve, either percutaneously from an arterial site (usually transfemoral, subclavian/axillary, or rarely carotid) or transapically from an incision made at the LV apex on the chest wall (usually via mini-sternotomy or anterior thoracotomy). The first TAVR was performed in 2002 by Cribier.

a. **Indications.** Patients with intermediate or high surgical risk being considered for TAVR should be evaluated by a multidisciplinary group including healthcare professionals in valvular heart disease, cardiac imaging, interventional cardiology, cardiac anesthesia, and cardiac surgery (ACC/AHA class I).

1. **(1) Symptomatic severe AS, inoperable or prohibitive risk for SAVR**. TAVR is recommended in these patients if predicted post-TAVR survival is greater than 12 months (ACC/AHA class I).
2. **(2) Symptomatic severe AS with high surgical risk for SAVR.** Either TAVR or surgical AVR is recommended on the basis of patient specifics and preferences (ACC/AHA class I).
3. **(3) Symptomatic severe AS with intermediate surgical risk.** TAVR is a reasonable alternative to surgical AVR (ACC/AHA class IIa). The safety and efficacy of TAVR in this group have shown noninferiority to surgical AVR (see Section **I.F.3.c**).

b. **Valve types.** Five percutaneous transcatheter aortic valves have received US Food and Drug Administration approval in the United States: Edwards Sapien XT and S_3 valves; Medtronic CoreValve, CoreValve Evolut R, and CoreValve Evolut PRO. Two additional valves have received Conformité Européene (CE) approval in Europe and are investigation use only in the United States: Boston Scientific Lotus and St. Jude Portico valves. Specifics of these valves are displayed in Table 15.3.

1. **(1) Edward Sapien**

1. **(a) Sapien** valve was a **balloon-expandable** bovine pericardial valve attached to a stainless steel stent with a polyethylene terephthalate fabric cuff. This valve is no longer available.
2. **(b) XT** is a **balloon-expandable** bovine pericardial valve attached to a stainless steel mesh frame with a polyester wrap.
3. **(c) S_3** is a **balloon-expandable** bovine pericardial valve with polyethylene terephthalate outer skirt to minimize the potential for paravalvular leak.

2. **(2) Medtronic**

1. **(a) CoreValve** is a **self-expanding** porcine pericardial valve attached to a flexible nitinol frame.

2. **(b) CoreValve Evolut R** is a **self-expanding** porcine pericardial valve attached to a nitinol frame with an extended skirt to minimize the potential for paravalvular leak.
3. **(c) CoreValve Evolut PRO** is a **self-expanding,** repositionable, supra-annular porcine pericardial valve with a porcine pericardial tissue wrap to minimize potential for paravalvular leak.

3. **(3) Boston Scientific**

1. **(a) Lotus valve** is a **controlled mechanical expanding** bovine pericardial valve on a nitinol frame with polycarbonate seal to minimize potential for paravalvular leak.

4. **(4) St. Jude**

1. **(a) Portico valve** is a **self-expanding** bovine pericardial valve on a nitinol frame with a porcine pericardial cuff within the stent to minimize the potential for paravalvular leak.

c. Outcomes. TAVR was developed to offer an alternative for patients with severe symptomatic AS who were not a candidate for open surgical replacement because of either an unacceptably high estimated surgical risk or where this is prohibited because of technical challenges (i.e., porcelain aorta, radiation heart disease). Outcomes data from recent studies are summarized below. However, **it is always important to keep in mind that morbidity and mortality figures from clinical trials, although useful, should not replace knowledge of these risks for individual procedures at one's own institution**. When choosing between surgical AVR and TAVR consideration of surgical risk, comorbidities including severe CAD who may be best served with surgical AVR and coronary artery bypass grafting (CABG), and patient preference should be taken into account. In addition, there is a relative lack of data on the long-term durability of TAVRs compared with surgical AVR.

TABLE 15.3 Current Available Transcatheter Aortic Valve Replacements Valves

	Deployment	Mechanism to Help Prevent Paravalvular Leak	FDA Approval in the Severe AS
Boston Scientific			
Lotus	Controlled mechanical expanding	Adaptive polycarbonate seal	No. Limited to investigati United States
		Edwards Sapien	
SAPIEN	Balloon expandable		Yes, but no longer availa
SAPIEN XT	Balloon expandable		Inoperable, intermediat valve-in-valve for AS/A
SAPIENT 3 (S3)	Balloon expandable	Polyethylene terephthalate outer skirt	Intermediate-, high-, or e
		Medtronic	
CoreValve	Self-expanding		High- or extreme-risk valve for AS/AR

TABLE 15.3 Current Available Transcatheter Aortic Valve Replacements Valves

CoreValve Evolut R	Self-expanding	Extended skirt	High- or extreme-risk pat
CoreValve Evolut PRO	Self-expanding	Porcine pericardial skirt	High- or extreme-risk pat
		St. Jude	
Portico	Self-expanding	Pericardial cuff	No. Limited to investigati United States

d. Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; FDA, US Food and Drug Administration.

e. [a]FDA approval for use in intermediate-risk patients is currently under review.

1. **(1) TAVR versus medical therapy in inoperable patients.** The Placement of Aortic Transcatheter Valves (PARTNER) cohort B trial was performed with the Edwards SAPIEN valve compared to medical therapy including PABV. The results of this study showed that the SAPIEN valve met noninferiority criteria with a significant reduction in mortality (20% absolute survival advantage) that persisted out to 5 years and a higher percentage of patients with NYHA class I or II symptoms at 1-, 2-, 3-, and 5-year follow-up. The Medtronic CoreValve underwent a prospective, nonrandomized trial, which showed favorable outcomes at both 1- and 2-year follow-up and with outcomes being driven by the patients underlying comorbid conditions rather than valve performance.
2. **(2) TAVR in high-risk patients.** PARTNER cohort A trial compared the SAPIEN valve (transapical or transfemoral approach) to surgical AVR in high-risk patients (mean STS-PROM 11.7%). The results showed similar mortality rates at 1 and 5 years with a stroke risk that was significantly higher at 1 year in TAVR but did not remain significant at 3 and 5 years. The CoreValve high-risk trial compared the CoreValve to surgical AVR showing noninferiority as well as superiority for 1- and 2-year mortality data based on prespecified criteria. The CoreValve had similar stroke risk at 1 year with a trend toward a lower stroke risk at 2 years compared with surgical AVR.
3. **(3) TAVR in intermediate-risk patients.** Three major trials have evaluated the outcomes of TAVR in an intermediate-risk population. The PARTNER IIA trial was a large randomized trial of over 2,000 patients comparing the SAPIEN XT valve to surgical AVR and showed similar rates for both 2-year mortality and risk of disabling stroke. The SAPIENT 3 valve was evaluated as an observational study via propensity score analysis with the surgical AVR population in the PARTNER IIA trial. These results showed that the SAPIENT 3 valve was noninferior and superior to surgical AVR for the primary composite endpoint at 1 year for all-cause mortality, disabling strokes, and moderate or severe AR. Last, the SURTAVI trial evaluated the combined results of the CoreValve (84%) and CoreValve Evolut R (16%) valves compared with surgical AVR and found it to be noninferior for the primary composite endpoint of all-cause mortality and disabling stroke at 2 years.

4. **(4) BAVs.** TAVR in BAVs is challenging because of association with a dilated aortic annulus, elliptical and eccentric opening complicating frame apposition, and increased risk of damage to the aorta. On the basis of registry data, BAV has been associated with a higher rate of moderate-to-severe paravalvular leak, which may be improved with the use of CT-guided valve sizing as compared with echocardiography.
5. **(5) Prosthetic dysfunction treated with valve-in-valve**. To date, no trial has evaluated valve-in-valve TAVR but a multinational registry has reported outcomes matched of 757 cases of valve-in-valve compared with native valve TAVR placed between November 2011 and September 2015. These results showed that valve-in-valve TAVR had superior safety outcomes including lower all-cause mortality (2.3% vs. 4.1%, $p = 0.03$), all-cause 1-year mortality (13.3% vs. 23.1%, $p < 0.001$), in-hospital stroke (0.4% vs. 2.1%, $p = 0.002$), stroke at 1 year (2.0% vs. 4.3%, $p = 0.002$), and lower rate of complication including major bleeding, vascular complication, and new-onset atrial fibrillation. Overall, the results show that valve-in-valve TAVR is a safe procedure and should be considered in inoperable patients and possibly in those with high surgical risk.
6. **(6) Future TAVR trials** include comparing the use of TAVR versus surgical AVR in patients with low surgical risk, asymptomatic severe AS (EARLY-TAVR), and moderate AS in patients with symptomatic heart failure (NYHA ≥ II) and reduced ejection fraction (LVEF < 50%; TAVR UNLOAD).

4. **Surgical therapy.** AVR is the surgical treatment of choice. It is preferred over repair because debridement of the aortic valve calcification often results in early postoperative AR from leaflet fibrosis and retraction, a process that progresses over time.

a. **Recommendations for the use of surgical AVR** in patients with AS according to the 2014 ACC/AHA valvular heart disease guidelines and 2017 Focused Update are given in Table 15.4. The major indications are severe AS with symptoms, when other cardiac surgery is needed, or LV systolic dysfunction develops as a result of severe AS.

b. **Surgical mortality rate** varies among patients with AS, depending on age and other comorbidities including concomitant CAD. In an otherwise healthy individual, mortality rate for isolated AVR in experienced centers should be <1%. Successful AVR is feasible and improves life expectancy, even in very elderly patients without multiple comorbidities. Surgical options include pulmonary valve autograft (i.e., Ross procedure), aortic valve homograft conduit, a pericardial or porcine bioprosthesis, mechanical valve, or rarely surgical repair. The relative advantages, disadvantages, and indications for use of different prostheses are outlined in Chapter 18.

TABLE 15.4 Recommendations for Aortic Valve Replacement in Patients with Aortic Stenosis

Class I

1. Symptomatic patients with severe AS
2. Asymptomatic patients with severe AS and LVEF < 50%
3. Either surgical AVR or TAVR is recommended for symptomatic severe AS if high surgical risk.
4. TAVR is recommended for symptomatic severe AS and deemed inoperable for surgical AVR if life expe
5. Severe AS and having heart surgery for another indication

Class IIa

1. Asymptomatic patients with very severe AS (aortic velocity > 5.0 m/s or mean pressure gradient ≥ 60 m

TABLE 15.4 Recommendations for Aortic Valve Replacement in Patients with Aortic Stenosis

2. "Asymptomatic" severe AS patients with decreased exercise tolerance or drop in systolic blood pressur
3. Symptomatic patients with low-flow/low-gradient AS with LVEF < 50% and low-dose dobutamine stre >4.0 m/s or mean pressure gradients ≥40 mm Hg and AVA <1.0 cm^2
4. Symptomatic patients with low-flow/low-gradient severe AS with LVEF ≥ 50%, systolic blood pressur volume index (<35 mL/m^2) if the valve disease is believed to be the most likely cause of symptoms
5. If intermediate surgical risk, TAVR is a reasonable alternative to surgical AVR for symptomatic severe A
6. Moderate AS and having heart surgery for another indication

Class IIb

1. Asymptomatic patients with severe AS, low surgical risk, and evidence of rapid disease progression m/s/y)

c. These recommendations apply to both surgical AVR and TAVR.

d. Abbreviations: AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; TAVR, transcatheter aortic valve replacement.

e. Adapted with permission from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.*2014;63(22):e57–e185; Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;70(2):252–289. Copyright © 2017 by the American Heart Association, Inc., and the American College of Cardiology Foundation.

1. **(1)** In the Ross procedure, the pulmonary valve and main pulmonary artery are removed as a unit and placed in the aortic position with reimplantation of the coronary arteries. A pulmonary homograft is placed in the pulmonic position. This procedure is best suited for pediatric and adolescent patients with growth potential because the autograft is capable of growth, does not require anticoagulants, and has an excellent hemodynamic profile. The procedure, however, is long and technically difficult and subsequently turns a single-valve problem into a double-valve problem. Problems with pulmonary homograft are common in adults who underwent this operation as are subsequent dilatation of the aorta in those with aortopathy such as with bicuspid valves.
Aortic valve homografts have been used to treat younger patients, especially those who wish to avoid anticoagulation, in the hope that greater durability of this valve might result than with a bioprosthesis. Unfortunately, more recent data suggest that any durability advantage of a homograft over a bioprosthesis in a middle-aged patient is slight. Moreover, the homograft tends to calcify and is often difficult to remove at subsequent reoperations. Therefore, enthusiasm for homografts has waned, except in the setting of endocarditis of native or prosthetic valves with pyogenic complications such as abscess or fistula or when the LVOT is small, in which case homografts maximize the flow area and minimize the pressure gradient.

f. **Bioprostheses** include porcine heterografts and bovine pericardial prostheses. These valves are most often used to treat patient older than 60 years because

structural deterioration is much slower in this age group compared with younger patients. These valves have a low risk for thromboembolism and do not necessitate long-term anticoagulation. Because of the sewing ring and struts, all prostheses, both mechanical and biologic, have a pressure gradient across them, even with normal function. The largest possible valve should be inserted to minimize this pressure gradient. The threshold to insert a bioprosthesis at a younger age continues to decline given the excellent quality of life these afford and with the developing innovation of valve-in-valve TAVR.

g. Mechanical valves. The most commonly used mechanical prostheses include the St. Jude, Onyx, and CarboMedics prostheses. These all require anticoagulation to minimize the risk of valve thrombosis and thromboembolism. These valves are durable if anticoagulation is maintained and careful antibiotic prophylaxis is used over the years. Mechanical valves are used with caution in older patients (>65 years) given the substantial increase in anticoagulation-related hemorrhage and resultant mortality in this population.

G. Special considerations

1. Management of asymptomatic patients with severe AS

a. High-risk patients. Most asymptomatic AS patients have low mortality and morbidity rates. A minority of asymptomatic patients, however, may die suddenly or have rapid progression of disease. These patients may benefit from AVR in the absence of symptoms. Accurate identification of such patients has been difficult. A transaortic flow velocity of >4 m/s predicts a 70% likelihood of needing an AVR within the subsequent 2 years, whereas a velocity of <3 m/s corresponds to a low likelihood (<15%) of needing an AVR in the subsequent 5 years. Patients with highly calcified valves and a rapid progression of disease (aortic velocity ≥ 0.3 m/s/y) or critical AS (aortic velocity ≥ 5.0 m/s or mean pressure gradient ≥ 60 mm Hg) may be considered for elective AVR if the transaortic flow velocity is >4 m/s. Other reasonable indications for AVR in patients with severe asymptomatic AS including LV dysfunction attributed to AS, exercise-induced hypotension, pulmonary hypertension (PASP > 60 mm Hg), a high likelihood of rapid progression, and before pregnancy. Additional high-risk features on exercise testing includes an increase in mean gradient ≥ 18 to 20 mm Hg with exercise, increase in PASP ≥ 60 mm Hg with exercise, lack of contractile reserve, and impaired functional capacity. Operating on an asymptomatic patient with severe AS is only reasonable when the surgical center performing the operation has a low mortality and morbidity for this procedure.

b. CABG and moderate AS. Studies suggest a benefit of concomitant AVR in patients undergoing CABG who have an AVA of <1.5 cm^2. Although concomitant AVR increases the risk of the initial surgery, the need for reoperation is significantly lower in these patients, and this may provide a survival benefit.

2. Patients with AS and severely reduced ejection fraction. LV systolic dysfunction in patients with AS can result from afterload stress imposed on the left ventricle by the stenotic valve or from primary contractile dysfunction (e.g., results from other causes of cardiomyopathy; Fig. 15.2). When LV systolic dysfunction results primarily from afterload mismatch, AVR often results in improvement or normalization or LV function. In contrast, patients with primary contractile dysfunction have an overall poor prognosis and are unlikely to benefit from AVR. It is important to determine the cause of LV dysfunction in patients with severe AS for prognostic and therapeutic purposes. These patients should be considered in two groups: high transvalvular gradients (mean gradient > 40 mm Hg) and low transvalvular

gradients (mean gradient < 30 mm Hg). The patients with low transvalvular gradients consist of three entities: **true severe AS with systolic dysfunction, pseudosevere AS, and paradoxical AS with preserved systolic function with reduced stroke volume index** due to marked LV hypertrophy and small LV size.

a. **High transvalvular gradient.** A high transvalvular gradient is a surrogate measure of high afterload mismatch. When the transvalvular gradient is substantial (e.g., mean gradient > 40 mm Hg), AVR can result in normalization of LV function and a relatively low operative mortality.

b. **Low transvalvular gradient**

1. **(1) Low-flow, low-gradient severe AS.** Patients with true anatomically severe AS (AVA < 1.0 cm^2) and low transvalvular gradients (mean gradient < 30 mm Hg) have a very poor prognosis without surgery. Despite a substantial operative mortality, survival appears improved in those treated surgically compared with medical management, especially if they demonstrate **contractile reserve** when challenged with dobutamine. Contractile reserve is defined as the ability to increase in stroke volume by >20% from baseline.

DSE helps appropriately differentiate this subset of patients from pseudosevere AS. DSE evaluates the compliance of the valve to determine if the small AVA is secondary to a fixed AS with afterload mismatch (true severe AS) or secondary to myocardial dysfunction with inadequate stroke volume to appropriately open a mild-to-moderately stenotic valve (pseudosevere AS). When administered dobutamine, patients with true severe AS experience an increase in both cardiac output and transvalvular pressure gradient and the calculated valve area increases by <0.3 cm^2 with the valve area remaining <1.0 cm^2. These patients are typically older, have CAD and may have significant mitral regurgitation (MR) and pulmonary hypertension. Because of their comorbidities, TAVR is increasingly the procedure of choice when this is feasible.

2. **(2) Pseudosevere AS** is identified as patients with an inappropriately low AVA <1.0 cm^2 arising secondary to impaired left ventricular function and submaximal opening of a mild-to-moderately stenotic valve. Dobutamine infusion will generate an increase in cardiac output without a significant increase in the transvalvular pressure gradient. As a result, the calculated AVA increases significantly (≥0.3 cm^2) and the valve area increases to more than 1 cm^2.

3. **(3) Paradoxical AS** results in low transvalvular gradients in the setting of preserved systolic function secondary to reduced stroke volume index (<35 mL/m^2) that occurs in the setting of marked LV hypertrophy and resultant small LV size or increased afterload due to other reasons such as hypertension or reduced aorta compliance. These patients are typically elderly women with a history of hypertension. It is important to recognize this group of individuals also benefits from AVR once they become symptomatic. Low transvalvular gradients can also be seen in patients in which the peak aortic valve gradients are not accurately detected or there are errors in measurement. Careful evaluation of valve hemodynamics and valve anatomy is important to ensure that the valve is truly severely narrowed. Heavy calcification of the valve on echo or CT is a useful pointer to this. Dobutamine echocardiography may also be used in a manner similar to those patients with reduced LVEF to determine whether valve area remains low and valve gradients increase with higher cardiac output.

3. **Subaortic stenosis.** Surgical removal of the membrane leading to subaortic obstruction is indicated for symptomatic patients or for asymptomatic patients with a peak pressure gradient >50 mm Hg. In patients with peak pressure gradient <50 mm Hg,

surgical intervention can also be considered if there is evidence of LV systolic dysfunction, concomitant moderate/severe AR, or a VSD. Surgery can also be considered in asymptomatic patients with peak gradient >30 mm Hg if they are planning to become pregnant or wishing to participate in competitive sports.

II. AORTIC REGURGITATION

A. Introduction. AR can develop from primary disease of the valve leaflets or from abnormalities of the aortic root or ascending aorta. The chronic and acute forms of AR are distinct disease entities, with different causes, clinical presentations, natural histories, and treatment strategies.

B. Etiology

1. Chronic AR. Disease of the valve leaflets can cause AR by inadequate leaflet coaptation, leaflet perforation, or leaflet prolapse. The most common causes of leaflet abnormalities and aortic root abnormalities that lead to the gradual development of AR are given in Table 15.5. Subaortic stenosis can also cause AR because of a high-velocity jet of blood that is a result of the outflow obstruction hitting the aortic valve, causing damage to the leaflets. Perimembranous ventricular septal defects are associated with AR as well. In addition to disease of native valve leaflets, structural deterioration of bioprosthetic or homograft valve leaflets are an important cause of chronic AR.

2. Acute AR. Acute AR can also result from abnormalities in the valve leaflets or in the aortic root. The causes of acute AR are limited (Table 15.6).

C. Pathophysiology

1. Chronic AR. AR results in diastolic regurgitation of LV stroke volume. This produces an increase in LV end-diastolic volume, thereby raising wall tension (i.e., Laplace's law). The ventricle responds to added wall tension by compensatory eccentric hypertrophy of myocytes. As a result, during the chronic compensated phase of AR, the left ventricle is able to adapt to an increase in diastolic volume without a significant increase in end-diastolic pressure. The left ventricle produces a larger total stroke volume with each contraction, preserving normal effective forward stroke volume. Over time, however, progressive interstitial fibrosis reduces LV compliance, leading to the chronic decompensated phase. Chronic volume overload results in impaired LV emptying, an increase in LV end-systolic volume and end-diastolic pressure, further cardiac dilation, and a fall in the ejection fraction and forward cardiac output.

TABLE 15.5 Major Causes of Chronic Aortic Regurgitation

Leaflet Abnormalities	Aortic Root or Ascending Aorta Abnormalities
Rheumatic fever	Age-related aortic dilation
Infective endocarditis	Annuloaortic ectasia
Trauma	Cystic medial necrosis of the aorta (isolated b syndrome)
Myxomatous degeneration	Systemic hypertension
Congenital aortic regurgitation	Aortitis (syphilis and giant cell arteritis)

TABLE 15.5 Major Causes of Chronic Aortic Regurgitation	
Systemic lupus erythematosus	Reiter syndrome
Rheumatoid arthritis	Ankylosing spondylitis
Ankylosing spondylitis	Behçet syndrome
Takayasu arteritis	Psoriatic arthritis
Whipple disease	Osteogenesis imperfecta
Crohn disease	Relapsing polychondritis
Drug-induced valvulopathy	Ehlers–Danlos syndrome

TABLE 15.6 Major Causes of Acute Aortic Regurgitation	
Leaflet Abnormalities	**Aortic Root or Ascending Aorta Abnormalities**
Acute infective endocarditis	Acute aortic dissection
Traumatic rupture of the valve	Traumatic injury to aortic root
Acute prosthetic valve dysfunction	
Post aortic balloon valvuloplasty	
Perivalvular leak or dehiscence of prosthetic valves	

2. **Acute AR.** Acute AR is usually a hemodynamic emergency because the left ventricle does not have sufficient time to adapt to the rapid increase in LV volume. The effective forward stroke volume and cardiac output fall acutely, potentially resulting in hypotension and cardiogenic shock. The sudden increase in LV diastolic pressure initially causes preclosure of the mitral valve in early diastole, protecting the pulmonary vasculature from elevated diastolic pressure. However, further LV decompensation leads to diastolic MR, which allows transmission of elevated diastolic pressure to the pulmonary vascular bed, resulting in pulmonary edema. The tachycardia that accompanies cardiac deterioration helps shorten the diastolic-filling period during which the mitral valve is open.

D. History and clinical presentation

1. **Chronic AR** is usually asymptomatic for a long time. The natural history of disease progression in asymptomatic severe AR is much slower compared with AS with an estimated annual progression (requiring AVR or death) rate of ~6%. After the development of LV dysfunction, patients gradually experience symptoms related to pulmonary congestion, including increased dyspnea with exertion, orthopnea, and paroxysmal nocturnal dyspnea. LV enlargement frequently produces an uncomfortable sensation in the chest that is exaggerated after premature ventricular contractions and in the supine position. Although angina is uncommon, it can be produced by latent CAD, decreased diastolic coronary perfusion pressure, nocturnal bradycardia and fall in arterial diastolic pressure, marked LVH, and subendocardial ischemia.

2. **Acute AR.** Patients with acute, severe AR usually present with signs of sudden hemodynamic deterioration such as weakness, altered mental status, severe shortness of breath, or syncope. If left untreated, these patients quickly progress to total cardiovascular collapse. When severe chest pain is part of the initial clinical presentation, aortic dissection must be strongly suspected.

E. Physical findings

1. **Chronic AR.** Patients with chronic AR can have a wide array of physical findings, especially during examination of the peripheral pulses and cardiac auscultation. The physical examination may yield clues about the cause of AR. Patients with AR should be examined for the peripheral manifestations of IE, signs of Marfan syndrome, evidence of chronic aortic dissection, and signs of collagen vascular disorders.

a. **Peripheral pulse examination.** The increased total stroke volume in chronic AR leads to an abrupt increase in arterial pressure during systole, followed by a rapid fall in arterial pressure during diastole. The widened pulse pressure accounts for a number of physical findings associated with chronic AR (Table 15.7). Patients with chronic AR may exhibit a bisferiens pulse, characterized by double systolic peaks with increased amplitude. The signs of hyperdynamic circulation are not specific to AR and can be seen in conditions that cause high-output heart failure, including sepsis, anemia, thyrotoxicosis, beriberi, and arteriovenous fistula.

b. **Palpation.** With severe AR, the apical impulse is typically enlarged and displaced lateral to the midclavicular line in the fifth intercostal space because of LV enlargement. The impulse may be sustained and hyperdynamic. A diastolic thrill may be palpable in the second left intercostal space, as may a systolic thrill caused by increased aortic flow.

c. **Auscultation.** The main auscultatory findings are outlined in Figure 15.7.

1. **(1) Heart sounds.** S_1 may be diminished in the presence of PR-interval prolongation, LV dysfunction, or preclosure of the mitral valve. S_2 may be soft, singly split (P_2 obscured by the diastolic murmur) or paradoxically split. An S_3 may be heard with severe LV dysfunction. An S_4 is often present and represents left atrial contraction into a poorly compliant left ventricle.

2. **(2) Diastolic murmur.** The hallmark murmur of AR is a blowing, diastolic, decrescendo murmur that starts immediately after A_2 and is best heard in the left upper sternal border with the patient sitting up and leaning forward slightly in full expiration. In general, the severity of AR correlates with the duration of the murmur more than with its intensity. Early in the course of disease, the murmur is typically short. As the disease progresses, the murmur may become pandiastolic. In the end stages of AR, the murmur may shorten again because of rapid equilibration of pressures in the aorta and left ventricle from an elevated LVEDP. In this situation, other signs of severe AR are usually present.

TABLE 15.7 Physical Signs Associated with Hyperdynamic Pulse in Chronic Aortic Regurgitation

Physical Sign	Description
Water hammer pulse	Rapid upstroke followed by quick collapse
de Musset sign	Head bob with each heartbeat

TABLE 15.7 Physical Signs Associated with Hyperdynamic Pulse in Chronic Aortic Regurgitation	
Traube sign	Pistol shot sounds heard over the femoral arteries in both systole and diastole
Müller sign	Systolic pulsation of the uvula
Duroziez sign	Systolic murmur over the femoral artery when compressed proximally and diastolic murmu systolic–diastolic murmur with increasing compression over femoral artery
Quincke sign	Capillary pulsations visible in the lunula of the nail bed
Hill sign	Popliteal cuff systolic pressure exceeding brachial cuff systolic pressure by >60 mm Hg
Becker sign	Arterial pulsations visible in the retinal arteries and pupils

3. **(3)** A **second diastolic murmur** may be audible at the apex in severe AR. The Austin Flint murmur is a middle-to-late diastolic rumble that is believed to be caused by vibration of the anterior mitral leaflet as it is struck by the regurgitant jet or by turbulence in the mitral inflow from partial closure of the mitral valve by the regurgitant jet. Unlike the murmur of true valvular mitral stenosis, the Austin Flint murmur is not associated with a loud S_1 or with an opening snap.
4. **(4)** A short **midsystolic ejection murmur** may be audible at the base of the heart, radiating to the neck. It reflects the increased ejection rate and large stroke volume traversing the aortic valve.

FIGURE 15.7 Physical findings in aortic regurgitation. LV, left ventricle; LVH, left ventricular hypertrophy.

2. **Acute AR.** The physical examination of patients with acute AR differs considerably from that of patients with chronic AR. The physical examination may be most notable for signs of hemodynamic compromise, such as hypotension, tachycardia, pallor, cyanosis, diaphoresis, cool extremities, pulmonary congestion, and altered mental status.

a. **Peripheral examination.** The signs of hyperdynamic circulation that characterize chronic AR are often absent in acute AR. The pulse pressure may be normal or only slightly widened. The heart size is often normal, and the point of maximal intensity is not displaced laterally. When aortic dissection is suspected, blood pressures should be taken in all extremities to detect the differences.

b. **Heart sounds.** S_1 may be diminished because of preclosure of the mitral valve. An S_3 often accompanies cardiac decompensation.

c. **Murmurs.** The early diastolic murmur of acute AR is shorter and lower in pitch than the murmur of chronic AR. In severe, acute AR, the murmur may not be audible when the diastolic pressure in the left ventricle and aorta equilibrates. The systolic murmur reflecting increased flow across the aortic valve may be heard but is usually not loud. The Austin Flint murmur, if present, is short.

F. Laboratory evaluation

1. **ECG.** The typical ECG in chronic AR shows LVH, left-axis deviation, and left atrial abnormality. Conduction abnormalities are unusual but can occur after the development of LV dysfunction. Premature atrial and ventricular beats are common. Sustained supraventricular or ventricular tachyarrhythmias are uncommon in the absence of LV dysfunction or concomitant mitral valve disease. In acute AR, the ECG is usually notable only for nonspecific ST-T–wave abnormalities.

2. **Chest radiograph.** In chronic AR, the chest radiograph may reveal marked cardiomegaly, with the heart being displaced inferiorly and leftward. Dilation of the aortic knob and root may be seen. In acute AR, the LV and left atrial dimensions are usually normal. Aortic dissection can lead to a widened mediastinum and/or a widened cardiac silhouette due to pericardial effusion. The chest radiograph is notable for signs of pulmonary congestion.

3. **Laboratory testing.** Chronic AR may lead to increased natriuretic peptides and evidence of their elevation is helpful when a decision about surgical timing is equivocal. Other blood tests may help in elucidating suspected underlying conditions such as connective tissue disorders or if endocarditis is possible.

4. **Echocardiography.** Two-dimensional and M-mode echocardiography are useful in determining the cause of AR, evaluating the aortic root, and assessing the overall LV size and function. Doppler echocardiography is useful for detecting AR and estimating severity. There are several different methods of estimating the severity of AR with color Doppler, pulsed wave Doppler, and continuous wave Doppler ultrasonography.

a. **Two-dimensional and M-mode echocardiography.** The cause of AR can be assessed using two-dimensional echocardiography. Rheumatic AR typically causes thickening and retraction of the leaflet tips, leading to failure of cusp apposition. Bacterial endocarditis, which can cause leaflet fibrosis and retraction, leaflet perforation, or flail of the valve cusp, should be suspected if a vegetation is detected. Prolapse of the aortic valve cusps can occur in many conditions, including IE, BAV, myxomatous degeneration, and Marfan syndrome. Aortic root abnormalities are also well visualized in the parasternal long-axis view. Aortic root dilation is most often idiopathic, although Marfan syndrome, Ehlers–Danlos syndrome, ankylosing spondylitis, Reiter syndrome, rheumatoid arthritis, syphilis, and giant cell arteritis are other potential causes. Symmetric dilation of the aortic root produces a central jet of AR, and focal dilation causes an eccentric jet. In the parasternal long axis, the transducer should be moved up one interspace to assess the ascending aorta. Infective destruction of the aortic wall and proximal aortic dissection flaps may occasionally be visualized on transthoracic images. M-mode echocardiography may reveal **premature closure of the mitral valve in severe, acute AR**. In acute AR and chronic AR, the regurgitant jet can strike the anterior mitral valve leaflet, causing it to reverberate or "flutter" in diastole. Reversed doming of the anterior mitral leaflet may be seen on two-dimensional imaging and generally indicates grade 3 to 4+ AR.

b. **Doppler and color flow imaging.** Doppler and color flow echocardiography is used to detect AR and to assess its severity. AR is identified by Doppler imaging as high-velocity pandiastolic flow originating immediately under the aortic valve. Color flow imaging allows the assessment of jet origin, size, and direction. Continuous wave Doppler provides measurement of jet velocity and timing of flow. The maximum length of the AR jet correlates poorly with severity of regurgitation when assessed angiographically. Several other Doppler measures are used to estimate the severity of AR (Table 15.8). The ratio of the jet width to LVOT diameter is measured in the parasternal long-axis view and correlates well with the angiographic severity of AR. The pressure half-time of the aortic regurgitant velocity is defined as the time required for the pressure gradient across the aortic valve to fall to half of its initial value. The pressure half-times of patients with mild, moderate, and severe AR have demonstrated considerable overlap. In general, shorter pressure half-times are associated with increased severity of AR, and a pressure half-time of <200 ms is nearly always associated with

severe AR. Quantitation of regurgitant volume and regurgitant fraction provides the most direct correlation with quantitative angiographic estimates of AR severity. Regurgitant volume is the difference between the stroke volume across the LVOT (representing the sum of forward flow and regurgitant flow) and that across the mitral valve inflow (representing forward flow), provided there is no significant MR. The regurgitant fraction is the ratio of the regurgitant volume divided by the LVOT stroke volume. The proximal isovelocity surface area (PISA) method is also used for estimating AR severity. The PISA method is used to calculate the effective regurgitant orifice (ERO) area. An ERO area ≥0.30 cm^2 is indicative of severe AR. The presence of a proximal convergence area on transthoracic echocardiogram at the aortic valve is indicative of at least moderate AR. Pulsed wave Doppler echocardiography should be performed in the proximal descending aorta to establish the presence of diastolic flow reversal. Some degree of flow reversal is normally seen early in diastole because of reflux of blood into the coronary vasculature, but if this is >40 cm/s and continues throughout diastole, then severe AR is likely, especially if this persists in the abdominal aorta. Flow reversal may also be seen with other conditions that cause blood to leak out of the arterial system such as patent ductus arteriosus or sizeable arteriovenous fistula.

TABLE 15.8 Echo-Doppler Assessment and Stages of Aortic Regurgitation

	Aortic Regurgitation		
	Mild	**Moderate**	**Severe, Asymptomatic**
Stage	B	B	C1/C2
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet width	<25% of LVOT	25%–64% of LVOT	≥65% of LVOT
Doppler vena contracta width (cm)	<0.3	0.3–0.6	>0.6
Quantitative (cath or echo)			
Regurgitant volume (mL/beat)	<30	30–59	≥60
Regurgitant fraction (%)	<30	30–49	≥50
Effective regurgitant orifice area (cm^2)	<0.10	0.10–0.29	≥0.30
Additional Essential Criteria			
Left ventricular size	Normal	Normal	Requires evidence of LV dilation C1 = LVEF (≥50%) and LVESD ≤ 50 mm C2 = LVEF < 50% or LVESD > 50 mm

TABLE 15.8 Echo-Doppler Assessment and Stages of Aortic Regurgitation

				indexed > 25 mm/m^2

c. Abbreviations: LV, left ventricle; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVOT, left ventricular outflow tract.

d. Reprinted from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(22):e57–e185. Copyright © 2014 American Heart Association, Inc., and the American College of Cardiology Foundation. With permission.

e. **TEE** is used to rule out vegetation or aortic valve ring abscess in patients who may have bacterial endocarditis. In pure AR, vegetation typically occurs on the LV side of the aortic valve. TEE is also used to visualize congenital valvular abnormalities (e.g., bicuspid valve, subaortic membrane) and to exclude aortic dissection.

f. **Stress echocardiography** is useful for assessing functional capacity and unmasking symptoms in patient previously classified as being asymptomatic or with equivocal symptoms. It can also assess for contractile reserve, which if absent is predictive or the development of systolic dysfunction both at follow-up (medical therapy) and postoperatively. Recent research also suggests that exercise tricuspid annular plane systolic excursion (TAPSE) <21 mm Hg is associated with RV dysfunction and independently associated with need for earlier AVR. Although contractile reserve and exercise TAPSE are not included as indication for AVR, they can be considered for use to help anticipate surgical timing in higher risk patients nearing recommendations for AVR including LVEF 50% to 55% or left ventricular end-systolic dimension (LVESD) approaching 50 mm or 25 mm/m^2 (Table 15.7). It is also important to acknowledge that afterload increases substantially with exercise, which can precipitate a fall in ejection fraction. This exercise-induced fall in LVEF is nonspecific and it should not of itself be used to indicate need for surgical intervention.

g. **Newer techniques.** Strain imaging is increasingly used to define LV dysfunction before this is apparent using LVEF. Abnormalities in global longitudinal strain may indicate early decompensation in AR patients. 3D echocardiography has the potential to provide more accurate LV volumes and dimensions in AR but is not yet widely used for this purpose.

5. **Cardiac catheterization.** Cardiac catheterization is not necessary for all patients with chronic AR unless there are concerns about AR severity, hemodynamic abnormalities, or LV function, despite noninvasive testing and the physical examination. All patients older than 50 years with severe AR should undergo coronary cineangiography before any definitive surgical procedure on the valve to detect CAD. The decision to perform cardiac catheterization in younger patients should be made on an individual basis after assessment of the patient's cardiac risk profile. Catheter manipulation in patients with AR may be difficult because of dilation of the ascending aorta. Caution should be exercised when manipulating catheters in patients with Marfan syndrome or cystic medial necrosis of the aortic wall to minimize the risk of vascular trauma. In addition to conventional coronary cineangiography,

aortography may be performed to evaluate the degree of AR when doubt about true severity remains after noninvasive testing. The grading of AR by angiography is given in Table 15.9. Right heart catheterization may be helpful in certain circumstances, such as new-onset heart failure or combined AR and AS.

6. **Advanced cardiac imaging.** If echocardiographic imaging is inadequate, such as poor acoustic windows, cardiac CT or cardiac magnetic resonance (CMR) imaging can be used to better evaluate both the cause and severity of AR as well as the aorta. Either modality can be used to better define the anatomy including but not limited to mechanism of AR, anatomic morphology of the valve (i.e., BAV), providing a more complete evaluation of the thoracic aorta including the degree of aortic dilatation or presence of a vascular connective tissue disorder, and using CMR to show evidence of early myocardial fibrosis. In addition to an anatomic evaluation, CMR can also provide a functional assessment including an accurate calculation of LVEF, left ventricular volumes, and quantification of regurgitation with flow mapping through calculation of regurgitant fraction. The assessment of left ventricular volumes is especially helpful in chronic severe AR when the left ventricle becomes spherical and linear dimensions may not be as representative of the degree of dilatation. CMR is highly reproducible and thus may be used in serial assessment of AR, which has a long asymptomatic period.

TABLE 15.9 Angiographic Grading of Aortic Regurgitation

Degree of Aortic Regurgitation	Left Ventricular Opacification
Mild (1+)	Faint, incomplete
Moderate (2+)	Faint, complete
Moderate to severe (3+)	Equal to aortic opacification
Severe (4+)	Greater than aortic opacification

G. **Natural history.** Moderate-to-severe AR may have a good prognosis for many years, provided the patient is asymptomatic and does not exhibit signs of LV dysfunction or severe dilation. Asymptomatic patients with normal LV function require AVR at a rate of only 4% per year. Ninety percent of such patients remain asymptomatic at 3 years, 81% at 5 years, and 75% at 7 years after the diagnosis is made. Patients with mild-to-moderate AR have had a 10-year survival rate of 85% to 95%. Patients with moderate-to-severe AR treated with medical therapy have a 5-year survival rate of 75% and a 10-year survival rate of 50%. After the development of LV dysfunction, progression to symptoms is greatly accelerated, with rates approaching 25% per year. In patients who develop NYHA class III to IV symptoms, without surgical intervention survival rates are 28% at 4 years. The natural history of AR has been defined on relatively few patients and at a time when routine imaging was not widely available. There is increasing evidence that the natural history may be less favorable especially in those who do not undergo surgical intervention.

H. **Therapy**

1. **Medical therapy**

a. **Chronic AR.** Vasodilators, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), calcium channel blockers, and

hydralazine have historically been used in the treatment of chronic AR to reduce the severity of regurgitation. However, patients with mild-to-moderate AR and normal systolic function do not appear to benefit from vasodilator therapy. Conflicting evidence exists for vasodilator treatment in asymptomatic severe AR. Therefore, the 2014 ACC/AHA valve guidelines limit their recommendation for vasodilator use to (1) concurrent treatment of hypertension with dihydropyridine calcium channel blockers or ACEI/ARBs for systolic blood pressure >140 mm Hg (class I indication) or (2) treatment in patients with severe AR with either symptoms or LV dysfunction and not a candidate for surgery because of their comorbidities (class IIa indication). β-Blockers are also reasonable to use in these nonsurgical candidates (class IIa indication), although it is important to avoid bradycardia, which increases diastolic filling time and increases the regurgitant volume in severe AR.

b. **Acute AR**. The goal of **medical therapy** in acute AR is hemodynamic stabilization before proceeding with surgical correction. For patients presenting with cardiogenic shock, intravenous vasodilators are used to reduce the afterload stress on the left ventricle, to lower LVEDP, and to augment forward cardiac output. In severe cases, temporary transvenous atrial/ventricular pacing and/or intravenous inotropic agents may be required for temporary hemodynamic support. β-Blockers may be used with caution when acute AR is caused by an aortic dissection. β-Blockers help reduce arterial d*P*/d*t*, which reflects the transmission of force from LV ejection to the arterial wall. Although this is an essential component of the treatment of acute aortic dissection, β-blockers increase the length of diastole by slowing the heart rate, which can exacerbate acute AR and contribute to cardiovascular collapse. If acute AR is associated with **endocarditis**, antibiotic therapy should be instituted as soon as all culture specimens are obtained. Patients with severe acute AR who are being triaged to surgery may be treated with rapid pacing to reduce the duration of diastole if therapeutic modalities such as intravenous vasodilators fail to produce a significant tachycardia. A **surgical evaluation** should be performed emergently for a patient with AR caused by aortic dissection or chest trauma. The goal of medical therapy in this setting is to maximize forward cardiac output and minimize propagation of aortic dissection if present.

2. Percutaneous therapy

a. **Insertion of an intra-aortic balloon counterpulsation device in patients with more than moderate AR or in the presence of aortic dissection is contraindicated.**

b. Patients with combined severe AS and at least moderate AR are poor candidates for PABV because the degree of AR is likely to increase after the procedure.

c. **Native AR.** The use of TAVR in native severe AR is generally included as an exclusion criteria for treatment of native valve disease. However, an observational study of 31 patients in Germany was performed using the JenaValve with a 30-day mortality of 12.9% and a 6-month mortality rate of 19.3%. The JenaValve is a porcine root valve sewn to a Nitinol self-expanding stent fitted with an outer porcine pericardial patch or skirt. The device also features a fixation clip to firmly anchor the valve despite the absence of calcification. This device is only deployable by a transapical approach. SAVR remains the treatment of choice in operable patients.

3. Surgical therapy

a. **Chronic AR.** The 2014 ACC/AHA guidelines on the indications for AVR in patients with chronic AR are given in Table 15.10.

1. **(1) Symptomatic patients.** The 2014 ACC/AHA guidelines recommend AVR symptomatic patients with severe AR regardless of the ejection fraction.
2. **(2) Asymptomatic patients**

1. **(a) LV systolic dysfunction.** Asymptomatic patients with chronic, severe AR and LV systolic dysfunction (ejection fraction < 50%) secondary to aortic valve disease are at high risk for the development of symptomatic heart failure within 2 to 3 years and, therefore, should be considered for prompt surgical intervention. The likelihood of LV dysfunction normalizing after surgery decreases with increased duration of dysfunction.

TABLE 15.10 Recommendations for Aortic Valve Replacement in Patients with Chronic Aortic Regurgita

Class I

1. Symptomatic patients with severe AR
2. Asymptomatic patients with severe AR and LVEF <50% (not attributed to another cause)
3. Severe AR and having heart surgery for another indication

Class IIa

1. Asymptomatic patients with severe AR, normal LV function, and severe LV dilatation (LVESD > 50 mm or in
2. Moderate AR and having heart surgery (mitral valve or CABG) or surgery on the ascending aorta

Class IIb

1. Asymptomatic patients with severe AR, normal LV function, and progression LV dilatation (LVEDD > 65 mm

Abbreviations: AR, aortic regurgitation; CABG, rtery bypass grafting; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ction; LVESD, left ventricular end-systolic dimension.

Adapted from Nishimura RA, Otto CM, Bonow RO, AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2):e57–e185. Copyright © 2014 American Heart Association, Inc., and the American College of Cardiology . With permission.

4. **(b) LV dilation.** Asymptomatic patients with normal LV systolic function at rest and evidence of severe LV dilation have an increased risk of sudden cardiac death and perioperative mortality increases significantly once they develop symptoms or LV systolic dysfunction. However, their prognosis after AVR is excellent and they should be referred for valve replacement if surgical risk is low. It is reasonable to send patients for AVR if their LVESD is >50 mm or indexed >25 mm/m^2. Surgery can also be considered in patients with left ventricular end-diastolic dimension (LVEDD) >65 mm if their surgical risk is low <1%.
5. **(c) Other cardiac surgery.** AVR is recommended for patients with chronic severe AR undergoing another cardiac surgery. AVR is also reasonable for patients with moderate AR if undergoing surgery on the mitral valve, ascending aorta, or CABG.

6. **(d) Aortic valve repair.** Many patients with prolapse of bicuspid valve as the cause of AR may be candidates for surgical repair of the aortic valve. Some patients with leaflet perforation caused by infectious endocarditis may also be candidates for repair in which a pericardial patch is sewn over the defect. Aortic valve repair has good durability when the initial result is excellent (minimal residual AR) but further surgery will be needed usually at 12 to 20 years. Leaflet sparing surgery on the aorta is increasingly feasible, and if the cause of the AR is impaired coaptation due to annular dilatation then experienced surgeons may be able to replace the aorta and reduce the severity of AR concomitantly without need for an AVR.

7. **(e) Postoperative**. Patients with severe AR may show initial worsening in LV function despite relative normalization of LV size. This is likely due to the hemodynamic changes produced by eradicating the regurgitation. Slow improvement with normalization or at least stabilization of function at about 6 months is common in these patients. Afterload reduction is indicated postoperatively in patients with impaired LV systolic function at least until there is normalization of LV systolic function.

I. Key suggestions

1. Acute, severe AR is usually a surgical emergency. Signs of congestive heart failure and mitral valve preclosure are ominous in acute AR.
2. Valve replacement can be performed without infection of the prosthesis in active endocarditis, even when antibiotics have only recently been started. An aortic valve homograft is the preferred prosthesis in the setting of endocarditis.
3. Aortic dissection should be suspected in any patient with chest pain and AR.
4. If LV systolic dysfunction is present for <12 months, LV function is likely to improve postoperatively.
5. Heart rate is usually normal until late in the course of disease, when a low effective stroke volume is compensated with tachycardia to maintain cardiac output.
6. Rapid atrial or ventricular pacing may be used as a temporary measure to manage acute AR caused by endocarditis or trauma to improve cardiac output. The diastolic-filling phase is shorter at higher heart rates; therefore, there is less time for valvular regurgitation.

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CHAPTER 16

Mitral Valve Disease

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I. INTRODUCTION

A. The **mitral valvular apparatus** consists of the anterior and posterior leaflets, the mitral annulus, the chordae tendineae, and the papillary muscles (PMs) (Fig. 16.1).

1. Normal function of the apparatus brings both leaflets together in systole, creating the coaptation zone.

2. The anterior portion of the mitral annulus is in continuity with the fibrous skeleton of the heart, making it less prone to dilation than the posterior annulus.

3. The coaptation line of the anterior and posterior leaflets is located in the posterior one-third of the valve orifice.

4. The middle scallop of the posterior leaflet is designated P_2, with the lateral scallop designated P_1 and medial scallop designated P_3. The corresponding areas of the anterior leaflet are designated A_1, A_2, and A_3.

5. The mitral valve leaflets are attached via the chordae tendineae to the PMs, which are part of the left ventricle.

B. Mitral regurgitation (MR) can occur as a result of malfunction of any of these components.

C. Mitral valve prolapse (MVP) exists when one or both mitral leaflets extend beyond the plane of the mitral valve annulus into the left atrium during systole.

D. Mitral stenosis (MS) is usually valvular and is caused more rarely by the fusion of subvalvular components.

II. MITRAL REGURGITATION

A. Clinical presentation

1. Signs and symptoms

a. With **acute, severe de novo MR**, an abrupt rise in pulmonary capillary wedge pressure (PCWP) causes pulmonary edema. The symptoms include rest dyspnea, orthopnea, and possibly signs of diminished forward flow, including cardiogenic shock.

b. Chronic MR is usually **asymptomatic** for years. The most common presentation is an asymptomatic murmur. **When symptoms develop**, exercise intolerance and exertional dyspnea usually occur first. Orthopnea and paroxysmal nocturnal dyspnea may develop as MR progresses. Fatigue is caused by diminished forward cardiac output. With the development of left ventricular (LV) dysfunction, further symptoms of congestive heart failure (CHF) are manifest. **Long-standing severe MR** may cause **pulmonary hypertension**,

with symptoms of right ventricular (RV) failure. Atrial fibrillation commonly occurs as a consequence of left atrial (LA) dilation.

2. **Physical findings**

a. **Inspection and palpation.** When LV function is preserved, carotid upstrokes are sharp, and the cardiac apical impulse is brisk and hyperdynamic. An early diastolic LV filling wave may be palpable because of the large volume of blood traversing from the left atrium to the left ventricle. A late systolic thrust may be present in the parasternal location because of systolic expansion of the left atrium (which may be difficult to differentiate from an RV lift). With the development of LV dilation, the apical impulse is displaced laterally. An RV heave and a palpable P_2 are present if pulmonary hypertension has developed. An elevated jugular venous pressure, hepatomegaly, ascites, and peripheral edema indicate secondary RV dysfunction.

FIGURE 16.1 Anatomy of the mitral valve apparatus. (Copyright © Cleveland Clinic Foundation. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2011-2018. All Rights Reserved.)

b. **Auscultation.** The main auscultatory findings are shown in Figure 16.2. A loud S_4 (not illustrated) can be heard sometimes, particularly with acute MR.

FIGURE 16.2 Auscultatory findings in mitral regurgitation. MR, mitral regurgitation.

In acute, severe MR, the systolic driving pressure across the mitral valve is reduced due to a high LA pressure and, as a result, the murmur is short and relatively soft. If the LA pressure is markedly elevated, the murmur of acute MR may be inaudible. With decompensated systolic heart failure, fine inspiratory pulmonary crackles may be evident.

3. The **differential diagnosis of holosystolic murmurs** includes MR, tricuspid regurgitation, and ventricular septal defect (VSD). All are high pitched, but the murmur of a VSD is often harsh in quality, unlike the blowing murmurs of MR and tricuspid regurgitation.

a. The murmur of **MR** is best heard in the apical position and often radiates to the axilla (although possibly to the base with anteriorly directed jets); those of tricuspid regurgitation and VSD typically do not. The murmur of posteriorly directed MR radiates to the back.

b. Tricuspid regurgitation is best heard at the left lower sternal border and radiates to the right of the sternum and left midclavicular line. Like all right-sided murmurs, tricuspid regurgitation is accentuated by inspiration.

c. A **VSD** murmur is heard at the left sternal border and often radiates throughout the precordium.

B. **Etiology and pathophysiology.** MR is more commonly myxomatous or ischemic, rather than rheumatic, in etiology. The causes of MR are summarized in Table 16.1.

1. In **acute MR**, the regurgitant volume that returns from the left atrium causes a **sudden increase in LV end-diastolic volume.** The left ventricle compensates for this by means of the Frank–Starling mechanism: Increased sarcomere length (preload) enhances LV contraction (inotropy). This occurs at the cost of increasing LV filling pressure and may cause symptoms of pulmonary congestion. LV wall stress (afterload) is reduced because blood

is ejected into the lower pressure left atrium as well as into the systemic circulation. Increased inotropy and reduced afterload cause more complete LV emptying and hyperdynamic function. Forward cardiac output declines, however, because much of the flow is directed to the left atrium. If the acute hemodynamic insult is tolerated, the patient's condition **may progress to a chronic compensated state**.

2. In **chronic compensated MR**, there is **dilation of the left ventricle with eccentric hypertrophy**.

a. Wall stress is normalized with the development of hypertrophy. Afterload reduction by the low-resistance left atrium is not as significant as it is in the acute phase. Preload remains elevated by the same mechanism as in acute MR. LA dilation helps to accommodate the increased preload at lower filling pressures. LV function is not as hyperdynamic as in the acute state but is in the high-normal range.

b. Patients may stay in this asymptomatic or minimally symptomatic phase for years; however, **contractile dysfunction may develop insidiously** during this phase. Increased preload, normal or decreased afterload, and increased sympathetically mediated contractility all continue to augment the ejection fraction (EF). However, because the regurgitant volume ejected back into the left atrium diminishes the actual forward stroke volume (SV), the **EF may overrepresent true cardiac function**. Thus, in severe MR, normal left ventricular ejection fraction (LVEF) is considered to be at least 60% and values below that are thought to represent contractile impairment.

3. In **chronic decompensated MR**, there is LV dysfunction along with progressive enlargement of the LV chamber with increased wall stress. LV dysfunction and enlargement increase the severity of MR, further contributing to the cycle of deterioration. **Irreversible LV contractile dysfunction** may be present by the time overt symptoms develop and this confers higher rates of postoperative heart failure and increased mortality.

C. Laboratory examination

1. The **electrocardiographic** findings are **nonspecific**. The principal features are LA enlargement and atrial fibrillation. LV hypertrophy and RV hypertrophy may also be seen in patients with severe MR.

TABLE 16.1 Causes of Mitral Regurgitation

Leaflet Abnormalities
Myxomatous degeneration of leaflets with excessive motion (most common)
Rheumatic disease: scarring and contraction lead to the loss of leaflet tissue
Endocarditis: can cause leaflet perforations and retraction in the healing phase
Aneurysms: usually from aortic valve endocarditis; aortic insufficiency produces jet lesion on the mitral v
Congenital:
Cleft mitral valve: isolated or with ostium primum atrial septal defect
Double-orifice mitral valve

TABLE 16.1 Causes of Mitral Regurgitation

Hypertrophic cardiomyopathy: systolic anterior motion of the mitral valve
Mitral Annular Abnormalities
Annular dilation
From left ventricular dilation: dilated cardiomyopathy, ischemic disease, hypertension
Normal 10 cm in circumference
With sufficient dilation, loss of adequate leaflet coaptation
Tethering of leaflet and chordae can occur and produce relative restriction of leaflet motion
Mitral annular calcification
Degenerative disorder, most commonly seen in the elderly
Accelerated by hypertension or diabetes
Also seen in renal failure with dystrophic calcification
Also seen with rheumatic heart disease
Marfan syndrome and Hurler syndrome
MR results from immobility of the annulus and loss of sphincter activity
Chordal Abnormalities
Chordal rupture (most severe form is flail leaflet) results in loss of leaflet support usually with myxomato
Rheumatic heart disease (chordal fibrosis and calcification)
Papillary Muscle Abnormalities
Rupture with myocardial infarction
Complete rupture typically not survived
Partial rupture more typically encountered
Dysfunctional papillary muscle
Ischemia
Posteromedial papillary muscle, single blood supply through posterior descending artery
Anterolateral papillary muscle, supplied by left anterior descending artery and left circumflex artery
Infiltrative processes: amyloid and sarcoid
Congenital: malposition, parachute mitral valve

2. MR, mitral regurgitation.

3. Chest radiography. Cardiomegaly with LA and LV enlargement may be seen in chronic MR. Interstitial edema, manifest as Kerley B lines, followed by alveolar edema may develop in acute cases or with progressive LV failure. Calcification of the mitral annulus may be visualized as a C-shaped opacity in the lateral projection.

D. Diagnostic testing

1. Echocardiography plays a pivotal role in the evaluation of MR. It is useful in **diagnosing MR and in determining its severity and cause**. MR **severity is graded semiquantitatively as follows**: 1+ for mild, 2+ for moderate, 3+ for moderately severe, and 4+ for severe regurgitation. Increasingly, **MR is quantified where feasible**. This is accomplished most often using the proximal convergence method (see Section II D.d). Quantification provides prognostically powerful information that is less affected by the ongoing loading conditions.

The American College of Cardiology/American Heart Association (ACC/AHA) class I recommendation is for the use of Doppler echocardiography to determine the mechanism and severity of MR, to assess the LA and LV size and function over time, to assess the pulmonary artery (PA) pressures, and to reevaluate periodically if more than mild, and after mitral valve surgery. The current ACC/AHA classification of MR severity by Doppler echocardiography is summarized in Table 16.2.

a. Color Doppler echocardiography allows the diagnosis of MR by means of visualization of the regurgitant jet or jets entering the left atrium and allows the assessment of severity.

1. **(1)** Jet length and area are used in this assessment. These measurements are **reliable with central jets**, but underestimation of MR may occur with eccentric jets. Because a jet directed against the atrial wall appears smaller than a free jet of the same regurgitant volume (Coanda effect), it is common practice to upgrade the estimated severity of MR by at least one grade in this situation. The direction of the MR jet can also aid in assessing the cause of MR (Table 16.3). Regurgitation caused by prolapse or flail (excessive leaflet motion) results in a jet direction opposite to the affected leaflet (i.e., posterior jet with anterior leaflet prolapse). MR caused by leaflet restriction (rheumatic and ischemic) is directed toward the affected leaflet.

1. **(a) Caveats**

1. **i.** MR is often assessed with **transesophageal echocardiography (TEE)**. Patients often receive sedation before TEE, and the sedation may reduce systemic blood pressure (afterload). This could make the MR appear less severe than it is under normal physiologic circumstances. This effect of sedation may be mitigated to some extent by increasing the afterload by handgrip or by the cautious administration of phenylephrine.

TABLE 16.2 Assessment of Severity of Mitral Regurgitation

	Mild	Moderate	Severe[a]
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet area	Small, central jet (<4 cm^2 or <20% LA area)	Signs of MR > mild present, but no criteria for severe MR	Vena contracta width > 0.7 cm (area > 40% of LA area) or w any size

TABLE 16.2 Assessment of Severity of Mitral Regurgitation				
Doppler	vena contracta width (cm)	<0.3	0.3–0.69	≥0.70
Quantitative (Echo)				
Regurgitant	volume (mL/beat)	<30	30–59	≥60
Regurgitant	fraction (%)	<30	30–49	≥50
Regurgitant	orifice area (cm^2)	<0.20	0.2–0.39	≥0.40

MR, mitral regurgitation; LA, left atrium; LV,

[a] In severe MR, evidence of LA and LV

al.

TABLE 16.3 Mechanisms, Direction of Color Jet, and Surgical Management of Mitral Regurgitation			
Jet Direction	**Leaflet Motion**	**Likely Cause**	**Surgical Method**
Anterior	Excessive	Posterior leaflet prolapse	Quadrilateral resection Annuloplasty Chordal shortening Shortening of papillary mus
	Restricted	Anterior leaflet restriction	Debridement
Posterior	Excessive	Anterior leaflet prolapse	Chordal transfer or shorteni
			Synthetic chords
	Restricted	Posterior leaflet restriction	Debridement, annuloplasty
	Normal	Ventricular dilation	Annuloplasty
Central	Excessive	Bileaflet prolapse	Resection, chordal transfer
	Restricted	Bileaflet restriction	Debridement
	Normal	Ventricular dilation	Annuloplasty
Commissural	Papillary muscle dysfunction		Reattach or fold papillary m
	Eccentric	Perforation or cleft	Pericardial patch

Reprinted with permission from Stewart WJ. raoperative echocardiography. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Publishers; 1998.

5. ii. In the evaluation of MR in the **intraoperative setting**, there may be fluctuations in afterload and preload.

2. **(b)** Multiple factors, such as hemodynamic considerations, geometric factors (constraint imposed by the LA wall), and instrumentation, may affect color Doppler measurements. This has led to the development of other measurements to quantify MR.

2. **(2)** The width of the vena contracta, which is the narrowest portion of the proximal regurgitant jet downstream from the orifice, is a **reliable indicator of the severity of MR**. A width **≥0.70 cm suggests severe MR**. High-resolution and zoom images must be used for an accurate assessment of the vena contracta or else TEE may be needed. There is some tendency for overestimation of the width of the vena contracta because of limited lateral resolution.

b. Pulsed-wave Doppler echocardiography of pulmonary venous flow may be useful in the assessment of the severity of MR (Fig. 16.3).

Sampling of the pulmonary veins results in three distinct waves: a systolic antegrade wave, a smaller diastolic antegrade wave, and a small negative wave (not shown in Fig. 16.3) that represents atrial reversal during atrial contraction. With increasing MR, there is a progressive decrease in the systolic wave of pulmonary inflow with eventual reversal. **Blunting of the systolic component** of pulmonary venous flow in the presence of normal LV function suggests at least moderately severe MR. **Systolic flow reversal**suggests severe MR. Blunted pulmonary venous flow is a less reliable indicator of substantial MR in the setting of atrial fibrillation or severe LV dysfunction, because these conditions can also cause systolic blunting.

c. **Pulsed-wave Doppler echocardiography of mitral inflow.** SV across the regurgitant mitral valve can be estimated and compared with the SV derived from pulsed-wave Doppler imaging across a competent valve (such as the aortic or pulmonary valve). The excess flow at the mitral valve over that derived at the aortic valve is **the regurgitant volume**. These methods are both tedious and technically difficult.

FIGURE 16.3 Pulmonary venous flow changes with increasing mitral regurgitation severity.

d. The **proximal isovelocity surface area (PISA)** or flow convergence method provides a quantitative assessment of MR (Fig. 16.4). With PISA, the flow on the upstream (proximal) side of the valve is the same as that going through the actual regurgitant orifice at the valve itself. Flow is the product of area and velocity. If we can measure flow going into the valve and the velocity at the regurgitant orifice itself, we can derive the area of the regurgitant orifice. PISA utilizes the quality of color Doppler flow leaking through the valve that sets up a series of concentric hemispheres. All the flow at the hemisphere where the color changes from blue to red is at the aliasing velocity (*Va*) which can be read off the machine. The cross-sectional area of a hemisphere is $2\pi r^2$ where r is the radius of the hemisphere which may be measured directly. The velocity baseline can be manipulated to maximize the size of the radius and make it easier to measure.

FIGURE 16.4 Flow convergence method. PISA, proximal isovelocity surface area; Regurg, regurgitant; Va, aliasing velocity.

Peak mitral flow rate (QFC) is derived as follows:

$$QFC = 2\pi r^2 Va$$

where r is the radius of the hemisphere and Va is the aliasing velocity at that hemisphere. **Regurgitant orifice area (ROA)**, a relatively load-independent measure of regurgitation, is derived from peak flow rate by dividing this by peak flow velocity (maximal MR continuous-wave velocity, ***Vmr***):

$$ROA = 2\pi r^2 Va/Vmr$$

The **regurgitant volume** (RV) may be further calculated by the equation ROA × VTI*mr*, where VTI*mr* is the velocity–time integral of the regurgitant jet.

If the forward SV is known, then the **regurgitant fraction** (RF%) may be derived as follows:

$$RF = RV/RV + SV$$

SV may be estimated in the LV outflow tract as area × VTI, as performed in the continuity equation.

ROA has been shown to be prognostically powerful in MR of ischemic or degenerative origin. **An ROA of 0.4 cm2** or greater is consistent with severe MR and is associated with poor long-term outcomes if the valve is not repaired or replaced. In ischemic MR (IMR), ROA of ≥ **0.2 cm2** is indicative of poorer long-term outcomes.

1. **(1) Simplified** proximal convergence method. The preceding calculation may be simplified to allow the ROA to be estimated with only one measurement. Using this method, MR velocity is assumed to be 5 m/s and the aliasing velocity is set at 40 cm/s. The ROA may be calculated as $r^2/2$. **Higher ROA indicates an increased severity of MR.**
2. **(2)** Inaccuracies in using proximal convergence method occur when the orifice is nonspherical, multiple jets are present, or the flow convergence zone is constrained as occurs with eccentric jets. The latter situation occurs with a flail leaflet, as regurgitant flow and ROA are typically overestimated by the use of the PISA method; accuracy may be improved by the use of angle-correction formulas.

2. Cardiac catheterization

a. The **amplitude of the v-waves** on hemodynamic tracings (which are a reflection of LA filling from the pulmonary veins during ventricular systole) can provide clues to the severity of MR, particularly in acute MR.

1. **(1)** Amplitudes of v-waves more than two to three times mean LA pressure suggest severe MR. However, in slowly developing MR, an abnormal v-wave may not be seen. The v-waves are also diminished by afterload reduction. The **absence of v-waves does not exclude severe MR.**
2. **(2)** Other conditions that may produce prominent v-waves are LV dysfunction with a dilated noncompliant left atrium, postinfarction VSD, and other situations in which there is increased pulmonary blood flow.

b. Left ventriculography allows the visual assessment of the severity of MR. It is affected by multiple factors such as the adequacy of the contrast injection to fill the ventricle, the placement of the catheter, and ventricular arrhythmia during injection. The grading system is as follows:

1. **(1) 1+ (mild):** clears with each beat; entire left atrium is never opacified

2. **(2) 2+ (moderate):** does not clear with a single beat; may faintly opacify the entire left atrium
3. **(3) 3+ (moderate to severe):** fills entire left atrium over 2 or 3 beats; complete opacification of the left atrium, equal in intensity to the left ventricle
4. **(4) 4+ (severe):** complete opacification of the left atrium in 1 beat; contrast material refluxes into the pulmonary veins

c. Coronary angiography is useful to detect **concomitant coronary artery disease** (CAD) in these patients. Those being considered for surgery to correct MR undergo coronary angiography, even in the absence of symptoms, if they are older than 50 years or have multiple risk factors.

E. Therapy. An understanding of the pathophysiologic mechanism of MR is essential to management.

1. Acute MR

a. Medical therapy. If there is adequate mean arterial pressure, pharmacologic therapy with **afterload reducing agents** may reduce the acute MR. Intravenous nitroprusside and nitroglycerin may reduce pulmonary pressures and maximize forward flow. If surgery is not immediately indicated, a switch to oral agents may be made. Angiotensin-converting enzyme (ACE) inhibitors (ACE-I) and direct-acting vasodilators (such as hydralazine) help maximize forward output and reduce regurgitant fraction.

b. Percutaneous therapy. The large sudden volume overload on a left ventricle that is not dilated or hypertrophied causes symptoms of pulmonary congestion and even cardiogenic shock. For such patients with acute hemodynamically significant MR, especially from postinfarction PM rupture, placement of an intra-aortic balloon pump (IABP) may serve as a temporary stabilizing measure until surgical repair can be undertaken.

c. Surgical therapy. Patients with acute, severe MR usually require urgent surgical intervention.

2. Chronic MR

a. Choosing the appropriate therapy (see Table 16.4 for a summary of the current ACC/AHA guidelines)

TABLE 16.4 Indications for Mitral Valve Surgery in Mitral Regurgitation

Class I

a. MV surgery is recommended for the symptomatic patient with acute severe MR

b. MV surgery is of benefit for symptomatic patients with chronic severe MR in the absence of severe <30%)

c. MV surgery is of benefit for asymptomatic patients with chronic severe MR and mild to moderate L and/or end-systolic dimension ≥ 40 mm)

d. MV repair is indicated over MV replacement in most patients with severe chronic MR who require s referred to surgical centers experienced in MV repair

Class IIa

a. MV repair is reasonable in experienced surgical centers (Heart Valve Center of Excellence) for asy severe MR and preserved LV function in whom the likelihood of successful repair is >95%

b. MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, an

c. MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV functio (PASP > 50 mm Hg)

TABLE 16.4 Indications for Mitral Valve Surgery in Mitral Regurgitation

Class IIb

a. MV surgery is reasonable for symptomatic patients with chronic severe MR because of a primary abn
severe LV dysfunction (EF < 30%) in whom MV repair is highly likely

b. MV repair may be considered for patients with chronic severe secondary MR because of severe LV dy
persistent symptoms despite optimal therapy for heart failure, including biventricular pacing

c. Transcatheter MV repair may be considered in symptomatic patients with chronic severe primary M
candidates because of severe comorbidities

Class III

a. MV surgery is not indicated for asymptomatic patients with MR and preserved LV function (EF > 60%)
the feasibility of repair exists

b. Isolated MV surgery is not indicated for patients with mild or moderate MR

b. EF, ejection fraction; MR, mitral regurgitation; MV, mitral valve; LV, left ventricular; PASP, pulmonary artery systolic pressure.

c. Adapted from 2014 Valve Disease ACC/AHA Valve Disease Guidelines. Reprinted with permission from Nishimura RA, Otto CM, Bonow RO et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary. *Circulation*. 2014;129(23):2440–2492. Copyright © 2014 American Heart Association, Inc.

1. **(1)** Most patients who have **moderately severe to severe MR** and are **symptomatic** should be considered for elective surgical treatment. Decisions need to be individualized based on the age of the patient, the likelihood of valve repair, comorbidities, LV function, and the likelihood that surgical intervention will improve symptoms and/or survival. Generally, **intervention for symptoms is indicated for severe MR if the cause of the MR is primary to the valve** (i.e., prolapse, rheumatic, or congenital in origin). When the **valve lesion is secondary to ventricular dysfunction,** either from ischemic heart disease or from dilated cardiomyopathy, **aggressive medical management of heart failure** (see subsequent text) is indicated first.
2. **(2)** In **severe MR because of dilated cardiomyopathy associated with severe symptoms** and refractory to medical management and cardiac resynchronization therapy (CRT) where indicated, mitral valve repair may lead to symptomatic improvement, but a survival benefit has not yet been demonstrated.
3. **(3)** Management of patients with **minimal or no symptoms but severe MR** is more complex. **The key is to identify patients before contractile dysfunction of the left ventricle becomes irreversible.** Watchful waiting until serious symptoms develop carries a risk for the development of severe LV dysfunction and a poor prognosis. The feasibility of mitral valve repair with improved postoperative survival and EF (see later) has been another incentive in the push for earlier surgical intervention. If the valve repair is not feasible, one may choose to wait longer before proceeding to surgical treatment. The 2014 valve guidelines **consider it reasonable to perform mitral valve repair in asymptomatic patients with severe MR** when repair is performed in an experienced center where the likelihood of repair exceeds 95% with an expected mortality <1% (Heart Valve Center for Excellence; Table 16.4).

d. **Timing of surgery.** A variety of clinical, echocardiographic, and invasively derived values appear to be predictive of the development of postoperative LV

dysfunction, decompensated heart failure, and death among patients with significant but asymptomatic MR. The timing of mitral valve surgery is a **decision that must be individualized** and depends on several variables, including clinical signs and symptoms, echocardiographic findings, catheterization data, hemodynamic data, operative risk, and repairability of the mitral valve. Generally, the variables to be considered in patients whose MR is asymptomatic are (a) LV size and function; (b) exercise capacity and LV size and function at peak exercise; (c) repairability of the valve; (d) severity of MR, including the presence of flail leaflet; (e) PA pressures; (f) atrial fibrillation; and (g) age and other comorbidities.

1. **(1)** LV size and function. As noted previously, contractile impairment is often occult in severe MR when conventional indices of LV function are used. Elastance measured at the time of cardiac catheterization is the best load-independent measure of true contractile function in MR. However, because it requires the construction of a series of pressure–volume loops for its calculation, it is rarely performed outside research laboratories. Fortunately, conventional indices of LV size and function do provide useful information in MR. Newer noninvasive techniques, such as two-dimensional (2D) strain imaging, are of interest because of their ability to detect subtle changes in LV function that precede reductions in EF. **In severe primary MR with preserved contractile function, LVEF should be in the high-normal range. Studies have indicated that once the LVEF is <60%, the likelihood of impaired survival and permanent LV dysfunction postoperatively is high.** Therefore, consideration should be given to surgical intervention before the LVEF drops to below 60%. Increased LV size and volume in end systole (more load-independent than end diastole) is also an indicator of increased likelihood of impaired survival and LV dysfunction postoperatively. When **LV end-systolic diameter is >4.0 cm, surgical intervention should be considered**.
2. **(2)** We have found that **exercise echocardiography** is very helpful in determining the likelihood of latent LV contractile dysfunction. **The ability of the left ventricle to cope with exercise is an indication of its contractile reserve**. In addition, **poor functional capacity** may indicate an adaptive response to MR (the patient was not truly asymptomatic) and may influence the decision to proceed with surgical treatment. We have found that a **failure to *increase* LVEF, or for end-systolic volume to *decrease* with stress, is predictive of postoperative LV dysfunction** and is a superior predictor of this eventuality than resting LVEF. In patients with severe asymptomatic MR, we perform stress echocardiography at 6-month intervals and recommend mitral valve surgery once end-systolic volume fails to decrease significantly at peak exercise or if LVEF fails to increase. This is particularly helpful in patients who wish to postpone surgical intervention as long as possible. We have also recently shown that mitral valve surgery can be safely postponed in patients with significant myxomatous MR as long as they achieve >100% predicted metabolic equivalents.
3. **(3)** The **feasibility of repair** depends on the cause of MR. This can be determined during the preoperative evaluation by echocardiography. **Repair in an experienced center is usually likely in MVP unless chordae to both leaflets are severed, severe damage from endocarditis has occurred, or there is extensive leaflet calcification.** Repair is usually feasible for a cleft valve and in less extreme forms of endocarditis such as leaflet perforation without chordal disruption, as well as in many cases of secondary MR (ischemic or dilated cardiomyopathy). Repair is more difficult to achieve in rheumatic involvement and when the valve leaflets or chordae are severely disrupted from any cause. **The threshold to intervene surgically is lower if repair appears feasible because of the lower surgical and long-term mortality and morbidity associated with repair compared with replacement.**

4. **(4)** The more severe the MR, the greater the volume load on the left ventricle usually, and the more likely that LV dysfunction will develop. One caveat here is that MR is not always holosystolic. Occasionally, apparently severe MR is seen without evidence of significant LV enlargement because the MR is occurring only in the latter part of the systole.

   The threshold to intervene surgically is lower as MR severity increases. In situations where MR severity is in doubt, a TEE should be performed and the quantitative assessment used as described previously. A flail leaflet usually (but not always) implies severe MR. A retrospective study suggested that earlier surgical intervention was associated with better long-term survival in patients with a flail leaflet, even if the condition was asymptomatic, with flail being considered a surrogate for severe MR. More recent quantitative studies suggest that once ROA is ≥ 0.4 cm^2, survival is better in those treated surgically, even in the absence of symptoms.

5. **(5)** Pulmonary hypertension (pulmonary artery systolic pressures [PASP] > 50 mm Hg) in the absence of another likely cause is an indication of severe MR and impaired survival and is **considered ACC/AHA class IIa indications for surgical intervention**. It can be assessed noninvasively from the tricuspid regurgitant velocity.

6. **(6)** The occurrence of **atrial fibrillation** in the setting of severe MR is considered an indication (IIa) for surgical intervention. A concomitant maze or more usually now a modified maze procedure (pulmonary vein and great vein isolation) may be performed with mitral valve repair, especially if atrial fibrillation has become persistent or frequent.

7. **(7)** Age and other comorbidities. Patients >75 years, those with concomitant CAD, or those with renal dysfunction have worse outcomes after surgical treatment. Patients with IMR have a worse prognosis than those with regurgitation from other causes.

e. Medical therapy

1. **(1)** The **role of medical therapy for asymptomatic, chronic MR caused by primary valve disease is not well established**. There is ***no*** evidence that pharmacologic agents delay progression of the disease or prevent ventricular dysfunction. Patients with severe MR should be evaluated semiannually with echocardiography and stress echocardiography, if indicated. Patients with moderate MR should be evaluated annually.

1. **(a)** The success of afterload reducers in acute MR has led to trials of vasodilators, such as **ACE-I and hydralazine**, in chronic MR. However, existing small trials have been largely negative. As a result, the ACC/AHA and European Society of Cardiology guidelines do not recommend the use of pharmacologic vasodilatation in chronic MR with preserved EF, although this is not necessarily reflected in common practice.

2. **(b)** Sympathetic overstimulation appears to be a key element of progression to LV failure in MR, and there is limited evidence for the experimental use of β-blockers in MR but no clinical evidence of utility of postponement of surgical intervention.

3. **(c)** MR secondary to LV dysfunction is managed with standard heart failure therapy, including ACE-I and β-blockers.

4. **(d)** Diuretics and nitrates have a role in the management of pulmonary congestion.

5. **(e)** Ventricular rate-controlling agents and antiarrhythmics are used for atrial fibrillation. **Digitalis and β-blockers** are the mainstay of therapy for rate control. In severe MR with atrial fibrillation, maintenance of sinus rhythm is unlikely if the regurgitation remains uncorrected.

2. **(2) In accordance with recent AHA guidelines**, endocarditis prophylaxis is not routinely indicated in patients with MR. These new guidelines recommend that prophylaxis be used only in patients with underlying cardiac conditions associated with the highest adverse outcome from

infective endocarditis, including prosthetic heart valves or prior repair surgery, previous infective endocarditis, certain classes of congenital heart disease, and in valvulopathy occurring post cardiac transplantation.

f. Surgical therapy

1. **(1)** Mitral valve replacement with transection of the subvalvular apparatus was once the only approach used in the surgical management of MR. Postoperative reduction of LV function and decompensated heart failure were common sequelae. Chordal preservation by leaving the subvalvular structures intact has been shown to reduce LV volumes and wall stress postoperatively and is now the technique of choice.
2. **(2)** The increasing success of **mitral valve repair** has greatly reduced the morbidity and mortality associated with severe MR. Mitral valve repair almost always involves placement of an undersized annuloplasty ring, which reduces annular diameter, improves leaflet coaptation, and significantly decreases MR. Additional components may include a pericardial patch at the site of leaflet perforation, chordal shortening or transposition, leaflet resection, and sliding valvuloplasty of the posterior leaflet to reposition the coaptation line. Artificial chordae are increasingly used in the repair of anterior leaflet prolapse.
3. **(3)** Although no randomized trials have compared repair with replacement, **comparative data suggest better postoperative LV function and survival with repair** (which in part reflects the selection of patients who are able to undergo repair). Long-term risk of thromboembolism and endocarditis is reduced with repair versus replacement, and the need for reoperation is similar. Excellent 20-year outcomes following repair have been reported from multiple large volume centers, with the estimated risk of reoperation approximating 10% at 20 years.
4. **(4) Minimally invasive** video-assisted approaches employing hemi-lower sternotomy and right thoracotomy incisions may be options in experienced centers and selected patients. In the latter, cardiopulmonary bypass is usually achieved via femoral artery and vein cannulation. These approaches have the benefit of smaller incisions, resulting in more rapid postoperative recovery but require considerable expertise. Introduction of robotic surgical instrumentation and high-definition three-dimensional (3D) imaging allows mitral valve repair through portlike incisions, with further reduction in procedural invasiveness. **Robotically assisted valve repair** has shown good results in a few centers, although there are currently no data for superior outcomes. Complex surgeries, particularly if they require concomitant coronary artery bypass grafting (CABG) or multivalvular repair, are performed with a standard sternotomy.
5. **(5) Mitral valve replacement** is indicated when repair is not technically possible. The choice of **mechanical or bioprosthetic** valve replacement depends on weighing the risk of chronic anticoagulation required with mechanical valves, against the reduced longevity of the bioprosthetic valves. Structural degeneration of bioprosthetic mitral valves typically affects 20% to 40% patients at 10 years and over 60% at 15 years but is highly related to patient age at the time of surgery. In older patients, a bioprosthesis will last longer and this is the valve of choice in those over age 70.
6. **(6)** Intraoperative echocardiography helps in the **assessment of complications** of valve repair or replacement.

1. **(a)** Residual MR is the most common problem after a pump run. If further repair is feasible, a second pump run should be considered to correct residual MR (if 1+ or greater). If further repair is not possible, valve replacement may be needed. A second pump run does not appear to increase in-hospital mortality.
2. **(b) Dynamic LV outflow obstruction** is an important potential complication of mitral valve repair. This is now uncommon in experienced centers. It is caused by anterior displacement of mitral leaflet

coaptation point when the posterior leaflet is redundant (typically >1.5 cm in height). The result is systolic motion of the mitral leaflet into the outflow tract, creating a pressure gradient across the outflow tract and the development of MR. This may be apparent immediately after surgery in the operating room, with intraoperative echo or later in the course. It is exacerbated by increased inotropy and small LV size. Many instances resolve with cessation of the use of sympathomimetic agents and volume repletion. In the operating room, if these efforts fail to correct the condition, more surgery to reduce the height of the posterior mitral leaflet (sliding annuloplasty) or, rarely, mitral valve replacement may be necessary. In the postoperative patient, volume repletion and judicious use of β-blockade are often all that is necessary, although occasionally surgical revision of the repair is needed. The development of a new apical systolic murmur in a patient who has undergone mitral valve repair should prompt an echocardiogram to exclude this complication.

g. Postsurgical follow-up care

1. **(1)** Baseline echocardiography should be performed postoperatively. This is ideally scheduled 4 to 6 weeks after the operation, but for the sake of convenience, it is often done before hospital discharge (within 3 to 4 days).
2. **(2)** MR can recur because of failure of the repair or because of progression of the disease that caused MR. Patients should undergo clinical evaluations at least once a year. **Yearly echocardiography** after the operation to assess for MR and LV function is reasonable.

h. Resynchronization therapy. LV wall motion abnormalities are often the major pathology in secondary (functional) MR, and CRT has demonstrated symptomatic benefit in carefully selected patients.

i. Percutaneous mitral valve repair and replacement. Percutaneous mitral valve repair is a developing catheter-based treatment option in which improved coaptation of the mitral leaflets is attempted using an implantable device. Current techniques emulate the existing surgical procedures, with the devices currently under investigation being classified into two functional approaches.

1. **(1)** A **clip** can be used to approximate the center of the mitral valve leaflets, thus giving a double-orifice valve in an approach that models the surgical Alfieri edge-to-edge repair. To date, this is the best studied percutaneous option and the only US Food and Drug Administration–approved device for percutaneous mitral valve repair. The Endovascular Valve Edge-to-Edge Repair Study II randomized 279 patients with 3 to 4+ MR to MitraClip (Abbott Vascular, Menlo Park, CA) versus surgical mitral valve repair/replacement. The primary composite end point for efficacy was freedom from death, from mitral valve surgery, and from 3 or 4+ MR at 12 months. About 55% of subjects in the percutaneous repair group met the end point at 1 year compared with 73% in the surgery group. All-cause mortality was equivalent in the percutaneous and surgical groups. There were significantly fewer adverse events in the percutaneous group, although significance was lost when blood transfusion was excluded as a complication. At 4-year follow-up, the overall rates of mortality and of 3+ or 4+ MR remained similar in both groups However, the need for mitral valve surgery for valvular dysfunction was higher in the percutaneous group.
2. **(2)** A **flexible ring** can be deployed and tightened in the coronary sinus (CS) in order to effectively reduce the mitral annulus area. Concerns regarding this procedure include the variable relationship between the CS and mitral annulus, as well as the proximity to the circumflex artery. **Investigational devices** include two stents deployed into the CS, with the connecting coil bridge being tightened over time called the Monarc (Edwards Lifesciences, Irvine, CA); a fixed length, double-anchor CS device called the Carillon Mitral Contour System (Cardiac Dimensions,

Kirkland, WA); and a CS anchor that is attached to the interatrial septum via a cord under tension called the Percutaneous Septal Shortening System (Ample Medical, Foster City, CA).
The clip may be more appropriate for repair of MVP, whereas annular remodeling is felt to be better suited for the repair of functional regurgitation.

Percutaneous mitral valve replacement is under investigation. None of the various devices have received approval for clinical use as yet. In patients with a very calcified mitral annulus or who have had a prior mitral valve ring placed, a stented prosthesis has been successfully deployed at the mitral position similar to that at the aortic position.

III. ISCHEMIC MITRAL REGURGITATION

A. Clinical presentation. IMR may present either acutely in the setting of active ischemia or infarction or chronically with long-standing CAD. Among patients with CAD, the presence of MR portends a worse prognosis. Acute severe IMR presents with cardiogenic shock and hemodynamic instability, with symptoms and signs consistent with those previously described for acute MR. The clinical presentation of chronic IMR also parallels that of other etiologies of chronic MR; in addition, a history of known CAD or cardiovascular risk factors should be sought.

B. Etiology and pathology

1. Ischemia or infarction may give rise to one or more of the following mechanisms of IMR. Those common in the acute setting include the following:

a. PM rupture or chordal avulsion
b. Altered LV geometry, causing PM displacement
c. Elongation of the infarcted PM and exaggerated contraction of the noninfarcted PM

2. Mechanisms common in the chronic IMR setting include (Fig. 16.5)

a. PM necrosis and segmental dysfunction of inferoposterior wall causing leaflet tethering and poor coaptation
b. Decreased mitral valve closing forces because of LV systolic dysfunction
c. LV cavity dilation causing mitral valve annular dilation

3. The anterolateral PM receives its blood supply from the left anterior descending and circumflex circulations; the posteromedial PM is supplied by the right coronary or left circumflex artery depending on the coronary dominance.

4. Of note, acute IMR is more frequently a result of geometric changes because of regional LV dysfunction (especially of the inferolateral wall) that induce leaflet tethering and prolapse, rather than ischemia of the PM itself.

FIGURE 16.5 Larger view (L). As evident in the figure, there is distortion of the left ventricular geometry with resultant annular dilation and papillary muscle displacement causing tethering of the chordae and restricted leaflet closure. All these changes lead to ischemic mitral regurgitation.

C. Laboratory examination and diagnostic testing

1. **Echocardiography.** The most important determinations are the assessment of valvular anatomy, quantification of regurgitation, and evaluation of LV structure and function. Echocardiography can often reveal the mechanism of IMR by evaluating for PM rupture, leaflet restriction, mitral valve tethering, and relevant regional wall

motion abnormalities. As previously described, the degree of regurgitation is quantified using color flow and Doppler techniques. Urgent transthoracic echocardiography and/or TEE is the investigation of choice in a patient with acute pulmonary edema where IMR is being considered as an etiology.

2. **Electrocardiogram (ECG).** In acute IMR, ECG is key in evaluating for the presence of active ischemia or infarction. As described above, branches from the left or right coronary systems can supply the PMs. However, it is in the setting of inferior or inferolateral MIs that acute IMR is most commonly seen. In chronic IMR, LA abnormalities, atrial fibrillation, and nonspecific ST–T changes may be seen.

3. **Chest radiography.** In acute IMR, findings of pulmonary edema may be present. Cardiomegaly with LA and LV enlargement may be seen in chronic IMR.

4. **Cardiac catheterization.** Evaluation of the patient with IMR will include angiography to assess the location, extent, and revascularization options of the CAD. In some cases, invasive hemodynamics may provide useful additional data regarding MR severity.

D. Therapy

1. Intravenous afterload reduction with nitroprusside and nitroglycerin +/− IABP insertion is often required when managing cardiogenic shock secondary to acute IMR. This scenario is associated with a **very poor prognosis**, and surgical intervention with coronary artery bypass and valve repair or replacement is usually the only hope for survival.

2. The medical management of chronic IMR with preserved EF remains controversial, as described above. If LV dysfunction is present, the use of a heart failure medical regimen is essential.

3. Controversy exists regarding the need for concomitant mitral valve surgery in patients with significant IMR who require coronary artery bypass surgery (CABG). A recent randomized trial did not show a clinically meaningful advantage of adding mitral valve repair to CABG in patients with moderate IMR. Also, when repair was compared to replacement in severe IMR, randomized studies did not show a significant difference in LV remodeling or survival at 1 year and at 2 years; however, recurrent MR was more likely with repair.

IV.MITRAL VALVE PROLAPSE

A. Clinical presentation.

Prolapse exists when either or both of the mitral leaflets protrude >2 mm beyond the annulus into the left atrium during systole, and the coaptation point of the leaflets lies superior to the plane of the annulus. A wide spectrum of pathologic changes and clinical symptoms have been observed, from mild degrees of prolapse diagnosed with echocardiography only to clinically evident severe MR. MVP is the most common cause of MR in the United States. **It affects approximately 2% of the population. Recent studies have suggested an equal prevalence among males and females**. **Males and older patients (age > 45 years) are disproportionately more likely to require surgical intervention** and to develop other major complications such as endocarditis.

1. **Signs and symptoms**

a. Most patients with MVP have **no symptoms,** and the diagnosis is made by means of routine examination or echocardiography performed for other indications.

b. Although in the past, many symptoms were attributed to MVP, including chest pain, panic attacks, and autonomic instability, more recent studies suggest that

these occur no more frequently in patients with MVP than in control populations. Most symptoms associated with adverse prognostic implications occur when significant MR is present.

c. Both atrial and ventricular arrhythmias have been reported in patients with MVP. However, the prevalence of these arrhythmias seems related to the degree of MR rather than MVP itself. Previous reports have shown that in MVP patients without significant MR, the prevalence of arrhythmias is similar to the general population, and becomes more prevalent with development of significant MR.

d. Transient ischemic attack or stroke has been reported in MVP. However, more recent studies in this area suggest no excess risk of cerebrovascular events among young patients with MVP.

e. When prolapse causes MR, symptoms referable to the valvular insufficiency may be present.

2. Physical findings

a. **Inspection.** There is a higher than expected incidence of **pectus excavatum** among patients with MVP. Straight back and scoliosis are also found. Patients often have low body weight and relative hypotension.

b. The main **auscultatory** findings are shown in Figure 16.6. The **midsystolic click** is the classic finding in prolapse. A systolic murmur is heard if MR is present.

FIGURE 16.6 Auscultatory findings in mitral valve prolapse.

c. Dynamic changes are elicited by **conditions that decrease LV size** (decreased venous return, increased contractility, or decreased systemic volume), which lead to earlier occurrence of prolapse, an earlier click, and increased duration of the murmur. These conditions include standing, the Valsalva maneuver, dehydration, and exposure to amyl nitrite.

d. Maneuvers that **increase LV size** by increasing venous return, decreasing contractility, or increasing systemic volume move the click and murmur later into systole. Examples include squatting and infusion of phenylephrine. The presence of a **click that responds to provocative maneuvers is sufficient for the diagnosis of prolapse**, even if an echocardiogram is not diagnostic.

Systolic click occurs at least 0.14 s after S_1, after onset of carotid upstroke. Multiple clicks can be heard later in systole from snapping taut of chordae (heard best with diaphragm at lower sternal border).

e. The **intensity of the murmur typically decreases with conditions that result in a later click and murmur**. An exception is exposure to amyl nitrite, which also reduces LV systolic pressure and the gradient that drives regurgitant flow. As such, the murmur is of lower intensity, although it occurs earlier in systole.

f. Aortic and pulmonic ejection sounds can produce systolic clicks. These occur earlier in systole than the click of mitral prolapse and may be differentiated on the basis of timing in conjunction with the carotid upstroke. Other causes of midsystolic clicks include septal and free wall aneurysms and mobile tumors such as myxoma. Clicks produced by these conditions do not change with maneuvers that alter LV volume.

B. Etiology and pathology. Prolapse may exist as a result of valvular abnormalities, deemed primary prolapse, or occur in the setting of normal leaflets (secondary prolapse).

1. Primary prolapse results from **myxomatous proliferation of the leaflets**. Myxomatous mitral valve disease describes thickening of the leaflets and chordae tendineae because of abnormal accumulation of **mucopolysaccharides**, with prominence of the spongiosa layer of the leaflets. Impaired tensile strength is more marked in the chordae than in the leaflets. Chordal elongation results in prolapse and loss of leaflet coaptation and may cause MR. **Thickening of the leaflets ≥5 mm is considered "classic" MVP** and is associated with greater future complications.

a. Within the pathologic spectrum of myxomatous mitral valve disease, there are two subtypes of diseases. **Barlow disease** is seen in younger patients, shows greater annular dilation, and has more marked leaflet redundancy and prolapse that may involve multiple segments. Conversely, **fibroelastic deficiency** occurs in older patients, is typically confined to the posterior middle scallop (P_2), and is associated with thinning and rupture of chordae.

b. Primary prolapse appears to have a genetic predisposition. There is a higher prevalence of MVP among family members of those affected, and an **autosomal dominant** mode of inheritance with variable penetrance has been postulated. Three loci, on chromosomes 11, 13, and 16, have been identified in families with multiple affected members. In addition, MVP is commonly identified in patients with Marfan, Loeys–Dietz, Ehlers–Danlos, and osteogenesis imperfecta syndromes.

c. Most **complications** of prolapse, particularly severe MR, are associated with primary prolapse. Men in their sixth decade of life represent the most common demographic group with such a presentation.

2. In **secondary prolapse**, there is relatively **normal valvular structure**. A disproportion between leaflet size and LV cavity size produces mechanical forces that may lead to leaflet prolapse. This form of prolapse particularly affects **younger women**. It may also occur with atrial septal defect, hyperthyroidism, emphysema, and hypertrophic cardiomyopathy. Normalization of the relative disproportion between leaflet size and cavity size often occurs with ageing among women, so the incidence decreases with age. **Secondary prolapse is usually of little clinical significance and is not usually associated with significant MR.**

C. Laboratory examination and diagnostic testing

1. **Echocardiography.** M-mode demonstrates late or holosystolic bowing of the mitral valve leaflet 3 mm or more below the C–D line. In 2D echocardiography, prolapse is defined as **>2-mm displacement of one or both mitral leaflets into the left atrium during systole in the parasternal or apical long-axis views**. Caution must be used in making the diagnosis with the apical four-chamber view because normal valve leaflets may appear to prolapse in this view owing to the saddle shape of the mitral annulus. With primary causes of prolapse, increased leaflet thickness (≥5 mm) and redundant leaflets and chordae are seen. Doppler echocardiography is used to assess the presence and severity of MR. Annual echocardiography is advised for those patients with moderate to severe MR.

2. **Electrocardiogram.** If there is severe MR, the findings described earlier are present. Otherwise, the ECG usually is normal or has nonspecific ST–T changes.

3. **Chest radiography.** Pectus excavatum or scoliosis can be present in some cases. If severe MR is present, the typical findings described earlier are seen. Otherwise, the **chest radiograph is usually normal.**

D. Therapy. For most patients, MVP carries a benign prognosis, and **periodic clinical follow-up examinations and reassurance** are all that is needed.

1. Endocarditis prophylaxis is not routinely indicated in patients with MVP.

2. Approximately 10% to 15% of patients, particularly those with redundant and thickened leaflets, eventually develop progressive MR. Chordal rupture is a contributing factor among these patients. **Management of MR** is outlined in Section **II.E.** Patients with evidence of primary MVP should avoid situations that might increase the stress on the chordae, such as sudden heavy lifting.

3. For patients with a history of **transient ischemic attacks, antiplatelet therapy with aspirin** (80 to 325 mg/d) is indicated. The ACC/AHA guidelines also recommend aspirin for poststroke patients with MVP who have no evidence of MR, atrial fibrillation, LA thrombus, or echocardiographic evidence of thickening (≥5 mm) or redundancy of the valve leaflets. However, long-term **anticoagulation therapy with warfarin** is recommended if any of these higher risk features are present, and in MVP patients with recurrent transient ischemic attacks while taking aspirin (international normalized ratio: 2.0 to 3.0). Aspirin is sufficient for patients with MVP and atrial fibrillation who are <65 years, have no MR, and have no history of stroke, hypertension, or heart failure.

4. Patients who experience palpitations should be advised to abstain from caffeine, alcohol, and tobacco use. **β-Blockers** are useful in the management of premature atrial or ventricular contractions and often alleviate symptoms. **Ambulatory electrocardiographic monitoring** is recommended for persistent palpitations. Ventricular tachycardia is an indication for **electrophysiologic testing** to assess the risk of sudden death and the possible need for **implantation of a defibrillator device.**

V. MITRAL STENOSIS

Although declining in incidence in the United States, rheumatic disease remains the predominant cause of MS. Other etiologic factors are listed in Table 16.5. In general, once symptoms begin to develop, there follows a period of about 10 years before they become debilitating. Once significant limiting symptoms develop, the 10-year survival rate is <15%.

A. Clinical presentation

1. Signs and symptoms

a. There is often a **long asymptomatic course**, consisting of a couple of decades.

b. When symptoms do develop, **dyspnea** is common. Predominant symptoms are exertional dyspnea initially, followed by paroxysmal nocturnal dyspnea and orthopnea, which reflect elevated pulmonary venous pressure.

c. Precipitating factors, such as exercise, emotional stress, pregnancy, infection, or atrial fibrillation with a rapid ventricular response, can produce or dramatically worsen symptoms by generating increased transvalvular gradients and LA pressure. **Atrial fibrillation with rapid ventricular response is a classic exacerbating factor** and may produce pulmonary edema, even in those with mild MS. The LA dilation is a predisposing factor for the development of atrial fibrillation.

d. Hemoptysis can occur and likely represents rupture of small bronchial veins from elevated LA pressure.

e. Hoarseness occurs when the dilated left atrium impinges on the recurrent laryngeal nerve (Ortner syndrome).

TABLE 16.5 Causes of Mitral Stenosis
Rheumatic: most common cause
Congenital
Parachute mitral valve: single papillary muscle to which chordae to both leaflets attach; results in MS or M
Supravalvular mitral ring
Systemic diseases: can cause valvular fibrosis
Carcinoid
Systemic lupus erythematosus
Rheumatoid arthritis
Mucopolysaccharidosis
Healed endocarditis
Prior anorectic drug use
Severe mitral annular calcification

f. MR, mitral regurgitation; MS, mitral stenosis.

g. LA dilation and stasis, particularly in the context of atrial fibrillation (persistent or paroxysmal), may cause thrombus formation and embolic events. **Cerebrovascular events, coronary embolization, and renal emboli and infarction** are all possible sequelae. The malformed valve is predisposed to the development of **endocarditis**.

h. Fatigue is common because of reduced cardiac output.

i. With long-standing MS and elevated pulmonary pressure, symptoms of **RV failure** may develop.

j. Patients with elevated pulmonary pressures may have **angina-like chest pain**, as a reflection of increased RV oxygen demand.

2. Physical findings

a. Inspection and palpation. Patients may have a **malar facial flush**. The jugular venous pulse can demonstrate a **prominent a-wave** if there is elevated pulmonary vascular resistance and the patient is still in sinus rhythm. **Jugular venous pressure is elevated with RV failure**. In advanced cases with low cardiac output, **peripheral cyanosis** occurs. The **carotid upstrokes are usually normal** but are of low amplitude if there is diminished cardiac output. The apex beat is not displaced and the impulse can have a tapping quality because of a palpable first heart sound. An apical diastolic **thrill** may be felt in the lateral decubitus position and has a quality that simulates a purring cat. If there is pulmonary hypertension, a **parasternal RV lift with a palpable P_2** is present.

b. Auscultation. The main auscultatory findings are shown in Figure 16.7.

1. **(1)** The **opening snap** is the most characteristic auscultatory hallmark of MS. However, as the mitral valve becomes more calcified and immobile, the opening snap may be lost (just as S_1 becomes softer).

2. **(2)** The **murmur** of MS is typically a low-pitched rumbling mid-diastolic murmur, heard best with the bell of the stethoscope with the patient in the left lateral decubitus position. Presystolic accentuation can be present whether or not the patient is in sinus rhythm (exact mechanism is unknown). Auscultation after a **brief period of exercise may accentuate the murmur** of MS as the increased output and heart rate increase the transvalvular gradient. The length of the murmur correlates better with the severity of MS than the loudness. **The longer the murmur and the shorter the time interval from S_2** to the opening snap, the more severe the MS.

FIGURE 16.7 Auscultatory findings in mitral stenosis (MS).

3. **(3)** Concomitant **conditions that result in decreased flow across the valve**, such as CHF, pulmonary hypertension, and aortic stenosis, may **reduce the diastolic murmur**. The presence of a loud S_1 may be the only clue to the presence of MS in these cases, particularly if pulmonary hypertension exists.
4. **(4)** Auscultation of the lungs may reveal fine inspiratory crackles. However, it is remarkable that some patients with severe MS have clear lung fields, possibly because of lymphatic hyperfunction clearing the transudated alveolar fluid that would be expected from the elevated LA pressure.
5. **(5)** Other **conditions that mimic** the clinical presentation of MS include LA myxoma and cor triatriatum. The tumor plop of myxoma may be mistaken for an opening snap, and tumor obstruction of the valve leads to a diastolic murmur. However, in this condition, the physical findings will vary with changes in position and from examination to examination. Other conditions in which a diastolic rumble may be present include atrial septal defect or VSD, the Austin-Flint murmur of aortic regurgitation (the murmur lessens with decreased afterload and is preceded by an S_3, and the S_1 is normal), and tricuspid stenosis (the murmur is heard at the left sternal border and typically increases with inspiration, known as Carvallo sign).

B. Etiology (Table 16.5)

1. In **rheumatic MS**, up to 50% of patients are not aware of a history of rheumatic fever. Rheumatic fever is now rare in developed nations, although it is unclear whether this is due to improvements in living conditions or a change in the virulence or immunogenicity of *Streptococcus pyogenes*.

a. In **acute** rheumatic fever, MR often predominates. Stenosis usually develops anywhere from 2 to 20 years later, and symptoms may not develop for many years thereafter. Although the incidence of rheumatic fever is roughly equal between men and women, rheumatic MS develops two to three times more frequently in women.

b. Thickening of leaflets with **fibrous obliteration** is a characteristic finding. Commissural and chordal fusion and chordal shortening contribute to the development of stenosis. Calcium deposition occurs on leaflets, chordae, and annulus, further restricting valvular function. These changes collectively produce a funnel-shaped mitral valve with a fish-mouth orifice.

2. Nonrheumatic MS causes include congenital malformation, extensive annular calcification in the elderly, radiation heart disease, and restrictive mitral valve repair for MR.

C. Pathophysiology

1. The normal area of the mitral orifice is 4 to 6 cm^2. When the valve area is <2 cm^2, a **pressure gradient between the left atrium and the left ventricle in diastole occurs**. As orifice area declines, both the transmitral pressure gradient and the LA pressure

increase, but these are also affected by the flow through the valve. **Although the transmitral pressure is a useful indicator of MS severity, it is critically affected by the cardiac output at any moment. The cross-sectional area of the mitral valve orifice is, for the most part, independent of flow considerations and thus is a more robust measure of the severity of MS.**

This is reflected in the 2014 ACC/AHA valve disease guidelines where severity of MS is determined based on the mitral valve area (MVA) and diastolic pressure half-time (P1/2, will be discussed in detail later) along with its hemodynamic effects on the LA (presence of LA enlargement) and pulmonary vasculature (presence of pulmonary hypertension). Because of the variability of the mean pressure gradient with heart rate and flow, it has not been included in the severity criteria. However, the gradient is usually >5 to 10 mm Hg in severe MS.

a. **Very severe stenosis** is defined by an **MVA ≤1.0 cm^2 with a P1/2 ≥ 220 ms**, accompanied by **severe** LA enlargement and **pulmonary hypertension** (PASP > 30 mm Hg).

b. **Severe** stenosis is defined by an **MVA ≤ 1.5 cm^2 with a P1/2 ≥ 150 ms,** also commonly accompanied by **severe** LA enlargement and **pulmonary hypertension** (PASP > 30 mm Hg).

c. **Progressive MS (mild to moderate)** is associated with an MVA **> 1.5 cm^2** and a **P1/2 < 150 ms.** There is usually **mild to moderate**LA enlargement and the pulmonary pressures are typically **normal** at rest.

The severity of the stenosis needs to be assessed also in terms of symptomatology and exercise capacity. Mixed MS/MR is often associated with greater symptomatic impairment than might be predicted from the severity of either lesion alone.

2. The **increased LA pressure is transmitted to the pulmonary vasculature**, resulting in symptoms of pulmonary congestion. The passive increase in pulmonary venous pressure may elevate pulmonary vascular resistance (reactive pulmonary hypertension). This condition is usually reversible if the stenosis is relieved. However, in long-standing, severe MS, obliterative changes in pulmonary vasculature may occur. Severe pulmonary hypertension can in turn lead to right-heart failure.

3. Up to 30% of patients have a **depressed LVEF**. This appears to result from decreased preload (decreased inflow into the left ventricle) or a rheumatic myocarditis. The former will normalize after a corrective mitral valve procedure; the latter will not.

4. In severe MS, there may be sufficiently low cardiac output to cause **symptoms of poor perfusion**. Chronically depressed cardiac output causes a reflex increase in systemic vascular resistance and increased afterload. This may further diminish LV performance.

D. Laboratory examination and diagnostic testing

1. Echocardiography has several critical roles in the evaluation of MS: initial diagnosis, determination of severity, evaluation of suitability for percutaneous balloon mitral valvuloplasty, and identification of concomitant valve lesions.

a. M-mode findings include dense echoes on the mitral valve and decreased excursion of the mitral valve. **Poor leaflet separation in diastole, anterior motion of the posterior leaflet, and decreased E–F slope on the anterior leaflet** are M-mode hallmarks of MS.

b. Two-dimensional findings include restricted motion and diastolic doming of leaflets (hockey stick sign) (Fig. 16.8). The leaflets and chordae are thickened and are often calcified in older patients.

c. Doppler echocardiography is **essential** in the assessment of stenosis severity.

1. **(1)** A **transmitral peak velocity** > 1 m/s suggests MS. However, this is not specific because tachycardia, increased inotropy, MR, and VSD may cause increased flow in the absence of MS.
2. **(2)** The **transvalvular mean gradient** (assessed by means of tracing mitral inflow) is also helpful in estimating mitral valve severity; however, it is highly dependent on flow and filling time and will vary greatly with heart rate.

d. Echocardiography is used to estimate the **MVA**.

1. **(1)** Direct planimetry of the orifice can be performed in the parasternal short-axis view.

1. **(a)** Optimal positioning is done by first obtaining a parasternal long-axis view and placing the mitral valve orifice in the center of the scan plane. The transducer is then rotated 90° to obtain the short-axis view. Measurements are obtained at the tips of the mitral leaflets.

FIGURE 16.8 Severe mitral stenosis—the parasternal long-axis view on the left shows the typical doming of the anterior mitral leaflet (with the so-called "hockey stick" appearance) with associated leaflet thickening. The parasternal short-axis view on the right shows the typical "fish-mouth" appearance with restricted mitral valve opening.

2. **(b)** Poor-quality 2D images and a thick, calcified subvalvular apparatus can make it difficult to obtain accurate measurements. Improper orientation of the scanning plane can produce oblique cuts across the valve and lead to overestimation of valve area. Scanning up and down until the typical fish-mouth appearance is seen helps in this regard. Dense fibrosis or calcification at the margins of the valve orifice can lead to underestimation of the valve area. Low-gain settings can cause dropout at the edges of the valve and overestimation of the valve area. High-gain settings can lead to underestimation. Planimetry is more difficult if commissurotomy has been performed, but remains the preferred method to assess the MVA by means of echocardiography. With the advent of **3D imaging via transthoracic echocardiography**, more accurate orifice mapping for planimetry is now possible (see below).

2. **(2)** Pressure half-time method. Impedance to LA emptying prolongs the decline in transvalvular pressure gradient. This prolongs pressure half-time (time that it takes for pressure to fall to one-half the starting value, which equates with the time for the velocity to decrease to 70% of peak velocity). The mitral inflow E-wave is used in the calculation.

1. **(a)** Empiric pressure half-time has been shown to correlate with valve area:

$$\text{Mitral valve area (in cm}^2\text{)} = 220/\text{pressure half-time}$$

2. **(b)** If a software package to perform the calculations is not available, pressure half-time can be calculated by multiplying the deceleration time by 0.29. If atrial fibrillation is present, 5 to 10 consecutive beats are obtained and averaged.
3. **(c)** It is important to have the Doppler beam parallel to the direction of blood flow.
4. **(d)** The pressure half-time method **is inaccurate if there are rapid changes in LA hemodynamics**, such as immediately after balloon valvuloplasty.

5. **(e)** Obtaining a pressure half-time may be very difficult if sinus tachycardia is present (E–A fusion). Severe aortic insufficiency also fills the left ventricle in diastole, decreases pressure half-time, and leads to overestimation of the MVA.

e. Stress echocardiography is useful in the evaluation of patients with symptoms when the **resting study is discrepant with symptoms or clinical findings** (ACC/AHA class I). Gradients can be assessed during (supine bicycle) or immediately after (treadmill) exercise. Measurement of tricuspid regurgitation velocity is used to estimate pulmonary pressures with stress.

f. **TEE** is indicated to exclude LA thrombus and assess MR prior to valvuloplasty, or if the TTE data are suboptimal (ACC/AHA class I), but is not indicated routinely if TTE data are adequate.

g. **Three-dimensional echocardiography (3DE)** can provide a 3D data set to determine the MVA. This method can avoid error in measurement related to correct alignment of the cut-plane with the level of the mitral valve tips and speeds up the time required for optimal planimetry. Using real-time 3D transesophageal technology, visualization of the mitral valve en face from the left atrium or left ventricle is possible at the time of percutaneous balloon mitral valvuloplasty. The main advantage of preoperative transesophageal 3DE is that it replicates the surgical view of the mitral valve that will be seen upon opening the left atrium.

2. Cardiac catheterization. Hemodynamic measurements obtained in a cardiac catheterization laboratory are used to **assess the severity of stenosis**. Simultaneous measurement of LV end-diastolic pressure, LA pressure (either directly or more commonly with PCWP as a surrogate), cardiac output (Fick method or thermodilution), heart rate, and diastolic filling period (seconds per beat) is required. LV pressure and PCWP (or LA pressure) tracings are made simultaneously (Fig. 16.9). A mean transmitral gradient is derived from the preceding measurements (planimeter area between the left ventricle and PCWPs during diastole; this area is multiplied by the scale factor of the tracing in millimeters of mercury per centimeter to obtain the gradient). The PCWP tracing ideally should be realigned by 50 to 70 ms to the left (with tracing paper) to account for the time delay in transmission of LA pressure to the pulmonary venous beds.

FIGURE 16.9 Simultaneous left ventricular and pulmonary capillary wedge pressure tracings used to measure mean gradient across mitral valve during diastole.

a. The **Gorlin formula:**

Gorlin derived the empirical constant of 37.7, which is the Gorlin constant (44.3) multiplied by 0.85 (the correction factor for the mitral valve).

b. A **simplified version of the Gorlin formula** proposed by Hakki et al. has been validated and provides a reasonable approximation of the valve area:

c. **Pitfalls.** PCWP cannot be used if the patient has pulmonary venous occlusive disease or cor triatriatum. The catheter must be properly wedged. In addition, **thermodilution cardiac output is less accurate** if there is severe tricuspid regurgitation or low cardiac output. **Immediately after valvuloplasty** MR or atrial septal defect, flow may lead to inaccurate estimations of mitral flow.

d. **Cardiac catheterization** is indicated in the evaluation of patients when echo-Doppler and clinical findings are discrepant or when echo findings are internally discordant or if pulmonary hypertension is disproportionate to MS severity as assessed by echo.

3. **ECG.** LA enlargement (P mitrale) is usually present when sinus rhythm persists. Signs of RV hypertrophy are seen with pulmonary hypertension. Atrial fibrillation is common and the fibrillatory waves are usually coarse.

4. **Chest radiography.** LA enlargement is apparent with a **double density** along the right-heart border. A convexity can be apparent below the PA, representing the LA appendage. Radiographic splaying of the carina with elevation of the left main bronchus and posterior displacement of the esophagus at barium swallow examination reflect LA enlargement. Kerley B lines may be present from increased pulmonary venous pressure. RV enlargement (decreased retrosternal air space on the lateral radiograph) may be present. Evidence of mitral valve calcification, or rarely LA calcification (McCallum patch), may be present.

E. **Therapy.** The **overall** management approach to the individual with MS should integrate symptomatic status, degree of stenosis, and suitability of the valve for percutaneous balloon mitral valvuloplasty.

1. **Medical therapy**

a. Patients **without symptoms** who have mild MS (valve area > 1.5 cm^2 and mean gradient < 5 mm Hg) need no specific treatment and, **in accordance with current AHA guidelines, do not require endocarditis prophylaxis**. In patients with rheumatic valve disease, guidelines for the **prevention of rheumatic fever** should be applied. Annual reevaluation is recommended, but a yearly echocardiogram is not indicated unless there is a change in clinical status.

b. Patients with only **mild symptoms of exertional dyspnea** can be treated with **diuretics** and salt restriction to lower LA pressure. **β-Blockers** blunt the chronotropic response to exercise and may improve exercise capacity. **Arterial vasodilators should be avoided**.

c. **Atrial fibrillation** can clearly exacerbate symptoms, and **cardioversion or rate control measures** are important to maintain diastolic filling time. **Embolism** is a much feared complication of MS and occurs in up to 20% of patients; risk is increased with advancing age and atrial fibrillation.

1. **(1)** Digitalis and **β-Blockers** are the preferred agents to achieve rate control.
2. **(2) Anticoagulation** with warfarin **is imperative** for patients with paroxysmal, persistent, or chronic **atrial fibrillation and MS**because they are at **high risk for thromboembolism** and this is also **indicated** in those with a history of **prior embolism or known LA thrombus** (ACC/AHA class I).
3. **(3)** Antiarrhythmic drug therapy may be used in an attempt to restore sinus rhythm, but long-term efficacy may depend on correction of the MS.

4. **(4)** Percutaneous balloon mitral valvuloplasty may be considered in asymptomatic patients with new-onset atrial fibrillation and severe MS who have a favorable valve morphology and no contraindications.

2. **Percutaneous or surgical therapy** (Table 16.6). **If more than mild symptoms** (New York Heart Association [NYHA] class II or greater) are present due to MS, the patient should be referred for surgical or percutaneous therapy. An asymptomatic patient, with severe (or very severe) MS and evidence of pulmonary hypertension at rest or with exercise, should also be referred for percutaneous therapy if the valve is suitable. Mortality increases substantially as symptoms progress. Results of natural history studies, conducted before valvotomy procedures were developed, indicate that young symptomatic patients have about 40% mortality at 10 years and almost 80% at 20 years. Elderly patients have 60% to 70% mortality at 10 years. Marked **pulmonary hypertension** (PASP > 60 mm Hg) is an indication for mechanical treatment, even in the absence of symptoms in severe (or very severe) MS. Rarely, for **patients with asymptomatic MS** who do not have pulmonary hypertension, surgical or balloon intervention may be warranted. Instances where this is indicated include **women with severe MS contemplating becoming pregnant**, those with severe MS who will need a major surgical procedure with massive fluid shifts, or those with repeated embolism despite anticoagulation. In the last instance, surgical intervention is usually indicated, and LA appendage ligation is performed simultaneously.

a. **Percutaneous balloon mitral valvuloplasty is considered the treatment of choice for symptomatic patients with severe MS who have favorable valve morphology.** The technique involves placement of a balloon-tipped catheter into the left atrium through a transseptal puncture and then across the mitral valve. The hourglass-shaped balloon (Inoue balloon) is inflated and deflated to increasingly larger diameters until the desired result is obtained.

TABLE 16.6 ACC/AHA Indications for Percutaneous Mitral Balloon Valvotomy

Class I

1. PMV is effective for symptomatic patients (NYHA functional class II, III, or IV), with moderate or se favorable for PMV in the absence of LA thrombus or moderate to severe MR

2. PMV is effective for asymptomatic patients with moderate or severe MS and valve morphology that pulmonary hypertension (PASP > 50 mm Hg at rest or > 60 mm Hg with exercise) in the absence severe MR

Class IIa

PMV is reasonable for patients with moderate or severe MS who have a nonpliable calcified valve, are and are either not candidates for surgery or at high risk for surgery

Class IIb

1. PMV may be considered for asymptomatic patients with moderate or severe MS and valve morpholo new-onset atrial fibrillation in the absence of LA thrombus or moderate to severe MR

2. PMV may be considered for symptomatic patients (NYHA functional class II, III, or IV) with MV area hemodynamically significant MS based on PASP >60 mm Hg, pulmonary artery wedge pressure of 2

TABLE 16.6 ACC/AHA Indications for Percutaneous Mitral Balloon Valvotomy

gradient >15 mm Hg during exercise

3. PMV may be considered as an alternative to surgery for patients with moderate or severe MS who h and are in NYHA class III–IV

Class III

1. PMV is not indicated for patients with mild MS

2. PMV should not be performed in patients with moderate to severe MR or LA thrombus

o. LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PMV, percutaneous mitral valvotomy.

1. **(1)** Typically, there is an increment in valve area of 1 cm^2, mainly as a result of splitting of the fused commissures. The mean valve area usually doubles with a 50% to 60% reduction in transmitral gradient.
2. **(2)** This procedure is **generally contraindicated in patients with >3+ MR** (the procedure normally increases MR by one grade) **or in whom there is an LA or appendage thrombus** (risk of procedural embolism). Severe tricuspid regurgitation (does not improve substantially) and severe pulmonary hypertension (if PA pressures do not fall, then substantial risk of right-to-left shunt across procedural atrial septal defect) are relative contraindications to the procedure.
3. **(3)** An **echocardiographic score** has been developed to help select patients who may be candidates for percutaneous valvuloplasty. There are four parts to the assessment (mobility, leaflet thickening, subvalvular thickening, and calcification) (Table 16.7). In general, extensive subvalvular disease results in a poorer outcome with valvuloplasty. Patients with extensive fluoroscopically visible mitral valve calcification also have a worse outcome after percutaneous therapy.

1. **(a)** A total echocardiographic score (adding the four components) **higher than 11** is associated with a poorer outcome and a suboptimal increase in valve area, a higher incidence of heart failure and restenosis, and higher mortality. Patients with high scores **should not undergo valvuloplasty** unless surgical treatment is impossible.

TABLE 16.7 Echo Score Assessment for Percutaneous Valvuloplasty in the Management of Mitral Steno

Mobility (grade 0–4, 0 being normal)

1. Highly mobile with only leaflet tips restricted

2. Mild leaflet restriction; base portions have normal mobility

3. Valve moves forward in diastole, mainly from base

4. No or minimal diastolic movement of valve

Subvalvular thickening (grade 0–4, 0 being normal)

1. Minimal thickening below leaflets

2. Chordal thickening up to one-third of chordal length

TABLE 16.7 Echo Score Assessment for Percutaneous Valvuloplasty in the Management of Mitral Stenc

3. Thickening extending to distal one-third of chords
4. Extensive thickening to papillary muscles
Thickening of leaflets (grade 0–4, 0 being normal)
1. Near normal (4–5 mm)
2. Marginal thickening (5–8 mm) with normal thickness of midleaflets
3. Thickening of entire leaflet (5–8 mm)
4. Extensive thickening of all leaflet tissues (>8–10 mm)
Calcification (grade 0–4, 0 being normal)
1. Single area of echo brightness
2. Scattered areas of increased brightness along leaflet margins
3. Brightness extending to the midportion of leaflets
4. Extensive brightness throughout the leaflet tissue

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3. **(b)** Echocardiographic scores of **9 to 11** represent a **gray zone** in which some patients have good results with valvuloplasty. Others have suboptimal results.
4. **(c)** Optimal results of balloon valvuloplasty are usually achieved when the echocardiographic score is **8 or less**.

4. **(4)** TEE plays a critical role during valvuloplasty. The most immediate concern is to **rule out LA and appendage thrombi**. If thrombosis is present, anticoagulation for at least 1 month is undertaken with repeat TEE to confirm resolution before valvuloplasty. TEE can also help guide balloon positioning; after each inflation, the degree of MR and the gradient can be assessed. The degree of residual MS can be estimated with planimetry of the valve orifice before and after inflation. The pressure half-time method is unreliable until 24 to 48 hours after the procedure.
5. **(5)** Echocardiography is useful in the determination of immediate **postprocedural complications** (Table 16.8). Among these is MR with an incidence estimated at 3% to 8%, depending on the series. The echocardiographic score is less predictive of the severity of postprocedural MR.
6. **(6)** The frequency of **restenosis of the valve** is variable, depending on the age of the patient and the immediate procedural increment in valve area. Data from the National Heart, Lung, and Blood Institute registry of all functional classes of patients show an 84% survival rate 4 years after treatment. Advanced age, high NYHA functional class, presence of atrial fibrillation, smaller initial MVA, higher pulmonary arterial pressure, and substantial tricuspid regurgitation are **associated with poorer long-term results**. These variables identify a population with more serious illness that

frequently necessitates intervention and should not preclude valvuloplasty. More postprocedural MR and lower postprocedural MVA are associated with poorer long-term results.

c. **Surgical treatment.** Closed **commissurotomy** was the earliest surgical approach used. This was performed through a thoracotomy (without cardiopulmonary bypass) and atriotomy with a valve dilator. This procedure is rarely used in the United States since the development of the percutaneous approach and improvements in open-heart surgery. **Open mitral valvotomy** involves direct visualization of the mitral valve (with cardiopulmonary bypass), debridement of calcium, and splitting of fused commissures and chordae.

1. **(1)** Severe subvalvular disease or valvular calcification often leads to the choice of **surgical intervention over valvuloplasty**. Coexistent disease in other valves (e.g., aortic stenosis or aortic regurgitation) that necessitates treatment also favors surgical intervention.
2. **(2)** Mitral valve replacement. Valve replacement is often required, especially when there is **extensive fibrosis and calcification or concomitant MR**.
3. **(3)** Mitral valve repair is more difficult but can be performed in selected cases with commissurotomy when there is mixed MS/MR.
4. **(4)** For patients with long-standing **atrial fibrillation**, a combined maze procedure (either surgical or using an intraoperative ablation catheter) can be performed in conjunction with the valve operation. LA appendage ligation may also be added to reduce future cardioembolic risk.

TABLE 16.8 Complications of Balloon Valvuloplasty

Mitral regurgitation
Cardiac perforation: incidence as high as 2%–4%
Embolization: incidence 2% in the National Heart, Lung, and Blood Institute registry
Residual atrial septal defect: most close within 6 months; can persist long term among as many as 10% of well tolerated

d. Comparison of balloon valvuloplasty and open commissurotomy. Studies in ideal patients for balloon valvuloplasty and commissurotomy suggest equal improvement in valve area and symptoms immediately postprocedure and in medium-term follow-up.

e. **Postprocedural follow-up care. Patients who have undergone balloon valvuloplasty or operations for MS should undergo baseline echocardiography**, preferably >72 hours after the procedure. In patients with a history of atrial fibrillation, warfarin should be restarted 2 to 3 days after the procedure. **Clinical follow-up examination** should be performed at least once a year and more often if symptoms develop. It has become common practice at many centers for patients to undergo **follow-up echocardiography on a once-a-year basis**, although no firm guidelines have been developed for this.

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CHAPTER 17

Tricuspid Valve Disease, Pulmonary Valve Disease, and Drug-Induced Valve Disease

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TRICUSPID VALVE DISEASE

I. INTRODUCTION. The **tricuspid valve (TV) apparatus** consists of three valve leaflets—septal, anterior, and posterior—along with the tricuspid annulus, the chordae tendineae, and the papillary muscles. Normally, the TV has an orifice area of 5 to 7 cm^2. The normal TV annulus is an elliptical and nonplanar structure, lying somewhat inferiorly and anterolaterally compared with the mitral valve (MV) annulus. The noncircularity and the nonplanarity of the TV have important mechanistic and therapeutic implications for correction of TV anomalies. Both tricuspid stenosis (TS) and tricuspid regurgitation (TR) can produce typical symptoms of right-sided congestive heart failure in their advanced stages. TV dysfunction can occur in both anatomically normal and abnormal valves.

II. TS. TS is rare as an isolated entity and is most commonly part of a multivalvular process. TS is usually organic in nature and is commonly encountered in conjunction with TR.

A. Etiology. Table 17.1 lists the causes of TS.

1. **Rheumatic heart disease (RHD)** by far is the most common cause of TS, accounting for >90% of cases. A large majority of patients with rheumatic TS have concurrent MV and aortic valve involvement. Rheumatic TS is characterized by thickening and fibrosis of the valve leaflets, eventually culminating in marked leaflet contracture and commissural fusion.
2. **Carcinoid heart disease** is encountered in the setting of primary intestinal carcinoid tumors with secondary metastatic spread to the liver. Once metastatic to the liver, this neuroendocrine malignancy secretes numerous vasoactive substances (e.g., serotonin, histamine, bradykinin), which directly affect the right-sided heart valves. Carcinoid valvular disease is characterized by thickened, retracted, shortened, and even fixed tricuspid leaflets, causing a mixed picture of regurgitation and stenosis. Unless there is a significant right-to-left shunt (via an atrial septal defect or patent foramen ovale), the left-sided heart valves are usually spared, owing to the clearance of vasoactive substances by the lungs.

TABLE 17.1 Causes of Tricuspid Stenosis

TABLE 17.1 Causes of Tricuspid Stenosis

Disease Entity
Congenital
Rheumatic
Infective endocarditis
Prosthetic valve failure
Carcinoid syndrome
Malignancy (e.g., myxoma and metastases)
Whipple's disease
Fabry's disease

B. Pathophysiology

1. TS produces a **diastolic pressure gradient** between the right atrium and the right ventricle, which is augmented when transvalvular flow increases—such as during inspiration. This typically occurs once the valve area falls below 1.5 cm^2.
2. A modest elevation of mean diastolic pressure gradient (i.e., ≥5 mm Hg) can raise right atrial pressure (RAP; i.e., >10 mm Hg) sufficiently to produce signs of **systemic venous congestion**, including hepatomegaly, ascites, and edema.
3. The right atrial *a wave* may be very prominent and may approach the level of the right ventricular systolic pressure (RVSP).
4. Resting cardiac output may be markedly reduced and may fail to augment with exercise, due to limited right ventricular preload.

C. Clinical presentation

1. **Signs and symptoms.** The presentation of TS varies depending on the **severity of stenosis**, the presence of **concomitant cardiac lesions**, and the **etiology of the valvular disease**.

a. **Fatigue** is common and related to low and relatively fixed cardiac output.

b. **Right upper-quadrant pain** can result from high systemic venous pressure and concomitant hepatomegaly, ascites, and abdominal distention.

c. Occasionally, patients will experience a **fluttering discomfort** in the neck, caused by the giant *a waves* transmitted to the jugular veins.

d. Severe TS may mask the typical symptoms of other coexisting valvular lesions, such as mitral stenosis (MS). In the case of MS, the flow limitation across the TV can minimize the pulmonary congestion, orthopnea, and paroxysmal nocturnal dyspnea usually associated with MS.

2. **Physical findings.** The diagnosis of TS is often missed without a high index of suspicion. Clues that should raise suspicion of TS include the presence of **elevated jugular venous pressure** and **accentuation of a diastolic murmur along the left sternal border with inspiration** (not present in MS).

a. Elevated central venous pressure may lead to marked hepatomegaly, ascites, and peripheral edema. In sinus rhythm, a giant *a* wave in the jugular venous pulse at the first heart sound (S_1) results from impaired right atrial diastolic filling during atrial systole.

b. **Diastolic murmur.** The murmur of TS is **low pitched**, **diastolic**, and best heard along the left lower sternal border in the third to fourth intercostal space or over the xiphoid process. If the rhythm is sinus, the murmur is prominent at end diastole (presystole). The low-pitched diastolic murmur may be obscured by the usually associated with MS murmur. Accentuation of the murmur **intensity with inspiration** (**Rivero-Carvallo sign)** or other preload augmenting maneuvers (e.g., leg raising and squatting) may serve to differentiate the two murmurs or at least identify a component of TS in the setting of concurrent MS.

c. An **opening snap** (OS) may be heard at the left lower sternal border.

d. Despite elevated neck veins and venous congestion, the patient may be comfortable lying flat due to the absence of pulmonary congestion. This apparent discrepancy between the severity of peripheral edema and the paucity of pulmonary congestion can help discriminate and identify TS from other valvular lesions.

e. Respiratory variation in splitting of the second heart sound (S_2) may be absent in patients with TS due to the relatively fixed diastolic filling of the right ventricle despite respiration.

D. Diagnostic testing. The hemodynamic expression of TS is a pressure gradient across the TV in diastole. A mean diastolic pressure gradient of 2 mm Hg across the TV establishes the diagnosis of TS during catheterization. Nowadays, hemodynamic diagnosis is rarely required, as the diagnosis is usually apparent on Doppler echocardiography.

1. Electrocardiogram (ECG). TS is suggested by the presence of right atrial enlargement on the ECG.

2. Two-dimensional (2D) **echocardiography.** The **echocardiogram is the most useful tool** in identifying TS. Typical findings **include reduction in the diameter of the TV orifice** and **thickening and diastolic doming of the tricuspid leaflets** (especially the anterior leaflet). Doppler interrogation of the TV will reveal increased transvalvular velocity; a mean pressure **gradient >5 mm Hg using continuous-wave (CW) Doppler** is generally diagnostic of TS. **Transesophageal echocardiogram (TEE)** is generally less useful than transthoracic echocardiogram (TTE) for assessing transvalvular gradients in TS, given that the TV is an anterior structure.

3. Three-dimensional (3D) echocardiography. Given the complex 3D structure of the TV, 3D echocardiography (transthoracic or transesophageal) may prove to be a useful adjunct to standard 2D echocardiography. Using this modality, all TV leaflets can be simultaneously imaged, potentially allowing for more accurate calculation of TV area and precise visualization of leaflet motion.

4. Given the accuracy of modern echocardiographic techniques, cardiac catheterization can often be bypassed. **Right heart catheterization can be used to confirm the diagnosis already suggested by Doppler echocardiography** and can serve as a prelude to therapeutic balloon valvuloplasty. The RAP is elevated and the *a wave* may be very tall, sometimes approaching the RVSP in magnitude. Simultaneous measurement of the right atrial and right ventricular pressures with dual catheters (or a dual-lumen catheter) enables the

calculation of the diastolic pressure gradient (Fig. 17.1). The measured gradient is highly dependent on cardiac output and heart rate. Maneuvers such as lifting the legs or administration of atropine may accentuate the gradient.

E. Therapy

1. **Medical therapy** consists of intensive sodium restriction and diuretics.
2. **Defining coexisting valvular lesions** is critical to properly managing TS. For instance, in patients with combined TS and MS, the former should not be corrected alone, as this may produce pulmonary congestion. If other valvular surgery is planned, concomitant treatment of TS should be considered if the gradient exceeds 5 mm Hg or the TV orifice area is <2.0 cm^2.

FIGURE 17.1 Tracings of simultaneous right atrial (RA) and right ventricular (RV) pressure waveforms in a patient with tricuspid stenosis.

3. **Severe stenosis requires balloon valvuloplasty or TV replacement.** The indications for surgery or balloon valvuloplasty are usually determined by the severity of concomitant mitral or aortic valve disease. Limiting symptoms due to predominant TS are considered an indication for valvuloplasty or surgery. Balloon valvuloplasty appears to be successful from both a symptomatic and a hemodynamic standpoint, but can result in significant TR, potentially necessitating valve replacement.
4. **Bioprostheses are favored** when valve replacement is necessary at the tricuspid position, as **mechanical prostheses are more prone to thrombosis** at this location.

III. TRICUSPID REGURGITATION

A. Etiology and pathophysiology. Any disease process that causes derangement of the TV apparatus (annulus, leaflets, chordae, and papillary muscles) can lead to TR. The most common cause of TR is not intrinsic valvular disease but rather dilation of the right ventricle, causing secondary (functional) TR. Table 17.2 lists the causes of TR.

1. The most commonly encountered type is the **functional or secondary TR**. Functional TR refers to the TR secondary to the left or the right heart pathology in the face of **normal TV leaflet morphology**. Functional TR is a dynamic entity that is regulated by several factors, including annular dilation, annular shape, pulmonary hypertension, ventricular dysfunction, and leaflet tethering. Severe right atrial enlargement due to long-standing atrial fibrillation may lead to annular dilation of the TV and significant TR.
2. TR with an **anatomically abnormal valve (i.e., primary TR)** may be a manifestation of congenital heart disease (e.g., Ebstein's anomaly, atrioventricular [AV] canal defects, and ventricular septal defect [VSD]). In addition, a variety of conditions such as RHD, myxomatous degeneration, carcinoid heart disease, radiation, endomyocardial fibrosis, and the hypereosinophilic syndrome may cause scarring/thickening of the TV apparatus, resulting in poor leaflet coaptation and TR.

TABLE 17.2 Causes of Tricuspid Regurgitation

Primary Causes
Rheumatic
Ebstein's anomaly

TABLE 17.2 Causes of Tricuspid Regurgitation
Carcinoid
Connective tissue disease (e.g., Marfan's syndrome)
Tricuspid valve prolapse
Trauma
—Blunt/penetrating injuries
—Iatrogenic secondary to pacemaker lead insertions, leaflet damage in setting endomyocardial biopsy
Tumors (myxoma, tumors of tricuspid valve leaflet)
Infective or marantic endocarditis
Papillary muscle dysfunction
Radiation injury
Toxic secondary to phen-phen or methysergide valvulopathy
Secondary (functional) Causes
Right ventricular dilation (dilated annulus)
Dilated right atrium (atrial fibrillation)
Pulmonary hypertension
Right ventricular dysfunction
—Global: cardiomyopathy, myocarditis, infarction
—Segmental: ischemia, infarction, fibrosis, arrhythmogenic right ventricular dysplasia

3. TR in association with **pacemaker or implantable cardioverter–defibrillator (ICD)** leads is increasingly recognized. This may occur due to injury to the tricuspid leaflets from the pacemaker leads. Removal of the leads and alternative placement sites such as coronary sinus or epicardial may reduce the TR. More commonly, if TR is severe, concomitant explanation of the pacemaker leads and TV repair is required.
4. Other iatrogenic causes of TR include recurrent endomyocardial biopsy in the setting of heart transplantation. This may lead to chordal damage or leaflet damage and may result in flail leaflet with severe TR. This occasionally may be severe enough to require corrective valve repair.

B. Clinical presentation

1. **Signs and symptoms.** The spectrum of symptoms of TR is wide and depends on its etiology and chronicity. **Isolated TR is usually well tolerated**. When TR and pulmonary hypertension coexist, cardiac output declines and patients may manifest symptoms of right heart failure. TR often coexists with MV disease; in these patients, the symptoms associated with MV disease usually predominate.

2. **Physical findings**

a. On general examination, patients with severe TR may have signs of weight loss, cachexia, and jaundice related to congestive hepatopathy and bowel edema.

b. The neck veins will show loss of the usual *x* wave and a prominent systolic wave, usually referred to as a *cv* wave, followed by a rapid *y* descent. The characteristics of the large *cv* wave in the jugular venous pulse are dependent on TR severity. With significant TR, the prominent *cv* wave has maximal height at S_2, and the rapid *y* descent is most prominent on inspiration. A venous systolic thrill and murmur in the neck may be present in severe TR. The right ventricular impulse is often hyperdynamic.

c. TR typically produces a **pansystolic murmur** at the third to fourth intercostal space along the left sternal border that increases with inspiration.

d. TR causes an increase in diastolic flow across the TV. This may be heard as an **early diastolic rumble** (short and low-pitched) along the left sternal border.

e. With **severe, long-standing TR**, there is **ventricularization of the right atrium** (the pressure gradient across the TV is minimized), and the TR **may be barely audible or absent**.

f. **Other findings.** A **right-sided third or fourth heart sound (S_3 or S_4) is often present along the left sternal border, which augments with inspiration. If pulmonary hypertension coexists, P_2** is accentuated. **Systolic pulsation** of the liver is often an associated physical finding, although this may be diminished once congestive cirrhosis develops.

C. **Diagnostic testing**

1. **Electrocardiography.** The findings are usually nonspecific. Incomplete right bundle branch block may be seen. Atrial fibrillation is commonly found in association with severe TR.

2. **Echocardiography.** The most common views used for the detection of TR are the parasternal right ventricular inflow, basal short axis, and the apical four-chamber views.

a. **Physiologic TR.** A small degree of TR is observed in about 70% of patients with structurally normal hearts, and the prevalence increases with age. Physiologic TR is usually represented by a small jet that does not extend >1 cm into the atrium.

b. **Two-dimensional echocardiography**

1. **(1)** Leaflet thickening may be seen in TR due to rheumatic or carcinoid disease. In functional TR, the leaflets usually appear normal. Tricuspid prolapse often occurs in patients with MV prolapse and may cause significant TR. In Ebstein's anomaly, the septal leaflet of the TV is displaced apically. Vegetations are evident with endocarditis, and a flail valve leaflet may be seen with iatrogenic damage (e.g., after endomyocardial biopsy) or following papillary muscle rupture with right ventricular infarction.

2. **(2)** With moderate to severe TR, a **right ventricular volume overload pattern** is seen, characterized by right ventricular enlargement, ventricular septal flattening or shift to the left in diastole, and paradoxical motion in systole. There is often associated dilation of the right atrium and inferior vena cava (IVC).

c. **Doppler analysis.** Assessment of TR involves incorporation of all of the Doppler information obtainable: size of the color jet, presence or absence of a proximal convergence zone (on the right atrial side of the valve), velocity profile, and eccentricity of the

TR jet. Eccentric, wall-hugging jets should be typically upgraded by one grade, as is done for mitral regurgitation, because these are generally not visualized fully by echocardiography.

1. **(1)** TR direction and severity are assessed with color-flow Doppler. The severity of TR is estimated in several ways, including

1. **(a) Jet area:** This measure is highly dependent on echocardiographic settings, particularly the pulse repetition frequency, and the direction and eccentricity of the jet.
2. **(b) Vena contracta width:** The narrowest portion of the jet just downstream from the valve orifice gives a rough estimate of the effective orifice area. A jet width of >0.7 cm suggests severe TR.
3. **(c)** Proximal flow convergence (see Chapter 16).
4. **(d) CW Doppler:** The signal intensity and contour of the TR jet on CW Doppler can help define TR severity. Severe TR produces a dense spectral recording along with a triangular, early peaking velocity.
5. **(e) Hepatic vein flow:** Systolic flow reversal in the IVC or hepatic veins is consistent with severe TR.

2. **(2)** The RVSP is estimated using the modified Bernoulli equation after measuring the peak TR jet velocity by CW Doppler. In the absence of pulmonic stenosis, the pulmonary artery systolic pressure (PASP) can then be estimated as PASP = RVSP + RAP.

3. **Cardiac catheterization.** In the presence of moderate to severe TR, right heart catheterization will show a dominant *v* wave in the RAP curve (Fig. 17.2), an RAP curve resembling that of the right ventricle, increased right ventricular end-diastolic pressure, and low cardiac output by thermodilution and Fick techniques.

FIGURE 17.2 Tracings of simultaneous right atrial (RA) and right ventricular (RV) pressure waveforms in a patient with tricuspid regurgitation.

D. Therapy

1. In the absence of pulmonary hypertension, mild to moderate degrees of TR can be well tolerated for many years, and surgery is not recommended. If right ventricular failure develops, **medical therapy** should be targeted at diuretic therapy and afterload reduction, as in other heart failure states.

2. **Surgical therapy.** When there is an **organic cause** of moderate to severe TR, **surgical repair or replacement** may be necessary depending on the symptoms and the degree of leaflet destruction/damage. Most commonly, surgery for TR is considered in combination with left heart valvular surgery. ACC/AHA recommends surgical repair of severe TR in the setting of multivalvular disease (class I). Several studies have demonstrated a significant improvement in the functional status among individuals undergoing concomitant TV repair with MV or AV surgery in comparison with those undergoing left heart valvular surgery alone. In addition to multivalvular disease, tricuspid annuloplasty is recommended in patients undergoing MV surgery when there is pulmonary hypertension or significant TV annular dilation (class IIb). In patients with MS and TR, a decision to repair the TV should be based on the severity of the TR, as well as the duration and severity of pulmonary hypertension (i.e., TR in the setting of long-standing pulmonary hypertension and MS is unlikely to improve with MV surgery alone). Usually tricuspid repair or annuloplasty is favored over prosthetic implantation where this is feasible. The other situations where TV repair may be considered include severe TR with deteriorating exercise capacity (ACC/AHA

class IIa) and progressive enlargement of an already dilated right ventricle (ACC/AHA class IIb).

3. Percutaneous approaches to treatment of significant TR are in evolution at present and a number of novel approaches have been described but lack substantial clinical validation as yet. These have included clip placement at the TV analogous to that at the mitral position and percutaneous implantation of a bioprosthesis. Bioprosthesis implantation in the IVC and SVC has also been attempted to reduce the systemic congestive effect of TR.

PULMONARY VALVE DISEASE

I. INTRODUCTION. The pulmonary valve is a trileaflet valve that separates the right ventricle from the pulmonary vasculature. Dysfunction of the valve can have adverse effects on the right ventricle by producing pressure and/or volume overload. A small degree of pulmonic regurgitation (PR) is a common finding in healthy adults. Acquired pulmonary valve disease is rare in comparison with other valvular disorders.

II. VALVULAR PULMONARY STENOSIS (PS)

A. Etiology

1. **Congenital.** PS is the most common pulmonary valve problem, occurring in approximately 10% to 12% of all adult patients with congenital heart disease. Valvular PS is typically an isolated abnormality, but it may occur in conjunction with VSD.

2. **RHD** can affect the pulmonary valve, although this is uncommon and usually occurs in the setting of multivalvular involvement. This can result in thickening and fusion of the valve leaflets, resulting in PS.

3. As with the TV, **carcinoid heart disease** (see Section II.A.2) can affect the pulmonary valve, causing formation of typical "carcinoid plaques." The plaques may result in constriction of the pulmonic valve ring, retraction and fusion of the cusps, and usually a combination of PS and PR.

Rarely, pseudopulmonary valve stenosis can occur as a result of **right ventricular outflow obstruction** from cardiac tumors or from an aneurysm of the sinus of Valsalva.

a. Although most cases of isolated PS are valvular, **obstruction may occur below the valve in the right ventricular outflow tract or above the valve at the junction with the main pulmonary artery**. Congenital PS is most frequently caused by a dysplastic valve and less frequently a bicuspid valve. Right ventricular hypertrophy from the pressure overload of the PS on the right ventricle may cause concomitant right ventricular outflow tract obstruction, which usually reverses following successful dilation of the valvular stenosis.

B. Clinical presentation

1. **Signs and symptoms.** Patients with isolated PS present most commonly in the fourth or fifth decade of life with signs and symptoms of right heart failure and dyspnea on exertion. Of note, many patients with moderate PS remain asymptomatic. When the stenosis is severe, patients may occasionally have retrosternal chest pain or syncope with exertion. If the foramen ovale is patent, right-to-left shunting may occur, producing cyanosis and clubbing.

2. **Physical findings**

a. PS causes a systolic crescendo–decrescendo murmur, heard best in the third and fourth intercostal spaces, with delayed peaking of the murmur in severe cases. The murmur typically increases with inspiration. A thrill may be felt in the suprasternal notch and at the left upper sternal border. S_2 is often split widely, and the degree of the splitting increases with worsening stenosis due to delay in P_2. The intensity of P_2 may be increased in mild stenosis but is usually diminished with severe stenosis. An ejection click can sometimes be heard along the left sternal border, and it may vary with respiration. As severity of PS increases, the click will move closer to S_1.

b. The right ventricular impulse may be palpated at the left sternal border and be hyperdynamic.

c. The jugular venous pressure can be normal. However, in patients with reduced right ventricular compliance, a prominent *a* wave may be seen in the venous pulse. A right-sided fourth heart sound (RV S_4) may be heard at the left lower sternal border.

d. In advanced cases, evidence of right-sided heart failure may be present.

C. Diagnostic testing

1. Electrocardiogram. In patients with moderate to severe PS, the ECG may show right-axis deviation and right ventricular hypertrophy.

2. Chest radiography may reveal **poststenotic dilation** of the main pulmonary artery and diminished pulmonary vascular markings.

3. Echocardiography is useful in diagnosing pulmonary valve stenosis and for quantifying the severity of the obstruction. The best images of the pulmonary valve are obtained from the short-axis view at the level of the base from the parasternal and subcostal windows. Transesophageal echocardiography is useful when the TTE images are suboptimal.

a. Leaflets. In adults, the leaflets can appear thickened and calcified with restricted motion. In children with congenital PS, the leaflets are noncalcified with doming of the valve.

b. Right ventricle. The right ventricle may be normal, especially in children. Right ventricular dilation and hypertrophy may be seen in adults, depending on the severity and the duration of this disease.

4. Doppler echocardiography is the preferred method for grading the severity of PS. This method of quantifying the degree of stenosis is well correlated with the direct measurement obtained during cardiac catheterization. The peak gradient is measured across the pulmonary valve by using CW Doppler with the modified Bernoulli equation. The following levels of severity have been defined in the 2014 ACC/AHA guidelines on the management of valvular heart disease:

a. Severe stenosis: a peak jet velocity of >4 m/s (peak gradient > 64 mm Hg).

b. Moderate stenosis: peak jet velocity of 3 to 4 m/s (peak gradient 36 to 64 mm Hg).

c. Mild stenosis: peak jet velocity of <3 m/s (peak gradient < 36 mm Hg).

D. Therapy

1. Mild to moderate PS generally has a good prognosis, and intervention is rarely necessary. Survival is excellent among patients with mild PS, with 94% patients alive as long as 20 years after diagnosis.

2. Patients with severe PS usually warrant a therapeutic intervention for relief of stenosis. The treatment of choice is **balloon valvuloplasty**, usually leading to a 75% decrement in the transvalvular gradient after a successful procedure. The procedure is usually successful if the valve is mobile and pliable. Prognosis and morbidity subsequent to the procedure are largely based on right ventricular function at the time of the procedure. The hypertrophic subpulmonary stenosis that may accompany valvular stenosis usually regresses after successful valvuloplasty. Valve replacement—either percutaneously (see Section **III**) or surgically—may be necessary if the valve is severely calcified or if there is severe concomitant TR.

3. The **ACC/AHA guidelines for intervention** in congenital PS are as follows:

Class I: Balloon valvuloplasty is indicated in symptomatic patients with a domed valve and peak instantaneous Doppler gradient of >50 mm Hg or >60 mm Hg in asymptomatic patients.

Class IIb: Balloon valvuloplasty may be reasonable in symptomatic patients with a dysplastic valve if the peak instantaneous Doppler gradient is >50 mm Hg or >60 mm Hg in an asymptomatic adolescent or young adult.

Class III: Balloon valvuloplasty is not indicated in symptomatic patients whose peak instantaneous gradient by Doppler is <30 mm Hg or asymptomatic patients with a peak gradient <50 and normal cardiac output.

4. **PS secondary to carcinoid syndrome has a very poor prognosis** (with a median survival of 1.6 years), and the valve often does not respond to balloon valvuloplasty. Valve replacement is often necessary.

III.VALVULAR PR

A. Etiology. PR is most commonly produced secondary to dilation of the valve ring due to pulmonary hypertension or dilation of the pulmonary artery.

1. **PR may occur secondary to rare congenital causes**, such as an absent, malformed, or fenestrated leaflet. In the setting of repaired tetralogy of Fallot, severe PR is a common and difficult problem, often contributing to progressive right ventricular dilation and dysfunction and contributing to severe arrhythmic disturbance.

2. Acquired causes of pathologic PR are much more common. **The most common acquired cause is pulmonary artery hypertension**, followed by infective endocarditis. Both carcinoid syndrome and RHD may cause PR but they are more likely to cause PS. Marfan's syndrome may cause PR secondary to dilation of the pulmonary artery. Iatrogenic PR may be caused by placement of a pulmonary artery catheter.

B. Clinical presentation

1. **Signs and symptoms.** Like TR, PR causes volume overload of the right ventricle. However, in the absence of significant pulmonary hypertension, it may be tolerated well for many years. Once symptomatic, the patients with PR present with the signs and symptoms of **right heart failure and exertional dyspnea**.

2. **Physical findings**

a. The murmur of PR is a relatively brief **low-pitched, diamond-shaped, diastolic murmur**, heard best in the third and fourth left intercostal spaces with a

widening of S_2. The murmur increases with inspiration, and **P^2 is accentuated** in the presence of pulmonary artery hypertension.

b. The **Graham Steell murmur** is a high-pitched, blowing decrescendo diastolic murmur starting immediately after P_2, which is accentuated by inspiration. This characteristic murmur occurs when PASP exceeds 70 mm Hg in the presence of PR.

c. A right ventricular S_3 and S_4 may be audible in the fourth intercostal space and will be augmented by inspiration. Depending on the severity and duration of the regurgitant valve, signs and symptoms of right heart failure may also be present on examination.

C. Diagnostic testing. The pulmonary valve is best evaluated initially with **echocardiography**, using the left ventricle short-axis view from the parasternal and subcostal windows. Minor degrees of PR are seen in 40% to 78% of normal individuals. Pathologic PR is relatively infrequent and should be diagnosed in the context of other structural abnormalities. Severe pulmonary valve regurgitation may be difficult to diagnose with Doppler as the flow disturbance is reduced because of a relatively low pressure difference from pulmonary artery to RV in this situation. MRI is the diagnostic modality of choice in this situation or if the severity of PR is in doubt. MRI allows quantitation of the PR and the impact of the regurgitation on RV size and function, important parameters in determining need for valve intervention.

1. Anatomic assessment. The right ventricular outflow tract and pulmonary valve should be interrogated for abnormalities such as leaflet hypoplasia, increased cusp number, and abnormal valve motion (i.e., doming).

2. Right ventricle. The size and function of the right ventricle can provide an indicator of the severity of PR (i.e., long-standing severe PR should be associated with right ventricular dilation and/or hypertrophy).

3. Color-flow Doppler will reveal a regurgitant jet toward the right ventricle during diastole. Jet length is determined primarily by the pressure difference between the pulmonary artery and right ventricle and, therefore, is an unreliable indicator of PR severity. The **vena contracta** is probably a better measure of PR severity.

4. CW Doppler will show a dense spectral signal and rapid equilibration of diastolic pressures in severe PR. Maintenance of the regurgitant velocity during diastole suggests that **pulmonary hypertension** is the cause of valve incompetence. Furthermore, increasing pulmonary artery pressures correlate with decreasing acceleration times of pulmonary artery flow. Pulmonary artery pressures can be obtained using Doppler flow measurements and the following equation. Pulmonary artery diastolic pressure (PADP) is only obtainable in the setting of PR:

$$\text{PADP} = 4(V_{\text{PR-E}})^2 + \text{RA}_{\text{pressure}}$$

where $V_{\text{PR-E}}$ is the end-diastolic PR velocity.

D. Therapy

1. Primary pulmonary valve regurgitation. The prognosis is very good; rarely is correction of the defect necessary, except in cases of intractable right heart failure.

2. **Secondary pulmonary valve regurgitation.** The prognosis due to endocarditis, carcinoid, or pulmonary artery hypertension is dependent on the prognosis and treatment of the primary disease. Treatment of the primary condition (e.g., repairing MV in the setting of pulmonary hypertension) often ameliorates the PR. Besides this, vasodilating therapies for pulmonary hypertension can reduce secondary PR. When a treatment is absolutely necessary, **the preferred approach is valve replacement with a bioprosthesis or a pulmonary allograft**. Percutaneous deployment of a prosthetic valve has been successfully accomplished in this setting and is another option in addition to surgery. Annulus repair is ideal in patients with coexisting left-sided valvular lesions.

3. **Percutaneous pulmonic valve intervention (PPVI).** A viable option for individuals with severe pulmonic stenosis or regurgitation from a native valve, failing pulmonic bioprosthesis, or surgical RV to pulmonary artery conduit.

a. **Methods.** Valves are implanted under general anesthesia using fluoroscopic guidance. Both venous and arterial access is required. After an initial right heart catheterization, angiograms are performed of the right ventricular outflow tract (RVOT) to obtain precise measurements of diameter and length to guide device selection. A balloon test inflation is performed before deploying the device to evaluate compliance of the RVOT. Concurrent nonselective aortogram is performed to exclude the potential for coronary artery compression. The conduit is usually prestented with a covered bare metal stent to reduce rates of PPVI stent fracture or bleeding out should a conduit rupture with high-pressure balloon inflation. The valve is then deployed via a femoral or internal jugular venous approach.

b. **Candidacy**

1. **(1)** Patients must have an adequate RVOT conduit size to allow seating of the device (no larger than 26 mm).
2. **(2)** Individuals must have adequate venous access to accommodate the introducer.

c. **Valve types.** There are two commercially available transcatheter pulmonic valves:

1. **(1) Melody:** Available in one length and can be implanted with a diameter of 18 to 22 mm
2. **(2) Sapien:** Available in two lengths and can be dilated to a diameter of 23 to 26 mm

d. **Results.** Long-term data are yet to be reported, but the procedure short and medium follow-up reveals low mortality with PPVI—outcomes for both devices seem to be similar. Both devices also show significant reductions in regurgitant fraction and stenotic gradients as well as improvement in NYHA functional class.

e. **Complications**

1. **(1) Coronary artery compression.** Occurs in 0% to 1% of all cases but is fatal thus necessitating balloon testing before device deployment
2. **(2) Conduit rupture.** Rupture requiring surgery occurs in 0.8% to 2% of cases
3. **(3) Stent fracture.** Most common complication. Occurs in 20% of cases without presenting. Prestenting cuts incidence in half. May cause embolization or restenosis.
4. **(4) Endocarditis.** Patients require prophylaxis for all dental procedures due to increased risk compared with native valves.

DRUG-INDUCED VALVE DISEASE

I. INTRODUCTION.

Most common forms of valve disease are inherited or acquired in response to a specific disease process. Over the last three decades, however, it has become clear that several pharmacologic agents may produce a cardiac valvulopathy, which mimics other etiologies of valvular disease.

II. DRUGS KNOWN TO CAUSE VALVE DISEASE

A. **Ergot** alkaloid derivatives (ergotamine and methysergide) used for migraine prophylaxis have been reported to cause valvulopathy since the early 1990s.

B. **Fenfluramine** and **dexfenfluramine**, the constituents of popular diet pills, were associated with valvular heart disease. This led to the withdrawal of a number of common diet drugs from the market.

C. More recently, valvular heart disease was reported in 24% to 28% of patients undergoing treatment of Parkinson's disease with **ergot-derived dopamine agonists (pergolide and cabergoline)**.

D. There is an increased risk of valvulopathy in individuals with heavy and frequent use of the recreational drug, **3,4-methylenedioxymethamphetamine (MDMA)**—popularly known as *ecstasy*.

III. PATHOLOGY AND PATHOGENESIS

A. Valves that are surgically removed from patients using these drugs are described as having a white, glistening appearance, with histologic evidence of a plaquelike process extending along the leaflet and encasing the chordae tendineae. These findings are **very similar to the findings seen in patients with valvular disease due to carcinoid tumors**, which also secrete vasoactive amines.

B. Subsequent research has indicated that valvulopathic drugs may act via their ability to stimulate the serotonergic receptors, particularly the 5-hydroxytryptamine (5-HT)$_{2B}$ serotonin receptor. This receptor is plentiful in normal heart valves and appears to be essential for normal cardiac development. Stimulation of the 5-HT$_{2B}$ receptor appears to cause an "overgrowth" valvulopathy.

IV. PREVALENCE.

Estimates of the prevalence of drug-induced valvular disease have varied widely. Initial studies based on case series suggested a prevalence of valve disease as high as 20% to 30% in the setting of fenfluramine exposure, but larger population-based studies suggest a much lower prevalence of around 10% to 12% (vs. 5% to 6% in control group). **Factors that appear to be associated with a greater prevalence of valvular disease include duration of treatment, use of combination agents, and shorter time from cessation of drug treatment to evaluation**. The prevalence of disease is highest in those who have been on a valvulopathic medication for **≥6 months**.

V. CLINICAL PRESENTATION.

Most commonly, patients seek advice on the basis of a history of taking ergot-derived medications or diet drugs, given the media attention associated with this condition and the legal action that has been mounted against the drug manufacturers. Patients may also present with symptoms of valve disease, such as dyspnea and fatigue. **The predominant findings on examination in patients with significant valve disease involve regurgitation of the AV, the MV, or the TV**. Although the right-sided valves are usually involved, the ergot derivatives may also affect the left-sided valves and cause valvular regurgitation. Aortic regurgitation is reported with increased frequency in those with anorexiant abuse than regurgitation at other valve locations.

VI. EVALUATION. Patients suspected of having valve lesions on examination should undergo echocardiography. The echocardiographic features simulate both rheumatic disease and carcinoid disease with **leaflet thickening and doming of the MV and thickening of the AV or the TV leaflets**. Despite the apparent restriction of motion of the leaflets, clinically significant **stenosis is rare**. Regurgitation, when present, may be of any grade or severity, although it is generally mild. However, severe regurgitation requiring surgery has been reported with diet drug induced valve disease.

VII. TREATMENT. Once drug-induced valve disease is suspected, the offending drug should be discontinued immediately. In the case of anorexiant-induced valve lesions, **mild improvement in the severity of the valvular regurgitation has been reported on medium-term follow-up after drug discontinuation**. Progression in the severity of valvular disease following drug discontinuation is relatively uncommon. Indications for the surgical intervention in drug-induced valvulopathy are similar to those of other disease processes. However, watchful waiting is a prudent approach in these patients given the potential for some reversibility of the valve lesions upon drug discontinuation. Endocarditis prophylaxis is not indicated in those with evidence of drug-induced valve disease, per the most recent ACC/AHA guidelines.

VIII. FOLLOW-UP. Patients with valve disease should be evaluated both clinically and with echocardiography initially every 6 months. In those with mild stable lesions, yearly evaluation is appropriate.

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CHAPTER 18

Prosthetic Heart Valves

Paul C. Cremer

For severe native and prosthetic valve dysfunction, valve replacement is often the treatment of choice with over 280,000 implants worldwide every year. This chapter discusses types of prosthetic valves, specific considerations for valve selection, and prosthetic valve dysfunction.

I. PROSTHETIC VALVE TYPES AND SELECTION

A. Types of prosthetic valves. Prosthetic valves are classified as mechanical or bioprosthetic (Table 18.1). Overall, 80% of replacements are with bioprosthetic valves, and 20% are with mechanical valves. For bioprosthetic valves, replacement may occur via a surgical or transcatheter approach. Each valve differs in its durability, thrombogenicity, and hemodynamic performance. Various mechanical and bioprosthetic valves are shown in Figure 18.1.

1. Bioprosthetic valves (Table 18.2)**.** These resemble native valves but have a less optimal hemodynamic performance, in part because of the reduction in flow profile by interposed stents and the sewing ring.

a. Heterografts

1. (1) Stented bioprostheses are the most frequently implanted biologic valves. The Carpentier-Edwards standard and Hancock standard are whole porcine valves, but more commonly, a composite valve is created by taking a cusp from three different pigs (e.g., St. Jude Epic, Carbomedics Synergy, or Medtronic Mosaic). Alternatively, stented bioprostheses may be made from pericardium, usually bovine. The pericardium may be sewn inside or outside the stent posts (e.g., Mitroflow, Trifecta). The durability of bioprosthetic bovine pericardial versus porcine valves is controversial, although the pericardial valves may have an advantage in younger patients.

TABLE 18.1 Types of Prosthetic Heart Valves

Biologic
Stented: pericardial or porcine bioprosthesis
Stentless: pericardial or porcine bioprosthesis, aortic homograft, pulmonary autograft (Ross procedure)
Sutureless
Transcatheter
Mechanical
Bileaflet

TABLE 18.1 Types of Prosthetic Heart Valves
Single tilting disc
Caged ball

2. **FIGURE 18.1** Photographic and radiographic appearance of different prosthetic heart valves. From left to right: Starr-Edwards caged ball, Kay-Suzuki caged disk, Björk-Shiley single tilting disk, St. Jude's bileaflet tilting disk mechanical valves, and Carpentier-Edwards xenograft. (Reprinted with permission from Garcia M. Principles of imaging. In: Topol EJ, ed. *Comprehensive Cardiovascular Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 1998:610.)

3. **(2) Stentless bioprostheses** are most often composed of porcine aorta, although some are tricomposite (e.g., Biocor, Cryolife-O'Brien), and others are made from bovine pericardium (e.g., Sorin Freedom). The porcine aorta may be long (e.g., Medtronic Freestyle) or designed for implantation under the coronary arteries (e.g., St. Jude Medical Toronto). Even though the stentless valves offer a better hemodynamic profile owing to the larger effective orifice area (EOA), convincing advantages in terms of mortality, left ventricular (LV) mass regression, and durability have not been demonstrated.

4. **(3)** Since the first-in-man **TAVR** done by Cribier in 2002, more than 200,000 patients have undergone TAVR worldwide. Currently, TAVR is the standard of care for inoperable patients and is comparable to surgical aortic valve replacement in high- and intermediate-risk patients. The technology has evolved rapidly with lower profile catheter and delivery systems, wider range of valve sizes, more precise valve positioning as well as retrievable and repositionable features, and reduced paravalvular aortic regurgitation. In the United States, the Edwards SAPIEN and Medtronic CoreValve are approved for commercial use, whereas more TAVR systems are available in Europe (Fig. 18.2).

TABLE 18.2 Surgical Biologic Valve Replacement
Stented pericardial replacement valve: Carpentier-Edwards Perimount, Carpentier-Edwards Magna, Synergy, Sorin Pericarbon MORE[a], St. Jude Biocor Pericardial, St. Jude Trifecta
Stented porcine replacement valve: AorTech Aspire, Carbomedics Synergy, Carpentier-Edwards standard standard and Hancock II, Labcor, Medtronic Mosaic[a], St. Jude Biocor, St. Jude Bioimplant, St. Jude Epic
Stentless pericardial: 3F-SAVR, Freedom Solo, Sorin Pericarbon
Stentless porcine: AorTech Aspire, Cryolife-O'Brien[a], Cryolife-Ross Stentless porcine pulmonary, E Medtronic Freestyle, Medtronic-Venpro Contegra pulmonary valve conduit, Shelhigh Skeletorized Supe pulmonic, St. Jude Medical Toronto[a], St. Jude Quattro stentless mitral
Sutureless: 3F Enable (ATS Medical), Edwards Intuity, Perceval S (Sorin), Trilogy (Arbor Surgical Technolo

[a]Withdrawn from market.

6. **FIGURE 18.2** Transcatheter aortic valve systems. **A:** Edwards Lifesciences SAPIEN 3 valve (Edwards Lifesciences, Irvine, CA); **B:** Medtronic CoreValve Evolut R (Medtronic, Minneapolis, MN); **C:** Symetis Acurate *neo* valve (Symetis, Écublens Vaud, Switzerland); **D:** JenaValve (JVT Research & Development Corporation, Irvine, CA); **E:** St. Jude Medical Portico valve (St. Jude

Medical, St. Paul, MN); **F:** Direct flow medical valve (Direct Flow Medical, Inc., Santa Rosa, CA); **G:** Medtronic Engager valve (Medtronic, Minneapolis, MN); and **H:** Boston Scientific Lotus valve (Boston Scientific, Marlborough, MA). Two TAVR systems are approved by the U.S. Food & Drug Administration (**A** and **B**). (Adapted from Vahl TP, Kodali SK, Leon MB. Transcatheter aortic valve replacement 2016. *J Am Coll Cardiol*. 2016;67:1472–1487. Copyright © 2016 American College of Cardiology Foundation. With permission.)

b. **Aortic homografts** are cryopreserved cadaveric human aortic valves. These are typically implanted stentless, with a short segment of the donor's aortic root for support. The coronary arteries require reimplantation. The hemodynamic profile of the homograft is similar to that of the native valve. Availability of homografts of different sizes can be a limiting factor.

c. **Autograft.** An autograft is a procedure in which the patient's own valve is moved from its normal anatomical position to another site. Typically, this is done with the pulmonary valve in patients with significant aortic valve disease. A pulmonary homograft is placed at the native pulmonary position. This operation is called the Ross procedure, after the surgeon who popularized it. This procedure has the advantage of placing a native valve at the hemodynamically most important position. It has been advocated for younger patients, and some reports suggest that the autograft may grow with the patient, which is advantageous in the adolescent age group. However, the initial enthusiasm with this procedure has been tempered by suboptimal outcomes in many adult patients, which can involve the autograft or the pulmonic homograft. Additionally, progressive root enlargement may occur in patients who have bicuspid aortic valves, which can also lead to autograft failure. The decision to proceed to autograft implantation in adults should be considered carefully and in consultation with a surgeon with extensive experience with this procedure.

2. **Mechanical valves** (Table 18.3)

a. **Bileaflet.** The most frequently implanted mechanical valves, bileaflet valves differ in their composition of pyrolytic carbon, the shape and opening angles of the leaflets, and the design of the pivots and sewing ring. For the aortic site, these valves also differ by implantation position, which can be intra-annular, partially supra-annular, or entirely supra-annular. In the open position, bileaflet valves have two large lateral orifices and a smaller central space. A built-in leakage volume is designed to reduce thrombus formation on disks.

TABLE 18.3 Mechanical Valve Replacement

Bileaflet mechanical valves: ATS, Carbomedics (standard, reduced cuff, Optifrom, Orbis, Top Hat), Medtronic Advantage, On-X, St. Jude medical (standard, HP, Masters, Regent)
Tilting disc: Björk-Shiley monostrut[a], Medtronic-Hall, Omnicarbon, Sorin Monoleaflet allcarbon, Ultracor
Caged ball: Starr-Edwards, Smeloff-Cutter

[a] Withdrawn from market.

c. **Single-leaflet tilting disk.** This valve (e.g., Björk-Shiley, Medtronic-Hall, and Omniscience) consists of a metallic sewing ring attached to a tilting disk made of pyrolytic carbon that rotates about an off-centered pivot axis, with a range of about 60° to 85° from the occluded to the open position. When open, the prosthesis has two orifices separated by the occluder. The major orifice is formed as the disk swings downstream to the

open position. The disk on the other side of the pivot axis swings proximally and forms the minor orifice.

d. Caged ball. The Starr-Edwards valve consists of a silicone ball within a cage attached to a metallic alloy ring. The ball is free to travel along the cage over a distance of 1 to 2 cm. Flow across the prosthesis is directed circumferentially around the ball. The hemodynamic profile is less favorable, but this valve has the longest follow-up, over 30 years in some studies.

B. Selection of valves. Table 18.4 summarizes the clinical factors that favor selection of a bioprosthetic versus a mechanical valve. The choice is largely dependent upon the age of the patient and the risks of anticoagulation therapy for a mechanical valve versus the risks of SVD and reintervention for biologic valves. Contemporary data to inform this decision are observational because there have been no randomized trials comparing biologic and mechanical valves in the past three decades. Importantly, patient preferences are emphasized, and there has been a shift toward using bioprosthetic valves in younger patients.

1. Valve repair. The feasibility of native valve repair instead of replacement should always be considered prior to surgery (Table 18.5). Currently, the greatest experience is with mitral valve repair. If feasible, mitral valve repair offers several potential advantages over replacement, including **preservation of LV function via conservation of the subvalvular apparatus, lower operative mortality, higher long-term survival rate, and freedom from anticoagulation**. Mitral valve repair may be considered for asymptomatic patients with severe primary mitral regurgitation, if there is a high chance of repair at high-volume centers.

An aortic valve with predominant regurgitation because of prolapse, but without severe stenosis or calcification, can also be repaired.

2. Bioprosthetic valves are indicated in patients with **a contraindication to chronic anticoagulation** and are preferred for older patients (**≥65 years old for the aortic position and ≥70 years old in the mitral position**) because of reasonable durability, favorable hemodynamic profile, and freedom from chronic anticoagulation. Approximately 30% of heterograft bioprostheses fail within 10 to 15 years of implantation, although the incidence of bioprosthesis failure is age-dependent (Table 18.6). Overall complication rates for aortic bioprosthetic and mechanical valves are similar at 12 years, with a higher rate of reintervention for bioprosthetic valves and a higher rate of hemorrhage with mechanical valves. The advent of newer low-profile bioprostheses and the apparent improved durability of later models have led to an increase in their use, especially in patients who wish to avoid anticoagulation. **Currently, for patients 50 to 70 years old, the choice of a bioprosthetic or mechanical valve is individualized**.

TABLE 18.4 Clinical Factors Leading to Selection of a Bioprosthetic versus a Mechanical Valve

Factors Favoring Bioprosthesis	Factors Favoring Aortic Homograft	Factors Favoring Mec
Age > 70 y	Endocarditis	Age < 50 y
Bleeding diathesis	Small aortic annulus in older patients	Combined multivalvula

TABLE 18.4 Clinical Factors Leading to Selection of a Bioprosthetic versus a Mechanical Valve

High risk of trauma	Other indications for ch
Poor compliance	Completed childbearing
Young woman considering pregnancy	High risk for reoperatio

TABLE 18.5 Characteristics Favoring Valve Repair versus Replacement

Favoring Valve Replacement	Favoring Valve Repair
Rheumatic valve disease	Mitral valve prolapse
Calcified and fibrosed valve	Excessive mitral valve leaflet mobility
Extensive leaflet destruction	Noncalcified bicuspid aortic valve with pro
Inexperienced surgeon	Aortic annular dilation with normal leaflets

3. **Transcatheter aortic valve replacement**, as mentioned, is now an option for patients with severe aortic stenosis who are either inoperable or high or intermediate risk for open heart surgery. A comprehensive evaluation for procedural eligibility and candidacy is required including coronary angiography to exclude significant coronary artery disease and computed tomography (CT) angiography to size the aortic annulus and assess suitability of iliofemoral access.

4. **Homografts.** The homograft is the **valve of choice in aortic valve endocarditis** and has the lowest valvular gradient among the bioprosthetic valves. Durability was thought to be superior to that of heterografts, but recent studies have not confirmed this finding, and only 10% are still functioning after 20 years. The primary operation is more difficult with homografts, because the coronary arteries require implantation. Reoperation is also more complex, because the homograft frequently calcifies and is difficult to remove and replace. The main indication for an aortic homograft is invasive endocarditis, especially with an aortic root abscess, where the risk of reinfection is high. Another indication is in older patients with a small aortic root and left ventricular outflow tract (LVOT), in order to maximize hemodynamics and minimize the transaortic gradient.

5. **Mechanical valves.** Mechanical valves are **more durable than bioprosthetic valves**; some can last >20 years. Mechanical prostheses are generally recommended for **patients ≤50 years** because of greater durability and for **patients already on permanent anticoagulation** for previous stroke or arrhythmia. The stroke risk of about 1% per annum for patients with a mechanical valve receiving appropriate anticoagulation management is similar to that for a bioprosthetic valve without anticoagulation. In **younger patients requiring combined aortic and mitral valve replacement**, mechanical valves may be preferred, given the more rapid rate of prosthesis deterioration in the mitral position. **Pregnancy should be discouraged in patients with mechanical prostheses** because of the high risk to the mother and the fetus. Given their lower profile, mechanical prostheses may be preferred in **patients with small ventricles**. Issues of **compliance with anticoagulation and risks of trauma** should be integrated into the selection of a mechanical valve.

TABLE 18.6 Heterograft Valve Failure Rate 10 Years after Valve Replacement Relative to the Patie

Patient's Age (y)	Failure Rate at 10 Y (%)
<40	40
40–49	30
50–59	20
60–69	15
≥70	10

6. From Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med.* 1996;335:412, by permission of the Massachusetts Medical Society. Modified with permission from Massachusetts Medical Society.

a. Bileaflet valves are the most popular mechanical prosthetic valves because of their favorable hemodynamic performance, longevity, and low rates of complications.

b. Starr-Edwards valves are older and have demonstrated durability. However, they are less popular today because of their thrombogenicity and suboptimal hemodynamic performance in comparison with tilting disk valves.

c. Manufacture of the Björk-Shiley valve was discontinued in 1986 following published reports of complications with **strut fracture**.

7. The decisions regarding valve type is a shared decision-making process that takes into account patient preferences, indications for and risks of anticoagulation, and risks of reintervention.

C. Follow-up after valve surgery. There is a **wide spectrum of clinical practice** in the follow-up of the asymptomatic patient after valve surgery. An echocardiogram should be performed between 4 and 6 weeks following surgery, after resolution of postoperative anemia, as a baseline for future reference. For **mechanical valves, anticoagulation** should be monitored regularly for life. **Endocarditis prophylaxis** is imperative for prosthetic valves, and patients should receive appropriate education. Annual or biannual echocardiography is reasonable **5 to 10 years after surgery**.

D. Anticoagulation. Table 18.7 summarizes the recommended targets for anticoagulation therapy in patients with mechanical heart valves. **Patients should receive a vitamin K antagonist, and oral direct thrombin inhibitors or anti-Xa agents should not be used**. The **embolic event rate is greater for mitral than for aortic** prostheses.

1. Immediate postoperative period

a. Mechanical valves. The approach to **postoperative anticoagulation** for mechanical prostheses varies widely. Early anticoagulation increases the risk of bleeding and tamponade. One approach is **warfarin, but not heparin, 3 to 4 days following surgery** when the epicardial wires are removed. Other centers recommend **low-dose intravenous heparin**, targeted for upper normal limits of activated partial thromboplastin time within 6 to 12 hours after valve replacement, and **full-dose intravenous heparin once the chest tubes are removed**. **Warfarin** is initiated within 24 to 48 hours following valve replacement. **Chronic anticoagulation for mechanical valves is associated with rates** of minor hemorrhage of 2% to 4% per year, major hemorrhage of 1% to 2% per year, and death of 0.2% to

0.5% per year. The bleeding risk is 5% to 6% in patients aged ≥70 years. Patient-related risk factors for thromboembolism are older age, atrial fibrillation, and LV dysfunction. All patients should also receive aspirin (75 to 100 mg daily).

b. Bioprosthetic valves. The **need for anticoagulation** in bioprosthetic valves is **controversial**. The risk of embolism is greatest in the early postoperative period, declines after 3 months, and is greater for mitral (7%) compared with aortic valves (3%). In patients with a low risk of bleeding, anticoagulation with a goal international normalized ratio (INR) of 2.5 can be considered for 3 months following bioprosthetic aortic valve replacement and up to 6 months after bioprosthetic mitral valve replacement. All patients should receive aspirin (75 to 100 mg daily). After TAVR, clopidogrel, in addition to life-long low-dose aspirin, is reasonable for 6 months. The use of anticoagulation after TAVR is evolving, given that thrombosis has been observed with four-dimensional (4D) CT, followed by resolution after warfarin therapy.

TABLE 18.7 Recommended Anticoagulation Therapy for Patients with Mechanical Prosthetic Valves

Prosthesis Type
Aortic valve, mechanical bileaflet, or current generation single tilting disk without risk factors[a]
Mechanical aortic valve, with risk factors[b]
Mechanical mitral valve

c. INR, international normalized ratio.

d. [a] In patients with a mechanical On-X aortic valve replacement and no risk factors, a lower target INR of 1.5 to 2.0 may be reasonable.

e. [b] Risk factors include atrial fibrillation, previous thromboembolism, LV dysfunction, hypercoagulable condition, or an older generation mechanical valve.

2. Management of anticoagulation in patients with prosthetic valves undergoing noncardiac surgery. Although the risk of thromboembolism increases when anticoagulant therapy is briefly discontinued, the decision to suspend therapy should be individualized.

a. For **major procedures** in which substantial blood loss is expected, **warfarin should be discontinued at least 3 days prior to the procedure** to achieve an INR of 1.6 or less. Hospital admission for **intravenous heparin administration** is often recommended for patients with **caged ball prosthetic valves, atrial fibrillation, severe LV dysfunction, or previous embolization. Postoperatively**, intravenous heparin therapy should be **resumed when it is considered safe and continued until therapeutic anticoagulation is achieved with warfarin. Low-molecular-weight heparin (LMWH) may be considered for patients with prosthetic valves as bridging therapy**.

b. For **minor procedures** (e.g., dental extraction) where blood loss is minimal, anticoagulation can be continued.

3. Pregnancy. Pregnant women have an increased incidence of thromboembolic complications. The use of warfarin through the entire course of pregnancy is

associated with warfarin embryopathy in as many as 6.4% of live births. Given its teratogenic effects, **warfarin should be discontinued during the first trimester of pregnancy, especially if the dose is greater than 5 mg daily. However, with ≤ 5 mg of daily warfarin, the risk of embryopathy is low (<3%), and after careful discussion, may be continued.** If warfarin is discontinued, **dose-adjusted LMWH** can be used during the first trimester with twice daily dosing and target anti-Xa level of 0.8 to 1.2 U/mL 4 to 6 hours after the dose. **Anti-Xa monitoring is essential because the therapeutic dose can increase by 50% during pregnancy**. Alternatively, a continuous infusion of unfractionated intravenous heparin can be used. Warfarin is used in the second and third trimesters, typically in conjunction with low-dose aspirin (75 to 100 mg). Prior to planned delivery, warfarin is discontinued, and continuous infusion of unfractionated heparin is used.

II.ASSESSMENT OF PROSTHETIC VALVES

A. Clinical presentation. The clinical presentations of prosthetic valve dysfunction can vary substantially. A discussion of the various entities is detailed in Section **III**.

1. History. This should include a thorough cardiovascular review in addition to questions pertinent to the function of the prosthesis.

a. The **indication** for placement of valve prosthesis, **position** of implantation, **type** of prosthesis, and the **year of implantation** should be elicited. The model and size of the prosthesis can be verified by the identification card provided by the manufacturer.

b. Other important questions involve **compliance with anticoagulation**, previous **endocarditis, thromboembolism, fever**, and perceived **change in the quality of the valvular click**.

2. Physical findings

a. The physical examination may be remarkable for a **new murmur, muffled prosthetic valve sounds, or evidence of embolic events**.

b. Prosthetic valves are associated with **distinct auscultatory events caused by prosthesis motion or altered flow patterns**. The prosthesis sounds may mask the normal heart sounds; significant valvular dysfunction may occur without audible changes. However, familiarity with the normal auscultatory findings in the prosthetic valve examination can provide valuable clues on prosthesis dysfunction prior to the more definitive imaging examination. Figure 18.3 summarizes the acoustic characteristics of common valve prostheses.

FIGURE 18.3 Acoustic characteristics of various mechanical and bioprosthetic valves. AC, aortic bioprosthetic closing sound; CC, closing click; DM, diastolic murmur; MC, mitral bioprosthetic closing sound; MO, mitral bioprosthetic opening sound; OC, opening click; P, pulmonary component of second heart sound; SEM, systolic ejection murmur; s1, first heart sound; S2, second heart sound. (From Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med*. 1996;335:410, with permission from the Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

B. Laboratory examination and diagnostic testing. The diagnosis of prosthetic valve dysfunction relies predominantly on echocardiographic findings, which can often identify degeneration prior to the onset of symptoms.

1. Two-dimensional echocardiography. By their design, almost all replacement valves are stenotic compared with normal native valves. The degree of stenosis

varies with the type and size of the valve. Thus, it may be difficult to differentiate mild obstruction from valve design, structural valve degeneration (SVD), or patient–prosthesis mismatch (PPM). Most mechanical valves and many biologic valves are associated with trace or mild transprosthetic regurgitation. The pattern of this "physiologic" regurgitation varies with the design of the replacement valve.

The interrogation of the prosthetic valve requires a systematic approach to the prosthetic apparatus, peak and mean gradients, and regurgitant flow. Oftentimes, **transesophageal echocardiography (TEE)** is performed to evaluate **symptomatic patients and patients with known or suspected endocarditis**. The 2D assessment of prosthetic valves is similar to that of the native valve, but is **limited by reverberation artifacts and acoustic shadowing**. In general, echocardiographic evaluation should be done to assess the following:

a. **Occluders and leaflets.** Failure of the leaflet or occluder to open or coapt properly may result from **pannus ingrowth** (see Section **III.H**), **thrombus formation** (see Section **III.E**), **or calcification of bioprosthetic leaflets**. Imaging of leaflets and occluders may be suboptimal with transthoracic echocardiography (TTE). Multiplane TEE provides higher temporal and spatial resolution of the prosthesis than TTE and allows improved assessment of leaflet mobility and abnormalities. Although the aortic prosthesis is less well visualized relative to the mitral prosthesis, TEE still provides a better visual inspection of the posterior aspect of the prosthesis and perivalvular structures than TTE. In particular, mechanical aortic valve leaflets can be difficult to assess when a mechanical mitral valve is also present.

b. **Sewing ring.** The orientation of the prosthetic valve in the annulus can be variable; however, **excessive motion** ("rocking") of the sewing ring is consistent with **dehiscence of the prosthesis**. Concomitant paravalvular regurgitation can be commonly identified with the use of color-flow mapping. Furthermore, adjacent echolucent structures identified in the evaluation of endocarditis may represent a pseudoaneurysm. In general, **flow into an adjacent echolucent space is pathologic**.

c. **Three-dimensional echocardiography.** 3D echocardiography is essential in the evaluation of prosthetic valves. Occluder motion and the sewing ring are often well evaluated, and the precise location of an abnormality relative to the sewing ring can be optimally demonstrated.

2. **Doppler evaluation.** Doppler evaluation complements the 2D examination and provides a **reliable indirect assessment of the prosthetic valve performance**. Pulsed-wave and continuous-wave Doppler are used to assess transvalvular gradients, from which EOAs can be derived.

a. **Imaging planes for TTE.** Prosthetic mitral and aortic regurgitation can be visualized in the **parasternal long- and short-axis views**. Acoustic shadowing from the aortic and mitral prosthesis can interfere with the color-flow map in the proximal portion of the aortic and mitral regurgitant jets. The apical views allow assessment of transvalvular pressure gradients but may underestimate the size of the mitral regurgitant jets because of acoustic shadowing. Pulmonary vein flows may not be available for the same reason. **Prosthetic aortic regurgitation** is also characterized from the **apical window**.

b. **Imaging planes for TEE.** On a short-axis view of the aortic valve (~40°), the origin of regurgitation (intravalvular or paravalvular) can be identified. The extent of the aortic regurgitant jet into the LV cavity can be visualized with a long-axis view (~120°). By systematically sweeping through the mitral valve from 0° to 120°, the origin and severity of

mitral regurgitation is appreciated. Continuous-wave Doppler, usually at 0° and 120°, is used to measure the peak and mean gradients across the prosthesis.

1. **(1)** Continuous-wave Doppler evaluation of the **aortic valve** is performed with a deep transgastric view using anteflexion to bring the aortic valve in line for Doppler interrogation.
2. **(2)** Continuous-wave Doppler can also be used to assess **mechanical prosthetic regurgitation**. Advantages of continuous-wave Doppler include excellent temporal resolution to allow identification of specific periods in the cardiac cycle and the ability to indicate the severity of a regurgitant jet by its signal intensity. Using 2D images and the color-flow map as a guide, continuous-wave Doppler allows interrogation of different parts of the prosthesis and can help to detect eccentric jets.

c. Normal Doppler findings

1. **(1) Prosthetic valve clicks.** The opening and closure of mechanical valve leaflets create a brief intense Doppler signal that appears as a narrow band on the spectral display.
2. **(2) Prosthetic valve velocities/pressure gradients.** The systolic spectral Doppler contour is frequently triangular, with an earlier systolic peak velocity. The expected normal velocities and pressure gradients for commonly used prosthetic valves are presented in Table 18.8. However, there is a large variability in these numbers depending on flow and other factors. Therefore, a postoperative baseline study, usually 4 to 6 weeks after surgery, is indicated for patients with prosthetic valves.
3. **(3) Physiologic prosthetic valve regurgitation.** Many prosthetic valves have regurgitant flow characterized by uniform color without aliasing. For a mechanical prosthesis, the physiologic prosthetic regurgitant flow typically has a regurgitant jet area of <2 cm^2 and jet length of <2.5 cm in the mitral position and a jet area of <1 cm^2 and jet length of <1.5 cm in the aortic position.

d. Assessment of prosthetic valve dysfunction

1. **(1) Prosthetic valve stenosis**

1. **(a) Transvalvular gradients.** Assessment of transvalvular gradients is the mainstay of the Doppler evaluation. **Each prosthetic valve is inherently stenotic and thus has a higher than normal peak velocity across it**. The continuous-wave Doppler gradient across the prosthesis obtained 4 to 6 weeks following implantation serves as a baseline for subsequent evaluations. High gradients may also be obtained in nonobstructive situations, such as high-output states, tachycardia, anemia, severe prosthetic leaks, or from the pressure recovery phenomenon. Pressure recovery occurs secondary to flow acceleration through a narrowed orifice, especially in the central orifice of a bileaflet valve in the aortic position. In this setting, the highest pressure measured through the prosthesis by Doppler overestimates the true pressure gradient by approximately one-third, and manufacturers take into account pressure recovery when determining normal gradients.

TABLE 18.8 Normal Doppler Values of Prosthetic Valves

Prosthetic Valve	Peak Velocity (m/s)	Mean Gradient (mm Hg
Aortic Position		
Starr-Edwards	3.1 ± 0.5	24 ± 4
Björk-Shiley	2.5 ± 0.6	14 ± 5
St. Jude	3.0 ± 0.8	11 ± 6

TABLE 18.8 Normal Doppler Values of Prosthetic Valves		
Medtronic-Hall	2.6 ± 0.3	12 ± 3
Aortic homograft	0.8 ± 0.4	7 ± 3
Hancock	2.4 ± 0.4	11 ± 2
Carpentier-Edwards	2.4 ± 0.5	14 ± 6
Mitral Position		
Starr-Edwards	1.8 ± 0.4	5 ± 2
Björk-Shiley	1.6 ± 0.3	5 ± 2
St. Jude	1.6 ± 0.3	5 ± 2
Medtronic-Hall	1.7 ± 0.3	3 ± 1
Hancock	1.5 ± 0.3	4 ± 2
Carpentier-Edwards	1.8 ± 0.2	7 ± 2

Modified from Nottestad SY, Zabalgoitia M. graphic recognition and quantitation of prosthetic valve dysfunction. In: Otto CM, ed. *The Practice of Clinical ography*. Philadelphia, PA: WB Saunders; 1997:803. Copyright © 1997 Elsevier. With permission.

3. **(b) Valve area calculations.** Calculation of orifice area in prosthetic valves is difficult given the complexity of the orifice (struts/disks), especially in mechanical prostheses. The following methods have been used to approximate orifice area:

1. **a. Continuity equation.** The continuity equation can be used to estimate the EOA of prosthetic aortic and mitral valves. For calculation of the prosthetic valve area in the aortic position,

$$\text{Area}_{\text{aortic prosthesis}} = (\text{LVOTd})^2 \times 0.785\ \text{TVI}_{\text{LVOT}}/\text{TVI}_{\text{aortic prosthesis}}$$

where TVI is time–velocity integral.

The aortic prosthesis TVI is determined from continuous-wave Doppler velocity through the prosthesis. LVOT TVI is determined by pulsed-wave Doppler. Mitral valve prosthesis TVI is determined from continuous-wave Doppler. For the mitral position,

$$\text{Area} = (\text{LVOT diameter})^2 \times 0.785 \times \text{TVI}_{\text{LVOT}}/\text{TVI}_{\text{mitral prosthesis}}$$

4. **(c) Pressure half-time (PHT).** For a mitral valve prosthesis, the PHT method is useful for assessing prosthetic valvular stenosis, especially in comparison to prior values obtained at similar heart rates, although it does not accurately estimate EOA. The PHT can help determine whether increased velocity is secondary to increased flow or to obstruction. If the peak velocity is increased but the PHT is not prolonged, then the increased velocity is most likely due to increased forward flow.

5. **(d) Dimensionless index. The LVOT and aortic valve prosthesis velocity ratio is the most helpful index for the evaluation of prosthetic valve stenosis**, especially in the absence of a reliable LVOT

diameter. The higher the index, the larger the EOA, and a normal aortic prosthesis has a ratio ≥0.30 to 0.35. A value ≤0.25 suggests prosthesis stenosis:

$$\text{Dimensionless index} = \text{velocity}_{\text{LVOT}}/\text{velocity}_{\text{aortic prosthesis}} \text{ OR } \text{TVI}_{\text{LVOT}}/\text{TVI}_{\text{aortic prosthesis}}$$

where TVI is time–velocity integral.

2. **(2) Pathologic prosthetic valve regurgitation.** The pathologic flow disturbance is **larger and wider than that seen with physiologic regurgitation**. Pathologic regurgitation may be related to calcified and fibrosed leaflets, disruption of the sutures securing the valve, or a perivalvular abscess with adjacent tissue destruction. Single or multiple jets may be present.

1. **(a)** Severe mitral prosthetic regurgitation is suggested by increased peak early diastolic velocity (>1.2 m/s) and normal mitral inflow PHT (≤150 m/s) (see Chapter 16).

2. **(b)** Severe aortic regurgitation is usually present when there is diastolic flow reversal in the descending thoracic or abdominal aorta (see Chapter 15).

3. **(3) Cinefluoroscopy.** Cinefluoroscopy is useful for assessing **mechanical prosthetic valves**. The image intensifier is moved to a position with x-rays parallel to the valve ring plane to determine the occluder's excursions in a caged valve. Despite the radiolucency of pyrolytic carbon disk valves, the opening angle can be measured from positioning the image intensifier parallel to the plane of the open leaflets. **The mitral prosthesis is best visualized from the right anterior oblique (RAO) cranial projections. The aortic prosthesis can be viewed from RAO caudal or left anterior oblique cranial projection.**

1. **(a)** Diminished motion of the disks suggests valve obstruction, whereas excessive rocking of the base ring suggests partial dehiscence of the valve.

4. **(4) Cardiac catheterization**

1. **(a) Invasive assessment** of the left ventricle can be performed safely in patients with bioprosthetic aortic valves. However, catheter-based evaluation of the mechanical aortic valves should be performed with a transseptal technique. Transseptal access may also be necessary for accurate measurement of prosthetic mitral valve gradients, because catheter-based assessment overestimates the mitral valve gradient because of a dampening of the pressure contour and intrinsic delay in the pulmonary capillary wedge tracing.

5. **(5) Magnetic resonance imaging** can be performed safely in patients with most prosthetic valves, because they are not ferromagnetic, but **imaging susceptibility artifacts** often preclude assessment of prosthetic valve leaflets. However, dedicated sequences can provide information about **blood flow velocities** and **regurgitant fractions**.

6. **(6) Multislice gated cardiac CT with retrospective image acquisition (4D CT)** allows adequate evaluation of prosthetic leaflet motion and abnormalities of both bioprosthetic and mechanical valves. Like cinefluoroscopy, 4D CT can be used to measure opening and closing angles of mechanical valves. In addition, 4D CT can assess bioprosthetic leaflet thickening, thrombosis, and calcification. Unlike echocardiography, 4D CT displays only a single heart cycle.

III. VALVE DYSFUNCTION AND COMPLICATIONS RELATED TO PROSTHETIC VALVES

A. Atrial fibrillation. Up to 50% of patients undergoing valve surgery experience postoperative atrial fibrillation. Management of atrial fibrillation is discussed elsewhere.

1. In **patients without a previous history** of atrial fibrillation, the **arrhythmia is often self-limited**.

2. For patients with **persistent atrial fibrillation beyond 24 hours, anticoagulation, direct current cardioversion, and a short course of antiarrhythmic therapy** can be considered.

B. Conduction disturbances. High-grade heart block requiring permanent pacemaker implantation has been described in 2% to 3% of patients after valve replacement and 8% following repeat valve surgery. It is caused by trauma to the bundle of His or from postoperative edema of the periannular tissue. Aortic or mitral annular calcification, preoperative conduction disturbance, advanced age, and infectious endocarditis are associated with higher rates of postoperative conduction abnormalities, leading to permanent pacemaker implantation.

C. Endocarditis. Approximately 3% to 6% of patients with prosthetic heart valves will experience prosthetic valve endocarditis.

1. Early prosthetic valve endocarditis (<60 days following implantation) is typically caused by *Staphylococcus epidermidis*.
2. Late prosthetic valve endocarditis has a microbiology similar to community-acquired native valve endocarditis.
3. **TEE is the imaging modality** of choice, with sensitivity of 95% and specificity of 90% in diagnosis. TEE is also useful in detecting invasive complications such as abscess, valve dehiscence, and fistula formation.
4. **Medical therapy.** Medical cure for prosthetic valve endocarditis caused by **staphylococci, gram-negative organisms, or fungi is rare. Streptococcal** prosthetic valve endocarditis responds to medical therapy alone in **50% of cases**. A high index of suspicion should be maintained for the presence of residual infection, and surgical reevaluation should be considered if medical treatment fails.
5. **Surgical therapy.** Valve replacement surgery is indicated in the setting of

a. Persistent bacteremia despite intravenous antibiotics
b. Tissue invasion or fistula formation
c. Recurrent embolization
d. Fungal infection
e. Prosthesis dehiscence or obstruction
f. New or worsening heart block
g. **New-onset or worsening** congestive heart failure

D. Hemolysis. Subclinical hemolysis is present in many patients with mechanical valves but **rarely results in significant anemia**.

1. **Pathophysiology and etiology.** Clinical hemolysis occurs in 6% to 15% of patients with **caged ball valves** but is uncommon with normal bioprosthetic or tilting disk valves. Clinical hemolysis is also associated with **multiple prosthetic valves, small prostheses, periprosthetic leaks, and prosthetic valve endocarditis**. Mechanisms involved in the generation of hemolysis include high shear stress or turbulence across the prosthesis, interaction with foreign surfaces such as cloth, and rapid deceleration of erythrocytes following collision with adjoining structures (e.g., struts or cardiac walls).
2. **Laboratory examination and diagnostic testing**

a. Diagnosis is made by **elevated lactate dehydrogenase, reticulocyte count, unconjugated bilirubin, urinary haptoglobin**, and presence of **schistocytes on blood smear**.

b. Echocardiographic findings consistent with mechanical hemolysis include **abnormal rocking of the prosthesis or regurgitant jets of high shear stress** (e.g., eccentric or periprosthetic regurgitant jets or those impacting a solid surface such as the left atrial appendage or sewing ring).

3. Therapy

a. Medical therapy. Mild hemolytic anemia can be managed with **iron, folic acid supplement, and if needed, blood transfusion.** β-Blockade and blood pressure control may reduce the severity of hemolysis. Paradoxically, treatment of the anemia may reduce the degree of hemolysis by limiting the need for high flow through the defective valve.

b. Surgical therapy. Repair of perivalvular leaks or valve replacement is indicated in **patients with severe hemolysis requiring repeated transfusions or in those with congestive heart failure**. Percutaneous approaches can also be considered, but are not feasible with extensive dehiscence or when there is active infection.

E. Thrombosis. Mechanisms of prosthetic valve dysfunction are highlighted in Figure 18.4. For thrombosis, the annual incidence of mechanical prosthetic valves is 0.2% to 1.8%. The incidence is highest in the tricuspid position, followed by the mitral and then the aortic position. Thrombus is suspected in patients with an **acute onset of symptoms, an embolic event, or inadequate anticoagulation**. Thrombosis at bioprostheses is uncommon, but may also occur.

1. Laboratory examination and diagnostic testing. TEE is the most widely employed diagnostic technique, although 4D CT is also useful. 4D CT or cinefluoroscopy can also be used to document restriction in occluder mobility. Echocardiographic features suggestive of thrombus include an irregular and mobile mass.

2. Therapy

a. Priority of therapy

1. **(1)** Heparin is typically initiated early in the course of evaluation.
2. **(2)** Warfarin is continued unless surgery is planned.
3. **(3)** TTE, TEE, 4D CT, or cinefluoroscopy can be performed as needed.

b. Medical therapy

1. **(1)** Fibrinolytic therapy is considered the treatment of choice for **right-sided prosthetic valve thrombosis** because the consequences of distal embolization are less severe than in left-sided prosthesis. Fibrinolytic therapy has an initial success rate of 82%, overall thromboembolism rate of 12%, and a 5% incidence of major bleeding episodes. For left-sided valves, there is a similarly high success rate (82%) with fibrinolytic therapy; however, the associated risks of death (10%) or systemic embolism (12.5%) are high. Thrombolysis should be considered for left-sided valves in patients with contraindications to surgery. Thrombolysis may be a reasonable alternative to surgery for mitral or aortic prosthetic valve thrombosis in patients with a small thrombus burden.

1. **(a)** The classical regimen for **streptokinase** is a 500,000 IU bolus given over 20 minutes, followed by an infusion of 1.5 million IU infused over 10 hours.
2. **(b) The regimen for rtPA (recombinant tissue plasminogen activator) is 10 mg bolus followed by 90 mg an hour for 9 hours**

FIGURE 18.4 Modes of prosthetic valve dysfunction. **A:** Layering thrombi on the nonflow side of stented bioprosthesis; **B:** A ring of pannus on the flow side (subvalvular) of a stented

bioprosthesis; **C:** Nodular cuspal calcifications of a stented bioprosthesis; **D:** Leaflet teat of a stented bioprosthesis; **E:** Thrombosed bileaflet mechanical valve; **F:** Subvalvular pannus ingrowth of a bileaflet mechanical valve. (Photos courtesy of Gosta B. Pettersson.)

3. **(c)** The use of **slow infusion low dose fibrinolytic regimens** have been reported in mechanical valve prosthetic thrombosis in pregnancy where 25 mg TPA without bolus was given over 6 hours and repeated after 24 hours as needed. This has been associated with low embolic and bleeding rates and successful thrombolysis in >90%and is endorsed for consideration in the 2017 ACC/AHA Valve Guidelines update.

4. **(d)** Thrombolysis should be stopped if there is no hemodynamic improvement after 24 to 72 hours. TEE is useful in the assessment of progress.

5. **(e)** Following successful thrombolysis, close **follow-up of anticoagulation along with serial Doppler echocardiography** is recommended.

2. **(2)** Anticoagulation with heparin and warfarin is generally recommended for a **small thrombus** (≤5 mm). The regimen consists of intravenous heparin followed by warfarin.

c. **Surgical approach.** The lowest surgical mortality reported has been approximately 5%. The risk profile of the individual patient must be balanced against the expertise and experience at each center.

1. **(1)** Valve replacement and debridement are generally performed for **left-sided prosthetic valve thrombosis**, unless the thrombus is small or the patient has a prohibitive surgical risk.

2. **(2)** Surgery is also indicated in the case of **unsuccessful thrombolysis** 24 hours following discontinuation of the infusion.

F. **Dehiscence.** Detachment of the sewing ring from the annulus may occur in the early postoperative period because of poor surgical techniques, excessive annular calcification, chronic steroid use, fragility of the annular tissue (particularly following prior valve operations), or infection. Late dehiscence occurs mainly from infectious endocarditis. **Abnormal rocking of the prosthesis** on echocardiography is an **indication for urgent surgery**.

G. **Patient Prosthesis Mismatch (PPM).** All prosthetic valves, with the exception of stentless aortic homografts, have effective orifices that are smaller than those of native valves. There is an **inherent pressure gradient and relative stenosis with each prosthesis**. Occasionally, when an inappropriately small prosthesis is placed, the **low EOA may cause symptoms**. PPM should be considered moderate if indexed valve EOA is >0.65 cm^2/m^2 but ≤0.85 cm^2/m^2, or severe if <0.65 cm^2/m^2. The impact and prevalence of PPM are controversial. Depending on the definition and surgical series used, this mismatch may occur between 20% and 70% of cases after aortic valve replacement. It has been shown in some series to be associated with worse hemodynamic function, less regression of LV hypertrophy, more cardiac events, and lower survival. Unlike most of the other risk factors, PPM can be avoided or its severity lessened by putting in place a prevention strategy at the time of the operation. **It is rare that PPM occurs to a degree that surgical explantation is necessary**.

Some important points to consider:

1. The projected indexed EOA should be systematically calculated at the time of the operation to estimate the risk of PPM.

2. In a patient with a **small annulus, a hemodynamically favorable prosthesis** like a stentless bioprosthesis, aortic homograft, or a tilting disk valve is preferred.

Alternatively, the aortic annulus may be enlarged surgically in order to accommodate a prosthesis of acceptable size.

3. Aortic prostheses <21 mm in diameter are not recommended for a large or physically active patient.

4. Young patients in particular, as well as those with poor LV function and/or severe LV hypertrophy, are more vulnerable to PPM.

H. Pannus formation. Valve obstruction occurs in up to 5% of mechanical valves per year. Valve thrombosis and pannus formation are responsible for the majority of mechanical prosthesis obstructions. Frequently, thrombus coexists with pannus. **Little is known about the causes** of fibroblastic proliferation in pannus formation. Foreign body reactions to the prosthesis, inadequate anticoagulation, and endocarditis have been implicated as potential causes. Pannus formation begins around the annulus of the valve and is more common in aortic than at mitral valve prostheses. A subacute presentation of fatigue or dyspnea in a patient who is well anticoagulated can suggest pannus formation. **TEE and/or 4D CT are/is generally required** to identify the cause of prosthetic valve obstruction, although pannus is difficult to image.

I. Embolic stroke. Following an embolic stroke, the risk of recurrent stroke is approximately 1% per day for the first 2 weeks.

1. If no evidence of hemorrhage is detected on CT scan at 24 to 48 hours, **intravenous heparin** may be administered after a small to moderate embolic stroke. **Maintaining anticoagulation** reduces the risk of recurrent stroke to one-third but **carries an increased risk of hemorrhagic transformation** of 8% to 24%, particularly during the first 48 hours.

2. In patients with **larger infarcts, anticoagulation is generally withheld for 5 to 7 days**.

3. Anticoagulation is withheld for 1 to 2 weeks in the setting of **hemorrhagic transformation** based on recommendations from neurosurgical and neurology consultants.

4. **Reoperation with placement of a tissue valve** may be needed for recurrent embolization.

J. Mechanical failure

1. **SVD** is defined as deterioration in bioprosthetic leaflets or supporting structures, not related to thrombus or endocarditis, which eventually results in hemodynamic dysfunction. As valves age, bioprosthetic SVD is expected and may manifest as stenosis, regurgitation, or both. SVD is usually gradual and due to the deposition of calcium on the leaflets. However, leaflet tears may produce a sudden clinical deterioration with the onset of severe regurgitation. Indications for reintervention are similar to those for native valve lesions, although repeat intervention is reasonable in asymptomatic patients with severe regurgitation given that further dysfunction could result in rapid clinical deterioration.

2. Failure of the current generation of **mechanical prostheses** is rare but may precipitate sudden hemodynamic compromise. Catastrophic failure occurs when a strut holding the occluder breaks, allowing the occluder to embolize, resulting in overwhelming regurgitation. Strut failure has been reported most commonly with the Björk-Shiley valve and results from fatigue of a metal weld.

3. In older ball-in-cage prostheses, ball **variance**, a structural deterioration of the occluder, can occur, giving rise to impaired occluder motion, sticking, and thromboembolism. This is rarely seen nowadays with improved prosthetic materials.

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CHAPTER 19

Infective Endocarditis

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I. INTRODUCTION

A. Infective endocarditis (IE) is **an infection of the cardiac endothelium**, macroscopically seen as vegetations. Despite modern medical and surgical therapy, IE is a serious and life-threatening condition. Mortality rates are 20% to 30% for both native and prosthetic valve endocarditis (PVE) and may be as high as 70% in certain high-risk patients. The clinical diagnosis is based on multiple elements, and **IE is best managed via multidisciplinary collaboration among cardiologists, cardiothoracic surgeons, and infectious disease specialists**.

B. The incidence of IE has remained constant over the last 30 years, accounting for 1 case per 1,000 hospital admissions. An estimated 10,000 to 15,000 new cases of IE are diagnosed each year in the United States, and the incidence has increased in the elderly and in illicit injection drug users. There has also been an increase in the number of acute cases, prosthetic valve infections, and cases because of gram-negative, rickettsial, chlamydial, fungal, and fastidious organisms.

C. Risk factors associated with infection include underlying cardiac structural abnormalities, intravenous (IV) drug use, immunosuppression, prolonged surgery, reoperation, catheter-related bacteremia, and sternal wound infection.

II. CLINICAL PRESENTATION

A. **Signs and symptoms.** The clinical manifestations of IE are highly variable, ranging from subtle symptoms to severe valvular regurgitation and cardiogenic shock. **Acute IE** presents as marked toxicity and progresses to valvular destruction and metastatic infection over several days to weeks. **Subacute IE** evolves over several weeks to months with mild or modest toxicity and rarely causes metastatic infection. The rate of progression depends upon the virulence of the causative organism, the age and underlying health of the patient, and the nature and extent of the underlying valvular disease.

1. The **hallmarks of IE are fever and a new murmur** (>85%); however, fever may be absent in patients who are elderly, uremic, or immunosuppressed. Murmurs may be absent with right-sided or mural infection or intracardiac device infections.

2. The patient often has nonspecific symptoms of fatigue, weight loss, malaise, chills, night sweats, and/or musculoskeletal aches.

B. **Physical findings.** A new murmur remains an important finding.

1. Congestive heart failure (CHF) occurs in up to 55% of cases and tends to be more common in those with aortic valve disease (75%) than in those with mitral (50%) or tricuspid (20%) valve involvement.
2. Neurologic findings may include stroke due to emboli (20%), encephalopathy (10%), mycotic aneurysm leak (<5%), meningitis, or brain abscess (<5%).
3. Additional physical findings reflecting **embolic or immune complex phenomena** include mucosal **petechiae** (20% to 40%), **splinter hemorrhages** (subungual dark linear streaks: 10% to 30%), **Osler's nodes** (painful, tender erythematous nodules on the pads of fingers or toes: 10% to 25%), **Janeway lesions** (erythematous, macular, nontender lesions on the fingers, palms, or soles: <5%), **clubbing** (10% to 20%), **arterial embolism** (peripherally or centrally), **splenomegaly** (30% to 50%), and **Roth's spots** (retinal hemorrhages: <5%). These classic physical findings are **neither sensitive nor specific** for the diagnosis of IE, and their frequency is continuing to diminish because of a decrease in *Streptococcus* viridans IE and an increase in *Staphylococcus aureus* IE.
4. A formal **fundoscopic examination** should be routine in all patients with suspected or documented IE. It may reveal **chorioretinitis or endophthalmitis**.
5. **Systemic** embolization occurs in 25% to 50% of cases of IE and may mimic acute coronary syndrome (coronary artery emboli), peritonitis (embolization to the spleen, kidney, or bowel), acute stroke (cerebral emboli), and pulmonary embolism (from right-sided IE) or cause a cold extremity with reduced or absent pulse. Septic emboli also cause Janeway lesions.

III. ETIOLOGY.

Table 19.1 presents the various etiologic factors.

A. Seventy percent to 75% of patients with IE have preexisting cardiac abnormalities. Mitral valve prolapse with regurgitation is the leading condition underlying IE in adults. Rheumatic heart disease as a substrate for IE is decreasing, with congenital heart disease underlying 10% to 20% of IE cases.

B. The source of infection can only be identified occasionally (e.g., dental procedures, an infected vascular catheter, or an infected skin lesion). In many patients, there is no history of an antecedent localized infection.

C. Native valve endocarditis

1. The most common microorganisms that cause native valve IE in adults are streptococcal and staphylococcal organisms (80%). Other important causes include *Streptococcus bovis, Enterococcus*, and the HACEK (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella*, and *Kingella*) group organisms. The HACEK group, accounting for roughly 3% of cases, includes fastidious gram-negative organisms that are normal flora in the upper respiratory tract. *S. bovis* IE is often associated with colonic polyps and colon cancer; as such, a colonoscopy is recommended for these patients.
2. IE in injection drug users is on the rise because of the epidemic of opioid abuse. It is most commonly because of *S. aureus* (60%), with a predilection for normal as well as abnormal cardiac valves. The valve most commonly affected in injection drug users is the tricuspid valve (60% to 70% of cases), followed by the mitral (30% to 40%) and the aortic valves (5% to 10%). More than one valve is involved in 20% of these patients. Despite the virulence of this organism, the disease tends to be **less severe** (mortality rates of 2% to 6%) than with left-sided IE. Septic pulmonary emboli occur in up to 75% of injection drug users with tricuspid IE.

TABLE 19.1 Frequency of Organisms Causing Infective Endocarditis

Organism	NVE (%)	IDU (%)	Early PVE (%)
Streptococci	60	15–25	5
Viridans *Streptococcus*	30–40	5–10	<5
Streptococcus bovis	10	<5	<5
Enterococci	10	10	<5
Staphylococci	25	50	50
Coagulase positive	23	50	20
Coagulase negative	<5	<5	30
Gram-negative (aerobes)	<5	5	20
Fungi	<5	<5	10
Culture negative	5–10	<5	<5

3. IDU, intravenous drug use; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.
4. Adapted from Fuster V, Harrington RA, Jagat N, eds. *Hurst's the Heart*. 14th ed. New York, NY: McGraw Hill; 2017.

5. *Enterococcal* IE is increasing in prevalence. The diagnosis must be considered in patients who have undergone recent genitourinary or obstetric procedures; these patients may not have underlying heart disease.

6. Other members of the Enterobacteriaceae (*Escherichia coli, Salmonella, Klebsiella, Enterobacter, Proteus, Serratia, Citrobacter, Shigella*, and *Yersinia*) are occasionally implicated in IE.

7. *Streptococcus pneumoniae* accounts for 1% to 3% of native valve IE, and it may present as part of the **"Osler triad,"** which also includes pneumococcal pneumonia and meningitis. Alcoholics are typically affected, and the mortality rate is high (30% to 50%).

8. The most common congenital heart anomalies predisposing to IE are bicuspid aortic valve, patent ductus arteriosus, ventricular septal defect, coarctation of the aorta, and tetralogy of Fallot. There is **no evidence** that secundum atrial septal defects increase the risk of IE.

9. *Staphylococcus lugdunensis* is a rare but destructive cause of IE. This organism is a coagulase-negative *Staphylococcus*; however, it differs from other coagulase-negative staphylococci in its aggressive nature and predilection for native valves. *S. lugdunensis* IE portends a high complication and mortality rate without surgical intervention.

D. **PVE** accounts for about 10% to 20% of all cases of IE. The greatest risk of infection is in the first 6 months after valve implantation and appears to be **similar in mechanical and bioprosthetic valves**. Recent studies have suggested that infection occurs with similar frequencies at the mitral and aortic positions.

1. PVE occurring within 2 months of surgery (early PVE) is commonly associated with intraoperative contamination and nosocomial infection and this usually implicates **coagulase-negative staphylococci** (30% of cases). The second most common pathogen in early PVE is *S. aureus* (20% of cases).
2. The microbiology of PVE with an onset of more than 2 months after surgery (late PVE) reflects the pathogens of native valve IE and is most commonly caused by streptococcal species, *S. aureus*, and *Enterococcus*. Coagulase-negative staphylococci cause <20% of infections in this period. Fungi account for 10% to 15% of late PVE cases and are associated with a higher mortality rate. Establishing the diagnosis of fungal PVE can be difficult because of the low yield from blood cultures. Despite aggressive antifungal therapy, these patients remain at risk for the development of PVE months or years later. *Corynebacterium* species and other coryneform bacteria, often called diphtheroids, are also an important cause of PVE during the first year after surgery (5%). Although they are often blood culture contaminants, diphtheroids in multiple cultures should not be ignored.
3. Increasingly prosthetic infections are being recognized as having a **biofilm** around them that insulates them from antibiotics within the bloodstream. Disruption of the biofilm mechanically by surgery is seen as necessary to eradicate the infection.
4. There have been reports of a mycobacterium (***M. chimaera***) causing endocarditis after open heart procedures and especially after prosthetic valve implantation. The offending organism appears to live in the heat control systems of the cardiopulmonary bypass circuit. *M. chimaera* requires molecular fingerprinting for detection.

E. **Pacemaker/defibrillator endocarditis** is increasing in frequency in clinical practice with the burgeoning number of devices being implanted. The incidence of endocarditis following device therapy ranges from 0.2% to 7%. The infection may involve the generator or defibrillator pocket, the electrodes, and valvular or nonvalvular endocardium.

1. Pacemaker/defibrillator endocarditis occurring within 1 to 2 months of surgery is likely caused by direct intraoperative microbial seeding. Late infection in the pocket produces a thinning of the overlying tissue and ultimately device erosion. The infection may eventually involve the electrodes and ultimately the endocardium. Hematogenous dissemination from distant sites of infection appears to be relatively rare, with the exception of *S. aureus* bacteremia.
2. The majority of infections in PVE are caused by staphylococci: *S. aureus* and coagulase-negative staphylococci. More than 90% of early infections are caused by coagulase-negative staphylococci, whereas late infections are caused by both *S. aureus* (50%) and coagulase-negative staphylococci (50%). Infection by gram-negative bacilli, enterococci, or fungi is rare.
3. Several studies demonstrated an increase in risk of in-hospital death and overall mortality in patients with device-related endocarditis. Mortality improves in device-related IE when treated with device removal and appropriate antibiotics but remains significantly higher than that of age-matched controls with similar comorbidities.

F. The incidence of **culture-negative endocarditis** may be as high as 10%. Blood culture–negative endocarditis is defined as endocarditis without positive cultures after inoculation of three blood samples. Cultures can be negative in IE when there is infection with a fastidious bacteria or fungus, the microbiological techniques are inadequate, or there

had been administration of antibiotic therapy prior to obtaining blood cultures. The latter reason is the most common cause of culture-negative IE, and the most common causative agents are *Streptococcus*or fastidious organisms such as fungi, HACEK organisms, anaerobes, *Legionella, Chlamydia psittaci, Coxiella, Brucella, Bartonella, Tropheryma whipplei*, and nutritionally deficient streptococci. *Bartonella henselae* infection is a rare cause of subacute IE, which is associated with exposure to cats. *Coxiella burnetii* causes Q fever and often infects previously damaged valves or prosthetic valves. *T. whipplei* is the cause of Whipple's disease, and this organism can be identified using periodic acid-Schiff staining of macrophages or polymerase chain reaction (PCR). **Nonbacterial endocarditis** (Libman–Sacks, marantic, and antiphospholipid syndrome) should also be considered in cases of culture-negative IE.

G. **Fungal endocarditis** (*Candida* and *Aspergillus*) usually occurs in association with **prosthetic valves, indwelling intravascular hardware, immunosuppression, or injection drug use. The most common cause is** Candida **species, but other causes include *Histoplasma* and *Aspergillus*. Fungal IE usually presents with large vegetations that extend into the perivalvular apparatus and embolize into large vessels and therefore requires surgical intervention.**

IV.PATHOPHYSIOLOGY.

The first step in the pathogenesis of vegetation is the formation of a **nonbacterial thrombotic endocarditis (NBTE)**, which usually results from endothelial injury followed by focal adherence of platelets and fibrin. Microorganisms circulating in the bloodstream in turn infect this sterile platelet–fibrin nidus.

A. **Vegetations classically occur along the line of closure of the valve leaflet.** The endothelium may be injured by regurgitant jets, leading to vegetation formation on the atrial surface of incompetent atrioventricular valves or the ventricular surface of incompetent semilunar valves. The foreign body, such as an intracardiac device, is not endothelialized initially and acts as a formation site for platelet–fibrin thrombi.

B. Bacteremia is the event that converts NBTE to IE when host defenses fail. The foreign material also impairs host defenses, rendering them more difficult to treat.

C. Vegetations often further impair valvular coaptation or cause perforation or chordal rupture, leading to worsening of regurgitation and CHF. Furthermore, the vegetations may dislodge, causing peripheral septic–nonseptic embolization.

D. The infection may extend to the surrounding structures, such as the valve ring, the cardiac conduction system, the adjacent myocardium, or the mitral–aortic intravalvular fibrosa. Consequently, conduction defects, abscesses, diverticula, aneurysms, or fistula may develop. Infections involving prosthetic valves commonly invade paravalvular tissue, resulting in abscess formation or valve dehiscence.

V.LABORATORY EXAMINATION

A. **Blood tests**

1. Laboratory findings often reflect nonspecific acute inflammatory response, manifest as a **modest leukocytosis**, a **normochromic normocytic anemia**, and a slightly increased or decreased **platelet count**. Other laboratory abnormalities may include an **elevated erythrocyte sedimentation rate**, C-reactive protein, rheumatoid factor, and/or a hypergammaglobulinemia. IE may also cause false-positive Venereal Disease Research Laboratory test and Lyme serologic test.

2. Decreased complement and an elevated blood urea nitrogen or creatinine may implicate renal dysfunction from an immune complex glomerulonephritis or drug toxicity.

3. Blood cultures are critical in the diagnosis and management of IE. However, if a patient is acutely ill, **therapy should not be delayed for more than 2 to 3 hours**, as a fulminant infection may be rapidly fatal. In recent reports, cultures were negative in 2% to 7% of cases with established IE, despite the best modern methods.

a. If the clinical condition allows, three sets of cultures should be drawn at three different venipuncture sites before empiric antimicrobial therapy is started. The first and last set should be drawn at least an hour apart if possible. Fungal cultures should be included when fungal infection is suspected, such as in immunocompromised hosts.

b. Intravascular infection leads to constant bacteremia originating from vegetations. Therefore, **it is unnecessary to await the arrival of a fever spike or chills to obtain blood cultures**.

c. The laboratory should be alerted if a **culture-negative IE or a fastidious infectious agent** is suspected, as it may be necessary to enhance the culture medium or prolong the incubation period. For example, the HACEK group (see Section **III.C.1**) needs prolonged incubation of up to 21 days. Serology for *Brucella, Legionella, Coxiella*, or *Psittacosis* may be revealing. Fastidious organisms can also be identified using PCR in valvular specimens. This technique does not require a culture medium; however, it does require excised valvular tissue. PCR has been shown to have a sensitivity of 41% and a specificity of 100% in recent studies, and thus it may provide important information about the causes of IE that could not be identified by culture.

d. Special attention should be paid to cultures positive for coagulase-negative staphylococci—in particular *S. lugdunensis*. Unlike other coagulase-negative staphylococci it often affects native valves, is destructive, frequently causes abscesses, and is associated with high mortality without surgical intervention. Thus, in the setting of high suspicion for IE, cultures positive for coagulase-negative staphylococci should not be disregarded as a contaminant and should be further speciated.

B. Histologic evaluation. Histopathology of resected valvular tissues remains the gold standard for the diagnosis of IE. It may demonstrate valvular inflammation, vegetations, and/or specific organisms. Detection of an etiologic agent in the vegetation using special stains or immunohistology can guide the choice of antimicrobial treatment. This is particularly useful in culture-negative IE, such as Q fever, *Bartonella* spp., or *T. whipplei* (Whipple's disease bacillus). **Good communication among cardiologists, surgeons, pathologists, and microbiologists helps ensure accurate diagnosis.**

C. Electrocardiography. All patients with suspected IE should undergo baseline and follow-up electrocardiogram (ECG).

1. ECG may reveal **conduction disturbances** reflecting intramyocardial extension of infection, ranging from a prolonged PR interval to complete heart block. A **new atrioventricular block** carries a 77% positive predictive value for abscess formation with 42% sensitivity.

2. Myocardial infarction due to embolization of vegetations occurs rarely.

D. Chest x-ray may reveal **CHF or pleural effusions.** Right-sided IE may cause **nonspecific infiltrates or pulmonary infarcts** owing to multiple septic pulmonary emboli.

VI. DIAGNOSTIC IMAGING TECHNIQUES

A. Echocardiography has a key role in both diagnosis and management of IE. The primary objective is to identify, localize, and characterize valvular vegetations and their effects on cardiac function. Vegetations may occur at intracardiac locations other than valves, such as the site of impact of a high-velocity jet or shunt. A limitation of echocardiography is that vegetations cannot always be distinguished from other noninfectious masses.

1. All patients in whom IE is suspected should undergo expedited baseline transthoracic echocardiography (TTE) to define underlying cardiac abnormalities, to determine the size and location of vegetations, and to explore the possibility of complications (e.g., aortic annular ring abscess). TTE has a low sensitivity for vegetations in IE (29% to 63%) but has close to 100% specificity. However, the finding of morphologically and functionally normal valves on TTE decreases the likelihood of IE. In one series, 96% of patients with normal valves on TTE also had a negative transesophageal echocardiography (TEE).

2. TEE has increased the diagnostic accuracy of IE. If IE is strongly suspected and the TTE is negative, then TEE should be performed because it is more sensitive in detecting vegetations, especially if TTE imaging is difficult. TEE is particularly useful for assessing posterior structures, abscesses, fistulae, perivalvular leaks, small vegetations, right-sided heart structures, masses on intracardiac devices, leaflet perforations, and prosthetic valves. The ability to detect paravalvular abscesses, fistulae, and paraprosthetic leaks has a major impact on management strategy. Intraoperative TEE can be used to evaluate the success of surgical interventions and the need for potential modification of reparative cardiac surgical procedures. A postoperative TTE should also be done as a baseline measure of cardiac anatomy/function for long-term follow-up. Although in most cases a TTE should be the first diagnostic test of choice, in certain circumstances TEE may be the optimal initial test to rule out IE. These include cases that involve *S. aureus* bacteremia, prosthetic valves, prior IE, limited echo windows, and bacteremia due to an organism that is known to commonly cause IE.

a. A negative result on TEE indicates a low likelihood of IE (provided adequate images are available). However, it does not completely rule out the diagnosis. The negative predictive value is >90%, but false negatives may occur early in endocarditis or if vegetations are small. Repeat TEE should be considered in 3 to 5 days if clinical suspicion is high or sooner if clinical findings change. Of note, a negative TEE should never override strong clinical evidence of endocarditis in the diagnosis of PVE.

b. Myocardial abscesses are more reliably detected with TEE (87% sensitive) than with TTE (28% sensitive). Detection of a perivalvular abscess is essential, as an abscess is a serious complication and a strong indication for surgical intervention.

c. In the setting of PVE, TEE is superior (82% sensitive) to TTE (36% sensitive) in the detection of vegetations due to acoustic shadowing of prosthetic valves, especially in the mitral and aortic positions. **TEE should be performed if PVE or pacemaker endocarditis is suspected but is not evident on TTE.**

3. Computerized tomography (CT): CT can be performed as complementary imaging to TEE in cases of endocarditis. Studies have shown that CT is advantageous when IE coexists with heavily calcified valves. It also can help define the extent of perivalvular abscess extension or pseudoaneurysm in native valve endocarditis (NVE) and especially PVE where acoustic shadowing makes characterization by TEE difficult.

4. Fungal endocarditis tends to cause larger vegetations than bacterial infections, whereas in Q fever vegetations are often absent. Care should be taken to differentiate bacterial vegetations from myxomas, papillary fibroelastomas, rheumatoid nodules, inflammation involving degenerative valvular lesions, Lambl's excrescences, and nonbacterial endocarditis. **It is essential to interpret images in conjunction with clinical data.**

5. One meta-analysis showed that the **risk of embolization in patients with large vegetations (>10 mm) was nearly three times higher than in patients with no detectable vegetations** or small vegetations. Prolapsing vegetations and involvement of extravalvular structures increase the overall risk of heart failure, embolization, and need for valve replacement. Vegetations that increase in size, despite appropriate therapy, are also more likely to be associated with adverse events requiring surgery.

6. TEE is indicated in patients with suspected pacemaker or defibrillator endocarditis. The sensitivity of TTE for detecting valvular or lead vegetations is 30%, compared with 90% with TEE.

B. Cardiac catheterization. Left heart catheterization with selective coronary angiography is indicated prior to surgical intervention if there is a suspicion of obstructive coronary disease. The abnormal rocking motion of a dehisced prosthetic valve may be noted on fluoroscopy. Care should be taken to avoid unnecessary coronary angiography or cardiac catheterization in aortic valve endocarditis because of the risk of embolization of vegetations.

C. Central nervous system (CNS) imaging. CT, magnetic resonance imaging (MRI), or cerebral angiography should be considered in any patient who has sustained a CNS complication, such as an embolic infarct, intracranial bleed, or mycotic aneurysm, or in the patient with persistent headaches. Endocarditis patients who **meet criteria for cardiac surgery should have a brain CT scan before surgery** to exclude occult cerebral embolization.

D. Body imaging. CT or MRI may be useful in the detection of metastatic infection. The value of CT may increase in the future as spatial resolution improves. **MRI** does not currently have a significant role in assessing cardiac manifestations of IE, owing to intrinsic problems related to temporal resolution.

VII. DUKE CRITERIA.

Given the complexity of IE, the diagnosis requires a high index of suspicion. The Duke schema is currently the most sensitive and specific diagnostic set of criteria available. It is particularly useful in diagnosing endocarditis in patients with *S. aureus* bacteremia, those with right-sided endocarditis, and those with negative blood culture results. However, these criteria have not been validated in PVE.

A. The criteria are divided into **definite** (pathologic or clinical), **possible**, and **rejected** diagnostic groups.

B. For a **definite pathologic diagnosis**, either (A or B) of the pathologic findings listed in Table 19.2A is sufficient.

C. For a **definite clinical diagnosis** (Table 19.2B), two major criteria, or one major and three minor, or five minor criteria are needed.

D. The **possible diagnostic** group has findings consistent with IE, including one major criteria and one minor criteria or three minor criteria.

E. For a **rejected diagnosis**, there is a firm alternative diagnosis for clinical manifestations or resolution of clinical manifestations, with antibiotics for 4 days or less, or no pathologic evidence of IE at surgery or autopsy, after antibiotic therapy for 4 days or less.

VIII. THERAPY. Owing to the complexity of IE, a team approach (cardiologist, cardiothoracic surgeon, infectious diseases specialist, and pathologist) in the diagnosis and management of this disease cannot be overemphasized. Effective therapy requires identification of the microbial cause, determination of a bactericidal regimen of proven efficacy, an understanding of the intracardiac pathology of IE and its implications for surgery, and effective management of extracardiac complications.

A. Medical therapy

1. Principles of therapy. Antibiotics are the mainstay of medical therapy. (Table 19.3 A–F)

a. Antibiotic regimens should be bactericidal and chosen in consultation with an infectious diseases specialist. **Measures of antibiotic effectiveness** include the minimum inhibitory concentration of antibiotic required to inhibit growth, the minimum bactericidal concentration of an antibiotic required to kill an organism, and the serum bactericidal titer (SBT), which is the highest dilution of a patient's serum that kills 99.9% of an inoculum. The SBT is especially helpful when treating unusual organisms, when using unusual antibiotic regimens, or when treatment is failing.

TABLE 19.2A Duke Criteria: Definite Pathologic Diagnosis

A. Microorganisms, as demonstrated by culture or histology in vegetation
Vegetation that has embolized
Intracardiac abscess
B. Pathologic lesions
Vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

b. Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2015;132(15):1435–1486. From Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633–638. Adapted by permission of the Infectious Diseases Society of America.

TABLE 19.2B Duke Criteria: Definite Clinical Diagnosis: Two Major Criteria, One Major and Three Criteria

Major Clinical Criteria
1. Positive blood culture results for IE

TABLE 19.2B Duke Criteria: Definite Clinical Diagnosis: Two Major Criteria, One Major and Three Criteria

A. Typical microorganisms (in two or more cultures)
- Viridans *Streptococcus*
- *Streptococcus bovis*
- HACEK group
- *Streptococcus aureus*[a]
- Community-acquired enterococci, in the absence of a primary focus

B. Persistently positive blood culture
- Recovery of a microorganism consistent with IE from two blood cultures drawn more than 12 h apar

or
- Recovery of a microorganism consistent with IE from all of three or a majority of four or more sepa and last draw at least 1 h apart

or
- Single positive blood culture for *Coxiella burnetii* or anti phase 1 IgG antibody titer > 1:800[a]

2. Evidence of endocardial involvement

A. Positive echocardiogram
- Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets absence of an alternative anatomic explanation

or
- Abscess

or
- New partial dehiscence of prosthetic valve

or

B. New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Clinical Criteria

1. Predisposition:
   - Predisposing heart condition
   - Injection drug use
2. Fever > 38.0°C (100.4°F)
3. Vascular phenomena
   - Major arterial emboli
   - Septic pulmonary infarcts
   - Mycotic aneurysm
   - Intracranial hemorrhage
   - Conjunctival hemorrhages
   - Janeway lesions
4. Immunologic phenomena
   - Glomerulonephritis
   - Osler's nodes
   - Roth's spots
   - Rheumatoid factor
5. Microbiologic evidence

TABLE 19.2B Duke Criteria: Definite Clinical Diagnosis: Two Major Criteria, One Major and Three Criteria

- Positive blood culture but not meeting major criteria as noted above
- Serologic evidence of active infection with organism consistent with IE

c. HACEK, *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella*, and *Kingella;* IE, infective endocarditis.

d. [a]Echocardiographic minor criteria have been eliminated.

e. Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2015;132(15):1435–1486. From Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633–638. Adapted by permission of the Infectious Diseases Society of America.

f. Anticoagulation is not recommended for routine use in IE. It does not prevent embolization related to IE. In fact, **simultaneous treatment with penicillin and heparin can increase the risk** of fatal intracerebral hemorrhage. Anticoagulation may be given in cases of IE in which there is another indication such as the presence of a prosthetic valve and in which the benefits outweigh the risks of adverse bleeding events.

2. Empiric therapy for IE is often started and continued until the etiologic organism is identified and the antibiotic sensitivities are known, especially in cases with hemodynamic compromise. Occasionally, empiric therapy is administered as a therapeutic trial to help confirm a diagnosis. Empiric therapy should cover the most likely pathogens, including staphylococci (both methicillin-sensitive and methicillin-resistant strains), streptococci, and enterococci. Vancomycin plus gentamicin is the recommended empiric regimen in NVE, with the addition of rifampin in PVE. Once an etiologic agent is identified, therapy should be narrowed (see Tables 19.3A–F). Unless clinical or epidemiologic clues suggest an etiologic factor, treatment for culture-negative IE is the same.

a. Renal function is an important consideration when using **aminoglycosides or vancomycin**. These antibiotics should be dosed according to estimated creatinine clearance. The following doses outlined are for normal renal function. A vancomycin dose should not exceed 2 g per 24 hours unless serum levels are monitored.

3. When initiating therapy for coagulase-negative staphylococcal PVE, the organism should be assumed to be methicillin-resistant until the laboratory definitively excludes this.

4. Antibiotic therapy **after surgery** is discussed in Section **VIII.B**.

5. Medical therapies for **specific organisms** are summarized in Tables 19.3A–F.

6. **Uncommon causes of IE.** *C. burnetii* IE is treated with doxycycline and rifampin, trimethoprim–sulfamethoxazole, or fluoroquinolones for at least 3 years and requires surgical intervention in cases of prosthetic valve involvement, CHF, or refractory infection. *Brucella* IE usually requires surgical intervention in combination with doxycycline and either streptomycin or gentamicin for 8 weeks to 10 months after surgery. *Pseudomonas* IE should be treated with high doses of piperacillin and tobramycin and requires surgical intervention in cases of left-sided infection.

7. **Fungal IE.** When fungal IE is diagnosed, the standard of care involves a **combined medical/surgical approach**.

TABLE 19.3A Therapies for Native Valve Infective Endocarditis Due Viridans *Streptococcus* or *Streptococcus bovis*

Medication	Dosage
Penicillin G	12–18 million U per 24 h continuously IV or in four to six divided do
or	
Ceftriaxone	2 g once daily IV or IM
or	
Penicillin G	12–18 million U per 24 h continuously IV or in six divided doses
or	
Ceftriaxone *plus*	2 g once daily IV or IM
Gentamicin *or* if penicillin allergic	3 mg/kg once daily IV or IM
Vancomycin	30 mg per 24 h in two divided doses

8. IM, intramuscular; IV, intravenous.

9. [a]For relatively resistant viridans *Streptococcus* or *S. bovis*, or known cardiac or extracardiac abscess, or for those with creatinine clearance <20 mL/min, penicillin G dosing is extended to 4 weeks.

10. Reprinted with permission from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2015;132(15):1435–1486. Copyright © 2015 American Heart Association, Inc.

TABLE 19.3B Standard Therapies for Susceptible Enterococci, for Resistant Viridans *Streptococcus*Infective Endocarditis, and for Prosthetic V Viridans *Streptococcus* or *Streptococcusbovis*

Medication	Dosage
Penicillin G	24 million U per 24 h continuously IV or in four to six divided dos
or	
Ceftriaxone	2 g once daily IV or IM
with or without	
Gentamicin	3 mg/kg once daily IV or IM
or	
If penicillin allergic, Vancomycin	30 mg/kg IV per 24 h in two divided doses

11. IM, intramuscular; IV, intravenous.

12. [a]If penicillin-susceptible strain (minimum inhibitory concentration ≤0.12 µg/mL), duration of gentamicin in combination with ceftriaxone is 2 weeks; if penicillin relatively resistant or fully resistant strain (minimum inhibitory concentration > 0.12 µg/mL), duration of gentamicin is extended to 6 weeks.

13. Reprinted with permission from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2015;132(15):1435–1486. Copyright © 2015 American Heart Association, Inc.

a. The mainstay of antifungal drug therapy is **amphotericin B** with or without **flucytosine** (a synergistic effect).

1. **(1)** Amphotericin B is infused in 5% dextrose over 2 to 4 hours at a dose of 0.7 to 1.0 mg/kg daily. Larger doses (1 to 1.5 mg/kg daily) are recommended for the management of PVE caused by *Aspergillus* spp.
2. **(2)** The major toxicity of amphotericin B is **renal dysfunction**. Liposomal preparations may be less nephrotoxic.
3. **(3)** The primary toxicity of flucytosine is **bone marrow suppression**; for this reason, flucytosine blood levels may be useful during therapy.

TABLE 19.3C Therapies for Infective Endocarditis Due to Staphylococci in Native Valve Endocarditis

Medication	Dosage	Duration of
Nafcillin or oxacillin	2 g IV every 4 h	6
Or for penicillin-allergic nonanaphylactoid patients		
Cefazolin	2 g IV every 8 h	6
Or for oxacillin resistant strains or penicillin-allergic patients with anaphylaxis		
If penicillin allergic,		
Vancomycin[a]	30 mg/kg per 24 h in two divided doses	6
Daptomycin	≥8 mg/kg dose	6

IM, intramuscular; IV, intravenous.

[a]Recommended for methicillin-resistant *Staphylococcus.*

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TABLE 19.3D Therapy for Infective Endocarditis Due to *Staphylococci* in the Presence of Prosthetic M

Medication	Dosage	Duration of Thera
Nafcillin[a] or oxacillin	2 g IV every 4 h	>6
Plus rifampin	300 mg orally every 8 h	>6
Plus gentamicin	1 mg/kg IV or IM every 8 h	2

IM, intramuscular; IV, intravenous.

[a]For methicillin-resistant *Staphylococcus* or for the
cillin-allergic patient, vancomycin, 30 mg/kg per 24 h IV in two divided doses, is substituted for nafcillin.

**TABLE 19.3E Therapy for Infective Endocarditis Due to HACEK (*Haemophilus, Actino*
Eikenella, and *Kingella*) Microorganisms**

Medication	Dosage	Duration
Ceftriaxone[a]	2 g once daily IV or IM in one dose	4
or		
Ampicillin	2 g IV every 4 h	4
or		
Ciprofloxacin	1,000 mg orally once daily *or* 800 mg IV every 12 h	4

IM, intramuscular; IV, intravenous.

[a]The third-generation cephalosporins or ampicillin–
actam therapy should be considered the drugs of choice. Length of therapy for prosthetic valve infective
carditis should be 6 weeks. A fluoroquinolone should be considered as an alternative agent for patients unable
erate β-lactam therapy.

Adapted with permission from Baddour LM, Wilson WR,
r AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of
lications. *Circulation*. 2005;111(23):e394–e434.

TABLE 19.3F Therapy for NVE or PVE Resulting from *Enterococcus* Species

Medication	Dosage	Dura
Ampicillin	2 g IV every 4 h	4–6
plus		
Gentamicin	3 mg/kg in two to three equally divided doses	
or with gentamicin resistance		
Ceftriaxone	2 g IV every 12 h	6
or with penicillin resistance		
Vancomycin	30 mg/kg per 24 h IV in two equally divided doses	6
Plus		
Gentamicin	3 mg/kg per 24 h in three equally divided doses	

b. Surgery should be performed because effective penetration of the medicine into vegetations is unlikely. Valve replacement becomes necessary in almost all cases of fungal IE.

c. After completion of 6 weeks of parenteral therapy, lifelong suppressive therapy with an azole is recommended to prevent relapse.

B. Surgical therapy (Table 19.4). Approximately one half of individuals with infectious endocarditis develop severe complications that require surgical treatment. There is mounting evidence that **early surgery** improves outcomes for patients with left-sided IE and refractory heart failure or intracardiac complications. Antibiotic therapy combined with valve replacement and cardiac reconstruction results in higher survival rates and fewer relapses or rehospitalizations and lower late endocarditis–related mortality than do antibiotics alone in patients with complicated IE.

1. The **fundamental principles** of operative procedures for IE involve debridement of infected tissue, removal of all nonviable tissue, reconstruction of the involved area, and restoration of valve competence. There is general consensus for surgical intervention in any of the following situations: refractory CHF due to significant valve dysfunction, native and PVE caused by *S. aureus, fungal, or other highly resistant organisms*, uncontrolled infection despite appropriate antibiotic therapy, most cases of PVE, and complications such as heart block or abscess formation. Controversial indications include the presence of more than one serious systemic embolic event or one embolus with a large residual vegetation. These latter indications are not absolute and must be implemented with a careful risk–benefit analysis (see the American College of Cardiology/American Heart Association guidelines for surgical intervention in Table 19.4).

TABLE 19.4 American College of Cardiology/American Heart Association Guidelines: Interventio

Class I

1. Decisions about timing of surgical intervention should be made by a multispecialty Heart Valve surgery, and infectious disease specialists
2. Early surgery is indicated in patients with IE who present with valve dysfunction that results in sympto
3. Early surgery is indicated in left-sided IE caused by *Staphylococcus aureus,* fungal, or other highly re
4. Early surgery is indicated in IE complicated by heart block, annular or aortic abscess, or destructive p
5. Early surgery is indicated in IE with evidence of persistent bacteremia or fevers lasting longer t antimicrobial therapy
6. Surgery is indicated in prosthetic valve and relapsing infection without other identifiable sources of in
7. Complete removal of pacemaker or defibrillator systems is indicated as part of early management i device infection

Class IIa

1. Early surgery is reasonable in IE presenting recurrent emboli and persistent vegetations despite appr
2. Complete removal of pacemaker or defibrillator systems is reasonable in patients with valvular IE without evidence of device infection.
3. Complete removal of pacemaker or defibrillator systems is reasonable in patients undergoing valve s

TABLE 19.4 American College of Cardiology/American Heart Association Guidelines: Intervention

Class IIb

1. Early surgery may be considered in patients with NVE and mobile vegetation >10 mm in length phenomenon
2. Operation without delay may be considered in patients with IE and an indication for surgery who h evidence of intracranial hemorrhage or extensive neurologic damage
3. Delaying valve surgery for at least 4 weeks may be considered for hemodynamically stable patients or intracranial hemorrhage

2. CHF, congestive heart failure; IE, infective endocarditis; NVE, native valve endocarditis.

3. Reprinted with permission from Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(25):e1159–e1195. Copyright © 2017 American Heart Association, Inc.

4. CHF (New York Heart Association class III or IV) is the strongest indication for surgery in IE, as 90% of all deaths result from CHF. It should be noted that the benefit of surgery persists even in the presence of comorbidities, such as acute renal failure, and surgery should not be delayed in the setting of life-threatening heart failure or cardiogenic shock if the patient is likely to recover after surgery.

5. PVE usually requires a combined medical/surgical approach.

6. **Patients with CNS infarcts or bleeds.** Special attention must be paid to the presurgical candidate who may have had a CNS infarct or bleed, because large doses of heparin are required for cardiopulmonary bypass. **The current recommendations are for early surgery without delay in patients with left-sided IE, a surgical indication, and evidence of CVA without intracranial hemorrhage or extensive neurologic damage on exam.** In cases of major ischemic CVA or intracranial hemorrhage surgery should be delayed for at least 4 weeks if the patient is hemodynamically stable. **If a mycotic aneurysm is found, the timing of surgery should be reconsidered, and any prosthesis that requires postoperative anticoagulation should be avoided.** A mycotic aneurysm should be clipped, or embolized **before** cardiac operation.

7. Metastatic infection, usually attributed to *S. aureus*, should be drained if accessible.

8. The optimal duration of **antibiotic therapy after surgery** for IE is not known.

a. For **native valve IE** caused by an antibiotic-resistant organism with subsequent negative cultures, preoperative plus postoperative antibiotic therapy should consist of a full course of recommended treatment.

b. For patients with **positive intraoperative cultures**, a full course of therapy should be given postoperatively.

c. Patients with prosthetic valves who are undergoing surgery for IE should receive a full course of antibiotics postoperatively when organisms are discovered in resected material.

C. The optimal management of **pacer or defibrillator endocarditis** has been controversial in the literature, especially regarding the necessity for device removal.

1. The success rate without removal of the entire device is low because typically the entire device is infected. Most studies suggest that the complete explantation of all hardware combined with antibiotic therapy is the optimal management.

2. The optimal route or duration of antibiotics remains unclear in the literature. Experience suggests that a prolonged course of IV antibiotics is needed.

3. The timing of device reimplantation is another important issue. It is prudent to provide sufficient duration of antibiotic therapy to eradicate bacteremia and to suppress or eradicate endocardial infection prior to reimplantation in order to minimize the risk of reinfection of the new device. Studies have shown that reimplantation is successfully performed at a median of 7 days (5 to 25 days) after explanation.

IX.COMPLICATIONS

A. Table 19.5 lists the complications of IE.

B. Valve ring abscess is a noteworthy complication of PVE, seen with mechanical and bioprosthetic valves and also occasionally seen in severe infection of native valves. Infection of the sutures used to secure the sewing ring to the periannular tissue may result in dehiscence of the valve. The clinical finding of a new perivalvular leak in a patient with PVE is worrisome. Risk factors for abscess formation include persistent fever, CHF, a history of IV drug use, infection with a virulent organism, and PVE.

TABLE 19.5 Complications

Cardiac complications
Congestive heart failure (leading cause of death)
Abscess (pericardial, aortic annular, or myocardial)
Conduction abnormalities (due to invasive disease)
Coronary embolism
Mycotic aneurysm (often clinically silent)
Valvular regurgitation (cusp/leaflet flail or perforation)
Valvular stenosis
Prosthetic dehiscence
Septal perforation (ventricular septal defect)
Extracardiac complications
Systemic embolism (stroke, renal infarct, splenic infarct, or ischemic limb)
Mycotic aneurysm

TABLE 19.5 Complications

Abscess
Immune complex deposition (glomerulonephritis)

X. RESPONSE TO THERAPY. Although a reduction in the size of vegetations during antimicrobial therapy suggests therapeutic success, vegetations may persist unchanged despite microbiologic cure. Significant enlargement of a vegetation during treatment indicates possible treatment failure and constitutes a relative indication for surgery.

A. Blood cultures should be obtained during therapy for IE to ensure eradication of the organism (see Section V.A.3).

B. Defervescence usually follows 3 to 7 days of successful antimicrobial therapy. **Persistent or recurrent fever may represent therapeutic failure, drug fever, a secondary nosocomial infection, or intracardiac or extracardiac abscess formation.** Generally, if fever persists for more than 7 days or if blood cultures are positive beyond the first week of antibiotic therapy, the treatment is considered a failure.

C. Relapses, should they occur, usually manifest clinically within 4 weeks and can be confirmed by blood cultures. With a combined medical and surgical approach, recurrent PVE occurs in 6% to 15% of patients.

D. **The frequency of emboli falls rapidly after 1 to 2 weeks of antibiotic therapy**, and the risk is considered to be greatest in the setting of large vegetations (>10 mm in diameter) and specific infections (*S. aureus* and *Candida*).

E. Medical management is successful in many patients with IE; however, surgery is required in approximately 50% of cases.

XI. PROGNOSIS. The prognosis depends on **the virulence of the causative organism, the underlying health of the patient, the valvular structures, the duration of the infection, and the presence or absence of CHF**. The overall mortality of IE is around 30% at 1 year. Notably, the mortality rates in early PVE (40% to 80%) are much higher than in late PVE (20% to 40%). Five-year survival rates after surgery for PVE have ranged from 54% to 87%. In *S. aureus* IE, mortality has decreased from 50% to 60% to 15% to 30% in recent years. The presence of the factors listed in Table 19.6 should trigger an early and aggressive management plan.

A. Park et al. created a validated risk score to predict 6-month mortality in IE. Patient factors including older age, dialysis, PVE, left-sided IE, virulent organisms, CHF, stroke, paravalvular complications, and persistent bacteremia were independently associated with a higher 6-month mortality. Early surgery during an index hospitalization was associated with a lower risk of mortality although it should be noted that surgery is performed less frequently in the highest risk patients.

TABLE 19.6 Factors and Complications That Predispose to a Poor Outcome

Congestive heart failure (leading adverse prognostic factor)
Nonstreptococcal disease
Aortic valve involvement

TABLE 19.6 Factors and Complications That Predispose to a Poor Outcome
Infection of a prosthetic valve
Older age
Abscess formation
HIV with CD4 count < 200 cells/mm^3
Delayed diagnosis
CNS or coronary embolization
Recurrent IE

B. CNS, central nervous system; HIV, human immunodeficiency virus; IE, infective endocarditis.

XII. PROPHYLAXIS. Revised IE prophylaxis guidelines from the American Heart Association (AHA) concluded that **only those patients at highest risk for adverse outcomes from IE require prophylaxis** prior to certain dental or surgical procedures (Tables 19.7A and B). This is based on studies suggesting that IE is more likely to occur from everyday activities such as flossing or brushing teeth than from dental procedures, and that only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis for dental, gastrointestinal, or genitourinary procedures. It is a standard practice (AHA guidelines) that at-risk individuals be counseled and advised to carry a card with current prophylaxis recommendations. A recent study suggests that an echocardiographic report, stating the endocarditis risk and need for prophylaxis, improves compliance with AHA recommendations.

A. In deciding the need for antibiotic prophylaxis, two factors must be considered: the risk associated with the specific valvular lesion (Table 19.7A) and the type of procedure to be performed (Table 19.7B). Patients for whom antibiotic prophylaxis for IE is recommended include those with **prosthetic valves or repair material including transcatheter devices, prior IE, postcardiac transplantation valvulopathy, and certain patients with congenital heart disease** (Table 19.7A). Routine IE prophylaxis is no longer recommended in cardiac conditions such as mitral valve prolapse, rheumatic heart disease, bicuspid aortic valve, calcific aortic stenosis, atrial septal defect, and ventricular septal defect.

TABLE 19.7A Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from I
Prophylaxis for Endocarditis Recommended
Prosthetic heart valves
Previous IE
CHD
Unrepaired cyanotic CHD (including palliative shunts or conduits)

TABLE 19.7A Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from I
Repaired CHD with residual defect at, or adjacent to, the site of repair
During the first 6 mo after repair of congenital heart defects using prosthetic material or device
Cardiac transplantation recipients who develop cardiac valvulopathy

B. CHD, congenital heart disease; IE, infective endocarditis.

C. Reprinted with permission from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;116(15):1736–1754. Copyright © 2007 American Heart Association, Inc.

TABLE 19.7B Recommendations for Prophylaxis in Dental or Surgical Procedures
Prophylaxis recommended only in patients at highest risk of adverse outcome from infective endocard
Oropharyngeal procedures
Dental procedures that involve manipulation of gingival tissue, the periapical region of teeth, or perfor
Tonsillectomy and/or adenoidectomy
Respiratory procedures
Invasive procedures involving incision
Miscellaneous
Procedures on infected skin or musculoskeletal tissue

D. Reprinted with permission from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;116(15):1736–1754. Copyright © 2007 American Heart Association, Inc.

E. Endocarditis prophylaxis following **dental or oral procedures** is directed primarily against viridans *Streptococcus*.

F. **Routine antibiotic prophylaxis solely to prevent IE is no longer advised prior to gastrointestinal or genitourinary procedures.** This is based upon an increasing frequency of antimicrobial-resistant strains of enterococci and a lack of evidence conclusively linking these procedures to IE.

G. Available evidence supports a shift in emphasis away from dental procedures and antibiotic prophylaxis toward a greater **emphasis on maintaining good oral hygiene** and improved access to dental care in patients at risk for IE.

H. Prophylaxis against viridans *Streptococcus* is advised in patients at highest risk of IE who undergo **invasive procedures of the respiratory tract** that involve incision or biopsy (i.e., tonsillectomy or adenoidectomy).

I. Routine endocarditis prophylaxis prior to **vaginal delivery** or hysterectomy is not recommended.

J. Incision and drainage or other procedures involving infected tissue may result in bacteremia. For nonoral soft-tissue infections, an antistaphylococcal penicillin or first-generation cephalosporin is an appropriate choice of prophylaxis.

K. Prophylaxis regimens are listed in Table 19.7C. **Cardiac surgical patients** who undergo placement of prosthetic heart valves or other prosthetic material should receive perioperative antibiotic prophylaxis, primarily directed against *S. aureus*. A first-generation cephalosporin is commonly used, but the choice of antibiotic should be influenced by the antibiotic susceptibility pattern at each hospital. Prophylaxis should be started immediately before the procedure, repeated during prolonged procedures, and continued for no more than 48 hours.

L. **A careful preoperative dental evaluation** is recommended so that, whenever possible, required dental treatment can be completed before cardiac valve surgery.

M. **Patients after cardiac transplantation** are at moderate risk for endocarditis because of continuous immunosuppression and the tendency for acquired valvular dysfunction (tricuspid regurgitation from endomyocardial biopsy or rejection).

N. Pneumococcal vaccination is recommended for all patients with prosthetic heart valves.

XIII. CONTROVERSIES

A. Therapy

1. Short courses of antibiotics (2 weeks) have shown some efficacy in the injection drug user population, as have oral antibiotics in the same population. However, IV antibiotics are recommended until conclusive data concerning alternative regimens are available. At least 5 to 7 days of inpatient therapy is advocated before considering outpatient treatment.

TABLE 19.7C Prophylactic Regimens

Clinical Situation	Antibiotic	Dose
Standard prophylaxis	Amoxicillin	2 g PO 1 h before pr
Unable to take oral medications	Ampicillin	2 g IV or IM within 30
	or	
	Cefazolin or ceftriaxone	1 g IV or IM within 30
Penicillin allergy	Clindamycin	600 mg PO 1 h befor
	or	
	Cephalexin	2 g PO 1 h before pr
	or	
	Azithromycin *or* clarithromycin	500 mg 1 h before pr

2. IM, intramuscular; IV, intravenous; PO, per oral.

3. Reprinted with permission from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;116(15):1736–1754. Copyright © 2007 American Heart Association, Inc.

4. Correct timing of surgery is often the most difficult and critical decision in the management of IE. It is important to balance the need for medical stabilization with timely surgery. Kiefer et al. conducted a large multicenter prospective study of over 4,000 patients

with IE and heart failure and showed that surgical intervention during initial hospitalization was associated with decreased in-hospital and 1-year mortality rates. The Early Surgery Versus Conventional Treatment in IE trial studied patients with left-sided IE, heart failure, and large vegetations randomized to either early surgery within 48 hours of diagnosis versus conventional therapy with surgery occurring some point after 48 hours but still within the index hospitalization. In patients with large mitral or aortic valve vegetations (>10 mm), early surgery was found to be associated with decreased mortality and embolic events when compared with conventional medical therapy (3% vs. 23%). In this trial, patients who had surgery within 48 hours also had a decreased rate of all-cause death.

5. Valve repair is a reasonable option for mitral, tricuspid, and, less often, aortic IE in which the infection has been controlled. The choice among mechanical, bioprosthetic, and biologic devices may be made according to the usual criteria. However, in the setting of aortic prosthetic endocarditis, a homograft is less likely to become infected than either a xenograft or a mechanical valve and is considered the optimal valve substitute.

6. Some observational studies have called into question the more relaxed guidelines on antibiotic prophylaxis citing a corresponding increase in the incidence of endocarditis with decrease in prescriptions for antibiotic prophylaxis. This data has yet to be substantiated by a larger randomized trial.

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SUGGESTED READING

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CHAPTER 20

Rheumatic Fever

Rayji S. Tsutsui
Brian P. Griffin

I.INTRODUCTION. Rheumatic fever (RF) is a systemic autoimmune disorder related to prior streptococcal infection and is the leading cause of heart disease in those under the age of 40 years living in developing nations.

A. The incidence of RF and prevalence of rheumatic heart disease **vary substantially among countries**. In many developing countries, the incidence of acute RF approaches or exceeds 200 per 100,000, whereas in the Unites States, it is estimated to be less than 1 per 100,000. Since the first half of this 20th century, there has been a gradual decline in the incidence of RF in the United States. This is due to improved public health and living conditions, the development of modern antibiotics, as well as a shift in the endemic strains of group A streptococcus (GAS). Localized outbreaks of RF have occurred in the United States as recently as the mid-1980s.

B. RF is more common among populations at high risk for streptococcal pharyngitis, such as military recruits, those in close contact with school-aged children, and persons of low socioeconomic status. It most commonly occurs between the ages of 5 and 18 years. RF affects both sexes equally, except for Sydenham chorea, which is more prevalent in females after puberty.

C. With difference in incidence world wide, it has been recommended to risk stratify patients according to population risk at large in order to help tailor the index of suspicion. Low-risk populations are those with RF incidence ≤2 per 100,000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1,000 population per year such as the case with United States.

D. RF can present in a variable manner particularly in high-risk populations such as the indigenous Australian population. Those include aseptic monoarthritis and low-grade fever.

E. Echocardiography has become an integral part of RF diagnosis. Carditis is one of the major presentation of RF. Classically, it is diagnosed by auscultation of a murmur that is consistent with aortic or mitral valve regurgitation. Indeed, valvulitis remains the most common presentation of RF. With improvement in Doppler echocardiography, the concept of subclinical carditis has arisen, where a patient may have echocardiographic findings of typical valvular disease but may not have a typical murmur on auscultation or a murmur was missed on examination. This subclinical carditis group is thought to comprise approximately 17% of prevalent RF cases.

II. CLINICAL PRESENTATION. The clinical manifestations of RF **develop 3 weeks after a GAS tonsillopharyngitis**. It is important to note that one-third of patients with RF do not remember having had a sore throat. Patients with RF present initially with a sudden onset of constitutional symptoms, including fever (101°C to 104°C), malaise, weight loss, and pallor. An exudative and proliferative inflammatory process involving collagen fibrils characterizes the acute phase of RF. **Multiple organ systems**, such as the dermis, central nervous system, synovium, and heart, may be involved. In addition, manifestations may include serositis and involvement of the lungs, kidneys, and central nervous system.

A. Diagnostic criteria

1. The **Jones criteria** are designed to aid in the diagnosis of the first episode of RF. It can be diagnosed when a **previous upper airway infection with GAS is detected in conjunction either with two major manifestations or with one major and two minor manifestations**. Major manifestations include arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. Minor manifestations include fever, arthralgias, high C-reactive protein (CRP) level or high erythrocyte sedimentation rate (ESR), and a prolonged PR interval on electrocardiogram (ECG) (Table 20.1).

2. In some circumstances, the **diagnosis of RF can be made without strict adherence to Jones criteria**, as in cases of indolent or recurrent carditis or isolated cases of chorea when other causes have been excluded.

TABLE 20.1 Diagnosis of Rheumatic Fever

GAS Infection	Major Jones Criteria		Minor Jones Criteria	
Culture	**Low Risk[a]**	**Moderate–High Risk**	**Low Risk[a]**	**M**
ASO titers	Carditis (clinical or subclinical[b])	Carditis (clinical or subclinical[b])	Polyarthralgia	M
Anti-DNAse B			Fever (≥38.5°C)	F
Other antistreptococcal antibodies	Polyarthritis only Chorea	Mono or polyarthritis, polyarthralgia Chorea	ESR ≥ 60 mm in the first hour and/or CRP ≥ 3.0 mg/dL	E
Streptococcal antigens	Erythema marginatum Subcutaneous nodules	Erythema marginatum Subcutaneous nodules	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	P

3. The diagnosis of rheumatic fever requires confirmation of a previous ***GAS infection*** with at least one of the methods listed above together with either ***two major criteria or one major criterion and two minor criteria***.

4. ASO, antistreptolysin O; anti-DNase, antideoxyribonuclease B; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A streptococcus.

5. [a]Low-risk populations are those with RF incidence ≤2 per 100,000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1,000 population per year.

6. [b]Subclinical carditis indicates echocardiographic valvulitis.

7. **Echocardiography** has become one of the cornerstones of RF diagnosis (i.e., carditis) in addition to the Jones criteria to allow for the diagnosis of subclinical carditis. A 2015 American Heart Association (AHA) statement recommends that echocardiography should be performed in all definite and suspected cases of RF and if evidence of carditis is not detected, it rules out the carditis diagnosis (Table 20.2).

B. Major manifestations (Table 20.1)

1. **Carditis/subclinical carditis.** This is the most serious and is often regarded as the most specific manifestation of RF, affecting 50% to 70% of patients. It may manifest as pancarditis affecting the endocardium, myocardium, and pericardium simultaneously.

a. Cardiac involvement ranges from an asymptomatic presentation to progressive congestive heart failure and death.

b. The most typical manifestations include **tachycardia, arrhythmias, new murmurs or pericardial friction rub, cardiomegaly, and heart failure**.

c. Heart failure is rare in the acute phase; if present, it is usually the result of myocarditis.

d. The most characteristic component of rheumatic carditis is a valvulitis (endocarditis) involving the mitral and aortic valves.

1. **(1)** Mitral regurgitation is the hallmark of rheumatic carditis. Aortic insufficiency is less common and is almost always associated with mitral insufficiency. As a rule of thumb, patients under the age of 30 years tend to present with isolated mitral regurgitation, whereas patients develop mitral stenosis during the third decade, with mixed mitral valve disease predominating thereafter.
2. **(2)** Subclinical carditis: No murmurs are heard but presence of valve thickening on echocardiography occurs in up to 17%.
3. **(3)** Acute mitral valve regurgitation produces an apical systolic murmur that may be accompanied by a mid-diastolic Carey Coombs murmur of relative mitral stenosis (a high-pitched early diastolic murmur that varies from day to day). Right-sided valves are rarely involved.
4. **(4)** Those valvular lesions that are diagnosed by echocardiogram but are clinically silent usually heal without scarring and have a good prognosis. Controversy exists whether echocardiographic findings of mitral regurgitation or aortic insufficiency constitute subclinical rheumatic carditis sufficient to meet the Jones criteria.

e. Pericarditis may cause chest pain, friction rubs, and distant heart sounds but is often clinically silent.

TABLE 20.2 Doppler Findings in Rheumatic Valvulitis

Pathologic Mitral Regurgitation (All Four Criteria Met)
Seen in at least two views
Jet length ≥2 cm in at least one view
Peak velocity > 3 m/s

TABLE 20.2 Doppler Findings in Rheumatic Valvulitis
Pan systolic jet in at least one envelope
Pathologic Aortic Regurgitation (All Four Criteria Met)
Seen in at least two views
Jet length ≥ 1 cm in at least one view
Peak velocity > 3 m/s
Pan diastolic jet in at least one envelope

f. From Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1806–1818, with permission; American Heart Association, Inc.

2. **Arthritis.** This is the **most common manifestation of RF but is the least specific**. It occurs in 80% of patients and is described as **painful, asymmetric, migratory, and transient. It involves large joints**, such as the knees, ankles, elbows, wrists, and shoulders. It is **more common in older patients and improves markedly with the use of salicylates** within 48 hours of treatment. Monoarthritis, oligoarthritis, and involvement of small joints of the extremities are less common. However, arthritis of the first metatarsophalangeal joint, enthesopathy, and axial involvement, especially of the cervical spine, have also been reported. **Arthritis of RF is benign and self-limiting** (lasting approximately 4 weeks) and does not result in permanent sequelae. Inflammatory changes without signs of infection are seen in the joint fluid. In low-risk populations, polyarthritis fulfills the arthritis criteria, whereas in high-risk populations, either polyarthralgia or monoarthritis and/or polyarthritis can be considered.

3. **Sydenham chorea.** Also known as Saint Vitus dance or chorea minor, this **extrapyramidal disorder is characterized by purposeless and involuntary movements** of face and limbs, muscular hypotonia, and emotional lability.

a. Initial manifestations include difficulty in writing, talking, or walking.

b. Sydenham chorea is a **delayed manifestation of RF**, usually appearing 3 months or more after an upper airway infection; it is often the sole manifestation of acute RF. Chorea has been reported in up to 30% of the patients. Most cases tend to follow a benign course, with complete resolution of symptoms in 2 to 3 months, although cases in which symptoms persisted for >2 years have been reported.

c. **Differential include tics, athetosis, conversion reactions, hyperkinesia, and behavioral abnormalities.**

4. **Subcutaneous nodules.** These usually measure 0.5 to 2 cm and are **firm, painless, and freely mobile nodules that can be isolated or found in clusters** over the **extensor surfaces** of joints (knees, elbows, and wrists), bony prominences, tendons, dorsum of foot, occipital region, and cervical processes. They are seen in up to 20% of patients with RF and last for a few days. The skin overlying the nodules is freely mobile and shows no signs of discoloration or inflammation.

5. **Erythema marginatum.** This is an **evanescent erythematous macular rash** with a pale center of irregular shape. It is **usually nonpruritic and tends to disappear after a few days**. It is highly specific, occurring in <5% of patients, and is obvious only in fair-skinned individuals. The lesions vary in size and do not typically affect the face. The rash may be induced by application of heat. Its presence is **suggestive of coexisting carditis**.

C. **Minor manifestations.** Fever and arthralgias are common, but nonspecific findings of RF can be used to support the diagnosis of RF when only a single major manifestation is present (Table 20.1).

1. Fever is encountered during the acute phase of the disease and does not follow a specific pattern.
2. Arthralgia is defined as pain in one or more large joints without objective findings of inflammation on physical examination.
3. Other clinical manifestations of RF include **abdominal pain, epistaxis, acute glomerulonephritis, rheumatic pneumonitis, hematuria, and encephalitis**. These are not included as diagnostic criteria for the diagnosis of RF.

III. ETIOLOGY AND PATHOPHYSIOLOGY

A. The association between tonsillopharyngitis–scarlet fever epidemics and acute RF in the 1930s, the findings of high levels of antistreptolysin O (ASO) in sera of patients with RF, and the confirmation of antibiotics as an efficient mode of prophylaxis of RF provide **strong evidence that GAS is the agent causing initial and recurrent attacks of RF**.

1. Acute RF is likely caused by an immunologic mechanism. Specifically, it appears that patients who develop RF demonstrate a hyperimmune response to GAS, and the level of the immune response correlates with the severity of the RF manifestations. Supporting evidence includes onset approximately 3 weeks following an upper respiratory tract infection, rarity before the age of 5 years when the immune system is still immature, and cross-reactivity between streptococcal cellular antigens and proteins present in human connective tissue.

a. The most important antigenic structures (M, T, and R proteins) are localized in the external layer of the bacterial cell wall.

b. The M protein not only is responsible for type-specific immunity but also has a powerful antiphagocytic action and is classically regarded as a marker of streptococcal rheumatogenic potential. Patients with acute RF possess high levels of antibodies targeted against this protein. Specific M serotypes of GAS have long been recognized as strong stimulators of a robust immune response and are associated with an increased risk of developing RF. Those M serotypes associated with impetigo or pyoderma may cause glomerulonephritis but are not associated with RF.

2. In epidemics of streptococcal pharyngitis, it is estimated that approximately **3% of untreated individuals will go on to develop RF**. However, recurrence of RF is seen in about 50% of patients with a history of RF. For endemic GAS pharyngeal infections, the incidence of RF is much less common.

B. Numerous epidemiologic studies favor a **familial and even genetic predisposition**. A monoclonal antibody to B-cell alloantigen (D8/17) is almost universally detected in patients with RF, whereas this antibody is present in <14% of the general population. In addition, susceptibility to RF has also been linked with D-related human

leukocyte antigen 1, 2, 3, and 4 haplotypes. These genetic markers may be useful in the future to identify individuals susceptible to acute RF.

IV. LABORATORY EXAMINATION AND DIAGNOSTIC TESTING. RF is a clinical diagnosis because there is no single laboratory study that is diagnostic of RF.

A. Supporting evidence of antecedent GAS infection can be obtained through cultures, antigen test, or serum antistreptococcal antibody test.

1. Although no consensus exists regarding which tests to order at what time, commonly ASO titers and cultures are initially obtained when RF is suspected. Other tests (see below) are useful only under certain conditions.

2. A negative throat culture is usually sufficient to withhold antibiotic treatment in most cases, especially if clinical suspicion of RF is low.

3. Elevated or rising ASO titers provide solid evidence for recent GAS infection. **A greater than twofold rise in ASO titers compared with convalescent titers is diagnostic.**

4. The probability of detecting a previous GAS infection can be increased by obtaining repeated ASO tests or by looking for antibodies to other streptococcal antigens, such as **antideoxyribonuclease B**.

5. A slide agglutination test is commercially available, which measures antibodies to several streptococcal antigens. However, it is **not well standardized and is not very reproducible**. Therefore, it is **not recommended** as a definitive test.

B. Biopsies

1. Aschoff nodules, a form of granulomatous inflammation, can be seen in the proliferative stage and are considered pathognomonic for rheumatic carditis. They are encountered in 30% to 40% of biopsies from patients with primary or recurrent episodes of RF. Such nodules are most often found in the interventricular septum, the wall of the left ventricle, or the left atrial appendage.

2. The histologic findings of endocarditis include edema and cellular infiltration of valvular tissue. Hyaline degeneration of the affected valve results in the formation of verrucae at its edge, preventing the normal leaflet coaptation. If the inflammatory process persists, fibrosis and calcification develop, leading to valvular stenosis.

3. Endomyocardial biopsy does not help in diagnosing first attacks of rheumatic carditis. It is **useful in distinguishing chronic inactive rheumatic heart disease from acute rheumatic carditis**. As such, it is rarely indicated except in cases where recurrent carditis is suspected but cannot be confirmed otherwise.

C. Other blood tests

1. As in any inflammatory process, **leukocytosis, thrombocytosis, or hypochromic or normochromic anemia** may be noted.

2. The favored tests to measure acute phase response are ESR and CRP. Although these tests are nonspecific, they may be helpful in monitoring the inflammatory activity of the disease. These levels are **almost always elevated during the acute phase of RF in patients with arthritis and polyarthritis and are usually normal in patients with chorea**.

D. Radiography. Chest radiography may identify increased cardiac size, increased pulmonary vasculature, or pulmonary edema.

E. Electrocardiography and echocardiography. In patients in whom carditis is subtle and signs of valvular involvement may be mild or transient, a baseline ECG may help provide evidence of carditis. **Echocardiography should be performed in all cases of suspected RF.**

1. The most common finding in the **ECG** is the presence of **PR prolongation and sinus tachycardia**. Myocarditis may prolong the QT interval. In cases of pericarditis, low-voltage QRS complexes and ST-segment changes in the precordial leads can be observed.

2. Echocardiography is likely to show mitral regurgitation or aortic insufficiency. Calcifications of the leaflets and subvalvular apparatus are present in the chronic, not acute, phase of rheumatic heart disease. Echocardiography/Doppler findings not consistent with carditis should be excluded in the diagnosis of a patient with a murmur. Transesophageal echocardiography should be considered if obtaining adequate images are difficult with transthoracic echocardiography particularly paying attention to the mitral and aortic valves.

V. THERAPY. It is generally recommended that **patients with suspected RF be admitted for close observation and workup**.

A. Secondary prophylaxis with penicillin has been shown to reduce not only streptococcal infections but recurrent attacks of acute RF as well. Patients with mild carditis should receive secondary prophylaxis for 10 years after the most recent attack or at least until the age of 25 years, whichever is longer. More severe valvular damage necessitates lifelong secondary prophylaxis.

B. Congestive heart failure should be managed with standard therapy (Chapters 8 and 9).

C. Aspirin and salicylates have been the preferred treatment for the inflammatory manifestations of RF specifically for the arthritis. Aspirin has been traditionally used in a dose of 80 to 100 mg/kg/d given at 4 hourly aliquots in children, and a total of 4 to 8 g/d given in aliquots every 4 to 6 hours for adults. There is increasing experience with the use of NSAIDS and especially naproxen instead of aspirin in the treatment of arthritis which may lessen the risk of Reyes syndrome in children and can be given less frequently. The dose of naproxen used is 10 to 20 mg/kg/d divided in doses every 12 hours with a maximum dose of 1,000 mg in children older than 2 and maximal dose in adults of 1,250 mg. In patients with any degree of cardiac involvement, **aspirin is preferred over corticosteroids** as steroids may lead to fluid retention and worsen heart failure symptoms. Neither aspirin nor corticosteroids, despite relieving symptoms of inflammation, prevent valvular damage.

D. If intolerant to aspirin, the recommended dose of **corticosteroid** (prednisone) is 1 to 2 mg/kg/d (maximum of 60 mg/d). Salicylate or steroid therapy does not affect the course of carditis except perhaps in severe carditis where steroids may have a role though this is controversial; therefore, the duration of anti-inflammatory therapy is somewhat arbitrary and is guided by the severity of disease and the response to therapy. Therapy should be continued until there is sufficient clinical and laboratory evidence of disease inactivity. After cessation of anti-inflammatory agents, relapse with mild symptoms may occur. If using a steroid, **a gradual reduction in steroid dosing is necessary to avoid relapses**.

If **symptoms are mild, they usually subside without specific treatment**. For **severe symptoms, treatment with salicylates** should be tried before restarting corticosteroids.

VI. PREVENTION.

See Table 20.3.

A. Primary prevention. The most important step in the management of RF is the eradication of GAS infection, which prevents chronic and repetitive exposure of antigenic streptococcal components to the host immune system. However, **no treatment can eradicate GAS completely in all patients because of high colonization rates**.

1. Early therapy is advisable because it reduces both morbidity and the period of infectivity. Therapy started as late as 9 days after the onset of acute streptococcal pharyngitis is still effective in preventing primary attacks of RF.

2. Penicillin is the agent of choice primarily for its narrow spectrum of activity, long-standing proven efficacy, and low cost.

a. Best results are achieved with a **single intramuscular (IM) dose of penicillin G benzathine**. An IM regimen is preferred in patients unlikely to complete a 10-day course of oral therapy or in patients with personal or family history of RF or rheumatic heart disease. This preparation is painful; **preparations that contain procaine penicillin are less painful**.

b. In comparison with the IM regimen, the oral regimen has several disadvantages, such as lower compliance because of its longer duration, more complicated dosing schedules, drug interactions, and, more importantly, socioeconomic factors. The oral antibiotic of choice is penicillin V (phenoxymethylpenicillin) (see Table 20.3 for dosage information). A broader spectrum penicillin, such as amoxicillin, offers no microbiologic advantage over penicillin.

3. Patients allergic to penicillin:

a. Oral erythromycin can be used. The recommended dosage is erythromycin estolate or erythromycin ethyl succinate for 10 days. The maximum dose of erythromycin is 1 g/d.

TABLE 20.3 Prevention of Rheumatic Fever

Drug	Dosage
Primary Prevention	
Benzathine (penicillin G)	600,000 U (≤27 kg)
	1.2 million U (≥27 kg)
	or
Penicillin V (children)	250 mg (2–3 times/d)
Penicillin V (adolescents and adults)	500 mg (2–3 times/d)
Penicillin-allergic patients	
Erythromycin ethyl succinate	40 mg/kg/d (2–4 times/d up to 1 g/d)
Erythromycin estolate	20–40 mg/kg/d (2–4 times/d up to 1 g/d)

TABLE 20.3 Prevention of Rheumatic Fever

Secondary Prevention	
Benzathine (penicillin G)	1.2 million U
or	
Penicillin V	250 mg
or	
Sulfadiazine	0.5 g (≤27 kg)
	1.0 g (>27 kg)
Penicillin- and sulfadiazine-allergic patients	
Erythromycin	250 mg

b. bid, twice a day; IM, intramuscular; qd, every day.

c. Although uncommon in the United States, **strains resistant to erythromycin** have been found in some areas of the world and have caused treatment failures. Other **macrolides, such as azithromycin**, have the advantage of a short treatment duration (5 days) and few gastrointestinal side effects. These can be used as second-line therapy for patients 16 years or older with GAS pharyngitis. The recommended dosage is 500 mg as a single dose on the first day followed by 250 mg once daily for 4 days.

d. Another alternative regimen for penicillin-allergic patients is a **10-day course with an oral cephalosporin**. A first-generation cephalosporin with a narrower spectrum of action (cefazolin or cephalexin) is preferable to the broader spectrum antibiotics such as cefaclor, cefuroxime, cefixime, and cefpodoxime. Several reports support the evidence that a 10-day course with oral cephalosporin is superior to a 10-day course with oral penicillin and a 5-day course with selected oral cephalosporins is comparable to a 10-day course with oral penicillin for the eradication of GAS.

e. Sulfa-derived antibiotics **(sulfonamides and trimethoprim) do not eradicate GAS** in patients with pharyngitis, and **tetracycline should be avoided** because of the high prevalence of resistant strains.

B. Secondary prevention. Prophylaxis for preventing recurrences should **start as soon as RF or rheumatic heart disease is diagnosed**, as recurrences can sometimes be asymptomatic.

1. Penicillin in doses of 600,000 IU (patient's weight < 27 kg) to 1.2 million IU (patient's weight > 27 kg) every 4 weeks is the recommended regimen in most circumstances. The interval is reduced to 3 weeks for individuals at high risk for developing acute RF or living in endemic areas.

2. The duration of prophylaxis depends on the individual situation. Table 20.4 provides additional information.

a. Prophylaxis for **recurrent RF in patients without cardiac manifestations** should be continued for 5 years after the last RF attack or up to the age of 18 years, whichever is longer.

b. For **patients with RF and carditis but no residual valvular disease**, prophylaxis should extend for a period of 10 years or till age 25 whichever is longer.

c. Indefinite antibiotic prophylaxis is recommended in **patients with severe valvular heart disease.**

3. The success of **oral prophylaxis** depends on the patient's understanding and adherence to the prescribed regimen. Oral agents are **more appropriate for patients at lower risk for rheumatic recurrences**. Some favor switching patients to oral prophylaxis when they have reached late adolescence or young adulthood and have remained free of rheumatic attacks for at least 5 years.

a. The preferred oral medication is penicillin V.

b. For **patients with true or suspected allergy to penicillin, sulfadiazine** can be used (Table 20.3). **Erythromycin** is an alternative.

c. It is important to keep in mind that even with optimal patient adherence, the **risk of recurrence is higher with an oral than with an IM prophylactic regimen**.

TABLE 20.4 Duration of Therapy for Secondary Prevention of Rheumatic Fever

Disease State	Duration of Therapy
RF + carditis + residual valvular disease	At least 10 y postepisode and at least until the age of 25 y. Lifelong p more severe valvular disease)
RF + carditis without valvular disease	10 y or at least till 25 y, whichever is longer
RF without carditis	5 y or until the age of 18 y, whichever is longer
RF after valve surgery	Lifelong

d. RF, rheumatic fever.

e. Data from Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1806–1818.

C. Endocarditis prophylaxis. Updated guidelines from the AHA published in 2007 recommend against routine prophylaxis for endocarditis in patients with rheumatic valvular disease undergoing dental or other procedures. Antibiotic prophylaxis is recommended only for patients with prosthetic valves, previous endocarditis, and certain forms of congenital heart disease and for heart transplant patients with vasculopathy (see Chapter 19).

D. Vaccines targeted against GAS. Several multivalent vaccines against GAS are currently in clinical trials. The M protein is the most promising target, but vaccine development has been complicated because there are multiple M-protein subtypes that are rheumatogenic. The use of a vaccine may prevent pharyngeal colonization, thereby removing population reservoirs, which allow for endemic disease.

VII. SCREENING

A. Screening in endemic areas. Given the significant burden of rheumatic heart disease, screening children and young adults has proven useful for those in endemic areas.

1. Screening generally involves three components: (1) eliciting a history of acute RF, (2) physical examination, and (3) echocardiography. Two screening approaches have been described in high-risk populations. First, physical examination including auscultation for murmur is followed by echocardiographic confirmation in those found to have a murmur. Alternatively, portable echocardiography is used for all followed by clinical examination of abnormal cases. Because auscultation has been shown to be clinician dependent and crude in detecting valve pathology, many cases of rheumatic heart disease go unidentified, favoring the echocardiographic approach to screening.

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CHAPTER 21

Tachyarrhythmias

Todd Senn

I. INTRODUCTION. Tachyarrhythmias have been classically categorized by their location and mechanism. Tachyarrhythmias can originate from ventricular tissue (ventricular tachycardia [VT]) or, alternatively, can originate from or involve supraventricular tissue (supraventricular tachycardia [SVT]). The three mechanisms of tachyarrhythmias include abnormal automaticity, triggered activity, and reentry.

A. Mechanisms

1. Abnormal automaticity. Automaticity refers to the ability of cardiac tissue to spontaneously generate pacemaker activity. There are both normal and abnormal sources of automaticity.

An example of **normal** accelerated automaticity is the rapid firing rates of a normal pacemaker focus, such as the sinus node (SN), atrioventricular (AV) node, or Purkinje system because of ischemia, metabolic disturbance, exercise, or pharmacologic manipulation. A clinical example would be accelerated **sinus tachycardia** or **junctional rhythm**.

Abnormal automaticity refers to tissues that under normal circumstances do not demonstrate automaticity, but can become automatic in the setting of ischemia, metabolic disturbance, or pharmacologic manipulation. Overall, abnormal automaticity is responsible for <10% of tachyarrhythmias. These latent or ectopic loci of cells generate automatic, spontaneous impulses that usurp control of the cardiac rhythm. These usually have a warm-up and cool-down period and cannot be induced by programmed electrical stimulation. A clinical example would be **accelerated idioventricular** rhythm (see Section **V.B.3.b**) or **multifocal atrial tachycardia** (see Section **II.E.3.c**).

2. Triggered activity refers to pacemaker activity that is dependent on afterdepolarizations from a prior impulse or series of impulses. Afterdepolarizations are oscillations in the membrane potential. If these reach the critical threshold for depolarization of the surrounding cardiac tissue, they may trigger an action potential, thereby precipitating further afterdepolarizations and perpetuating the pacemaker activity. The two categories of afterdepolarizations are **early** and **delayed**.

Early afterdepolarizations (EADs) occur before repolarization of the cardiac tissue is completed (during phase 3 of the action potential) and may be the mechanism responsible for the ventricular arrhythmias of the **long QT syndromes (LQTSs)**, as well as **torsade de pointes** ("twisting of the points") produced by class I and class III antiarrhythmics, sympathetic discharge, and hypoxia. Antibiotics such as macrolides, certain azole antifungal agents, some psychotropic medications such as haloperidol, and several nonsedating

antihistamines have been shown to produce EADs. Rapid heart rates and the administration of magnesium have been shown to suppress EADs.

Delayed afterdepolarizations (DADs) occur after the repolarization of the surrounding tissue is complete (during phase 4 of the action potential) and are thought to be the mechanism of triggered atrial tachycardia, arrhythmias of **digitalis toxicity**, and rare VTs responsive to calcium channel blockers. These have been demonstrated in various cardiac issues, including parts of the conducting system, myocardial cells, and valve tissues. Increases in intracellular calcium are associated with DADs, such as those caused by digitalis preparations or excessive sympathetic stimulation. Drugs that block the influx of calcium (such as calcium channel blockers and β-blockers) and drugs that decrease the sodium current (such as lidocaine and phenytoin) suppress the occurrence of DADs, whereas rapid heart rates augment DADs.

3. **Reentry. Reentry is the most common cause of tachyarrhythmias.** In order for reentry to occur, **three conditions** must be met:

- Two functionally distinct conducting pathways must connect to form a circuit.
- Unidirectional conduction block occurs in one of the pathways because of differences in refractory periods (block occurs in pathway with the longer refractory period).
- Slow conduction occurs down the unblocked pathway (which has the shorter refractory period), allowing the blocked pathway time to recover excitability and sustain the arrhythmia.

Reentrant circuits can occur in the SN, the atrium, the AV node, between the atrium and ventricle via bypass tracts, and within the ventricle itself. The typical substrate for malignant reentry in the ventricle is **scar or ischemia**, which can produce regions in the heart that **depolarize and repolarize heterogenously**. Therefore, the impulse can spread to an area that has already repolarized after being previously depolarized. This can set up a circular movement of the impulse resulting in sustained tachyarrhythmias such as VT. Reentry can typically be induced by premature electrical stimulation during electrophysiologic (EP) testing.

Elucidation of the mechanisms of tachyarrhythmias has led to the development of catheter-based treatment strategies and more advanced medical therapy.

II.SUPRAVENTRICULAR TACHYARRHYTHMIAS

A. Sinus tachycardia

1. **Clinical presentation.** Sinus tachycardia manifests as sinus rhythm with a rate above 100 beats/min. Although the rate may be as high as 200 beats/min in younger individuals, it is generally **150 beats/min or less in older individuals**.

2. **Pathophysiology.** The SN is an epicardial structure that is located laterally near the junction between the superior vena cava and the right atrium. Under normal circumstances, the rate of SN discharge is governed by sympathetic and vagal stimulation. Sinus tachycardia generally reflects **an underlying process, metabolic state, or effect of medication**. Fever, hypovolemia, shock, congestive heart failure (CHF), anxiety, pulmonary disease including pulmonary embolism, anemia, thyrotoxicosis, caffeine, nicotine, atropine, catecholamines, or withdrawal from alcohol or drugs (both therapeutic and illicit) can cause sinus tachycardia. Sinus tachycardia can be appropriate, where it represents a normal physiologic response, **or inappropriate**, as in defects in vagal or sympathetic tone or an intrinsic problem with the SN itself.

The **clinical consequences of sinus tachycardia vary** based on the presence or absence of underlying heart disease. Patients with significant coronary artery disease (CAD), left-ventricular (LV) dysfunction, or valve disease may not tolerate sinus tachycardia. Patients with inappropriate sinus tachycardia may experience significant symptoms such as palpitations, dyspnea, and/or chest pain.

3. **Diagnostic testing.** Electrocardiography is the primary diagnostic test. The main differential is between sinus tachycardia, sinus node reentry tachycardia (SNRT) (see Section **II.B**), and inappropriate sinus tachycardia. Inappropriate sinus tachycardia is characterized by the following features: **(a) heart rate > 100 beats/min, (b) P-wave axis and morphology during tachycardia similar or identical to that during sinus rhythm, (c) exclusion of secondary causes of sinus tachycardia, (d) exclusion of atrial tachycardias, and (e) symptoms clearly documented to be related to resting or easily provoked sinus tachycardia**.

Therapy is generally directed at the elimination of the underlying cause whenever possible. If withdrawal from a therapeutic medication is suspected, then reinstitution or slow tapering of this medication can be attempted, if clinically appropriate. In the case of **inappropriate sinus tachycardia, β-blockers and calcium channel blockers** may be necessary to control the heart rate. **Ivabradine,** a new agent that affects the I_f channel, can also be considered. In **medically refractory cases, catheter ablation for sinoatrial nodal modification** may be considered.

B. **SNRT** accounts for 2% to 5% of all supraventricular tachyarrhythmias.

1. **Clinical presentation.** SNRT is most frequently seen in patients with structural heart disease or CAD, especially in inferior myocardial infarctions (MIs). The rate varies from 80 to 200 beats/min. SNRT's characteristic abrupt onset and termination (paroxysmal nature) along with its ability to be induced and terminated by pacing imply that the underlying mechanism is reentry and distinguish it from sinus tachycardia and inappropriate sinus tachycardia.

2. **Pathophysiology.** Reentry occurs within or adjacent to the SN and then conducts via the normal conduction pathway to the rest of the heart. The morphology of the P-wave is identical to the underlying sinus morphology. Block at the AV node may occur, but it does not slow the tachycardia. In fact, a Wenckebach-type block often occurs with this rhythm. The development of a bundle branch block does not affect the cycle length or the PR interval.

3. **Therapy.** Vagal maneuvers or adenosine may successfully terminate this arrhythmia. **Rapid atrial pacing** can be used to induce and terminate this tachycardia. Various agents such as β-blockers, calcium channel blockers, digoxin, or amiodarone may help prevent recurrences. SN ablation or modification is rarely necessary.

C. **Atrial fibrillation** (AF) is the most common sustained arrhythmia, occurring in up to 1% of the general population. The prevalence of AF increases with age, affecting up to 10% of the population older than 80 years (see Chapter 24).

D. **Atrial flutter.** Atrial flutter is the **second most common of the atrial tachyarrhythmias**. Its reported incidence varies from 0.4% to 1.2% in hospital reports of electrocardiogram (ECG). The **clinical significance of atrial flutter is generally due to its association with AF** (with all of the attendant risks of AF) and/or its association with rapid rates of ventricular response.

1. **Clinical presentation.** The clinical presentation may vary widely depending on the presence of underlying heart disease, the ventricular rate, and the overall condition of the patient. It is **occasionally reported to persist for days** and, less commonly, for weeks or longer. Careful examination of the jugular venous pulse may reveal **frequent, regular a-waves** that correspond to the atrial flutter rate. Like AF, it is **commonly seen after open heart surgery, as well as with other conditions commonly associated with AF**, such as pulmonary disease, thyrotoxicosis, atrial enlargement because of any cause including mitral/tricuspid valve disease, and SN dysfunction.
2. **Pathophysiology.** "Typical" atrial flutter is the **result of a macroreentrant circuit in the right atrium**. Atypical atrial flutter generally involves other macroreentrant circuits around scar tissue or surgical incisions.
In typical atrial flutter, the reentrant circuit most commonly travels in a counterclockwise rotation down the right atrial anterolateral free wall across the cavotricuspid isthmus (area of slow conduction) and up the interatrial septum. Clockwise rotation of this circuit may also be seen.

Atrial flutter has been classified into type I and type II based on the following characteristics:

Type I atrial flutter can be terminated with rapid atrial pacing and typically has an atrial rate in the range of 240 to 340 beats/min in the absence of drug therapy.

Type II atrial flutter cannot be terminated with rapid atrial pacing and typically has an atrial rate in the range of 340 to 440 beats/min in the absence of drug therapy.

Types I and II are not synonymous with typical and atypical atrial flutters. Type I atrial flutter can include typical and atypical atrial flutters. Type II atrial flutter is less well characterized than type I with respect to etiology and therapy; therefore, **we refer to type I atrial flutter throughout this discussion**.

3. **Laboratory examination.** The **diagnosis can be difficult when the AV conduction is 2:1**, because the flutter waves may be superimposed on the QRS complex and/or the T-waves. When the diagnosis is uncertain, one should **consider maneuvers or medications to slow the ventricular response**, thus revealing the atrial flutter complexes.
Vagal maneuvers include carotid sinus massage and Valsalva maneuver. **Caution must be exercised** when attempting carotid sinus massage **in patients with known or suspected carotid disease** or vagal maneuvers in **patients with CAD who are at risk for ischemia**.

Agents for rate control include the intravenous calcium channel blocking agents **verapamil and diltiazem** and the intravenous β-blockers **esmolol and metoprolol**. **Adenosine** can be administered if the diagnosis is in question: 6 mg rapid intravenous push, followed by 12 mg if there is no response (a second 12-mg dose can be given if there is no response). The half-life of this medication is very short, approximately 9 seconds. This causes transient (lasting seconds), complete AV block. Patients should be connected to a transcutaneous pacing device during the administration of this medication for reasons of safety. The clinician can also record from a **temporary atrial epicardial pacing wire** (placed at open heart surgery). This results in an ECG with clearer atrial complexes and thus simplifies diagnosis. This strategy also allows a method of delivering rapid atrial pacing in an attempt to terminate the atrial flutter.

On the surface ECG, typical counterclockwise atrial flutter shows the **classic negatively directed "sawtooth" waveform** in the inferior leads (II, III, and aVF) (Fig. 21.1). Conversely, the atrial depolarizations are positive in these leads in clockwise atrial flutter (Fig. 21.2).

The **atrial rate** in the absence of drug therapy is **240 to 340 beats/min**. The **QRS complex should be the same as that seen during sinus rhythm** although aberrant conduction may occur, and the QRS may be slightly distorted by the atrial flutter waves. The **ventricular response** can be irregularly irregular, because of varying degrees of block (2:1, 4:1, and so on), but is more **typically regular as a fixed ratio of the flutter rate**.

4. **Therapy.** Medical therapy differs very little from that for AF (see Chapter 24). Control of the ventricular response rate with a β-blocker, a calcium channel blocker, or digoxin is critical prior to initiating therapy with agents such as the class IA or IC agents. The class IA or IC agents may either enhance AV nodal conduction through their vagolytic effects, thereby enabling 1:1 (AV) conduction, or slow the atrial rate to a point where 1:1 conduction is facilitated. The conversion from atrial flutter to AF after cardioversion is substantially reduced by the administration of antiarrhythmic drugs prior to direct current cardioversion (DCC), thereby increasing the chance of converting to sinus rhythm.

FIGURE 21.1 "Typical" atrial flutter, leads II and III. **FIGURE 21.2** "Atypical" atrial flutter, lead II.

a. **Anticoagulation.** There are no prospective data looking at the incidence of thromboembolic events with atrial flutter. However, retrospective data suggest an increased incidence of thromboembolic events. The American College of Cardiology/American Heart Association/Heart Rhythm Society 2014 guidelines recommend managing anticoagulation in atrial flutter in a manner similar to that for AF, including cardioversions. Optimal management needs to be individualized with the patients' profile for thromboembolic risk, dictating the type and duration of therapy using the CHA_2DS_2-VASc score. There is also recent evidence to support the use of the novel anticoagulants for use as anticoagulation and their safety for use in DCC.

b. **Direct current cardioversion.** DCC is the preferred and most effective therapy for most patients. A starting energy as low as 25 to 50 J is often effective. Because DCC may result in conversion from atrial flutter to AF, a second shock is sometimes necessary to convert AF to sinus rhythm. Rapid atrial pacing should be considered as the **first line of therapy for all patients who have epicardial atrial pacing wires in place after open heart surgery**. It may be considered via a transesophageal pacing lead or via a transvenously placed pacing lead in patients for whom DCC fails or who are not candidates for DCC. **Before attempting to rapidly pace the atria, one should confirm absence of ventricular capture** by first pacing at a relatively slow rate while observing for such a phenomenon. Once this is confirmed, the atrium is paced at a rate of 10 to 20 beats/min faster than the underlying atrial flutter rate. Once atrial capture is attained, the rate is increased steadily until the hallmark negative-sawtooth waveform converts to a positive waveform. The pacing is then either halted abruptly or slowed rapidly to an acceptable atrial pacing rate. In cases that require extremely rapid rates of pacing (>400 beats/min) or high amplitudes of pacing stimulus strength (>20 mA), there is an increased tendency for the atrial flutter to convert to AF. **When pacing via a transesophageal lead, a higher stimulus strength (up to 30 mA) may be necessary. Because this type of pacing can**

be quite painful, a sufficient energy to convert the atrial flutter should be used initially to minimize the conversion attempts.

c. **Percutaneous therapy**. Radiofrequency ablation (RFA) of the cavotricuspid isthmus is often curative, with an efficacy >90% for the long-term elimination of atrial flutter. Despite the high success rate of catheter-based therapy, a significant number of patients may subsequently develop AF (>80% at 5 years).

Atrial tachycardias. This term encompasses a number of different types of tachycardias that originate in the atria. These tachycardias account for between 10% and 15% of the tachycardias seen in older patients, usually in the setting of structural or ischemic heart disease, chronic obstructive pulmonary disease, electrolyte imbalances, or drug toxicity (particularly digitalis).

Clinical presentation. These tachycardias are **infrequently seen in younger, healthy patients without underlying heart disease**. They are **typically paroxysmal**, but if incessant, they can lead to a tachycardia-induced cardiomyopathy.

Diagnostic testing

. **ECG.** The **P-wave axis** or morphology is usually different from that of sinus rhythm. One exception is atrial tachycardias originating from the right superior pulmonary vein, which is anatomically close to SN. The axis can be used to predict the origin of the atrial tachycardia. Atrial rhythm is regular, except with automatic atrial tachycardia, which displays a warm-up period (see Section **II.E.3.a**). A **QRS complex that is generally identical to sinus rhythm** (QRS can be wide if aberrant conduction occurs) follows each P-wave. PR interval is within normal limits or prolonged. Nonspecific ST-T–wave changes may be present. When an AV block is present, there is an **isoelectric baseline** between P-waves in all leads. EP study has become critical in determining the underlying mechanism of these tachycardias, because the clinical differences are subtle and overlapping.

Subclassifications. The current subclassifications are **based on mechanisms** and include automatic atrial tachycardia, triggered atrial tachycardia, and intra-atrial reentry.

Intra-atrial reentry is usually a disorder **seen in those with underlying heart disease or history of atrial arrhythmia**, such as AF or atrial flutter. The mechanism is not well understood. The ventricular rate is typically 90 to 120 beats/min because of the frequent occurrence of 2:1 AV block, such that hemodynamic effects are generally minimal. This rhythm can be difficult to distinguish from other supraventricular tachyarrhythmias. One clue is that despite any AV conduction block, the rhythm continues. The ability to terminate with adenosine and β-blockers is variable. **RFA may be effective**, with success rates >75%. **Antiarrhythmics** (the same drugs as for AF and atrial flutter) **have been disappointing in the prevention of recurrence**.

. **Automatic atrial tachycardia** appears to be generated by an ectopic atrial focus, which usually arises from regions around the crista terminalis in the right atrium and around the base of the pulmonary veins in the left atrium. The mechanism is not well understood. Automatic atrial tachycardia is **seen more often in younger patients**, displays a **warm-up phenomenon** (the supraventricular tachyarrhythmia accelerates after its initiation), **does not respond to vagal maneuvers, and is more likely to be incessant**. Automatic atrial tachycardia can be induced with treadmill testing or with administration of isoproterenol. Atrial stimulation during EP has no effect on either initiating or terminating this arrhythmia. **Propranolol** has been used successfully to suppress automatic atrial tachycardia. **Catheter ablation is the preferred therapy when the**

tachycardia is incessant or associated with a cardiomyopathy. Although adenosine may transiently slow automatic atrial tachycardia, it is unlikely to terminate it. Likewise, verapamil has been used without success.

a. Triggered atrial tachycardia is the least common of the atrial tachycardias and is virtually never incessant. It is more likely to appear in **older individuals**. It can be induced with rapid atrial pacing and is cycle length–dependent. The mechanism of triggered atrial tachycardia is thought to be due to DADs (see Section **I.A.2**) secondary to digitalis toxicity or sympathetic discharge. Catecholamines may play a role in the initiation of this arrhythmia, and thus exercise testing and isoproterenol may provoke it. Verapamil and adenosine have been shown to terminate triggered atrial tachycardia. β-Blockers have been less effective. **RFA** is preferred when the tachycardia is very symptomatic and not responsive to medication.

b. Multifocal atrial tachycardia

1. **(1) Clinical presentation.** This atrial arrhythmia is uncommon and estimated to occur in 0.37% of hospitalized patients. The atrial rate is generally 100 to 130 beats/min. It occurs most often in elderly, critically ill patients and is frequently **associated with concurrent pulmonary disease, particularly chronic obstructive pulmonary disease**. It may also be seen in CHF and can degenerate into AF.
2. **(2) Pathogenesis and diagnostic tests.** The mechanism appears to be abnormal automaticity or triggered activity arising from distinct atrial sites. The diagnosis requires the following criteria: (1) atrial rate > 100 beats/min, (2) P-waves with three or more different morphologies, (3) varying P–P, P–R, and R–R intervals, and (4) the P-waves separated by isoelectric intervals. Loss of AV conduction of each P-wave is uncommon, making it possible to distinguish multifocal atrial tachycardia from AF.

Therapy is directed at the underlying illness, with little role for antiarrhythmics. Calcium channel blockers in high doses may be useful, or amiodarone when antiarrhythmic therapy is deemed necessary. Maintenance of electrolyte balance, particularly potassium and magnesium, may suppress the occurrence of multifocal atrial tachycardia.

c. Atrioventricular nodal reentrant tachycardia (AVNRT)

1. **(1) Clinical presentation.** AVNRT usually has a narrow QRS complex with a ventricular rate typically in the range of 150 to 250 beats/min, although faster rates are infrequently observed. AVNRT is generally seen in patients without underlying heart disease. Palpitations and dyspnea are common presenting complaints. Angina, CHF, and rarely shock may be seen in those with a history of underlying heart disease. Syncope may occur due to rapid ventricular rates or due to a prolonged pause or bradycardia seen occasionally when this tachycardia terminates.
2. **(2) Pathophysiology.** The mechanism in AVNRT is a reentrant circuit composed of separate fast and slow atrial pathways involving the AV node. In 50% to 90% of patients with **"typical" AVNRT**, the antegrade conduction to the ventricles travels over the slow pathway and the retrograde conduction to the atria occurs over the fast pathway. The initiating event may be either a premature atrial complex (PAC) or a premature ventricular complex (PVC). The PAC blocks the fast pathway antegradely and conducts down the slow pathway, then backs up the fast pathway after it has repolarized. Less commonly, a PVC conducts retrogradely to the atria via the fast pathway and then returns to the ventricles via the slow pathway. In the remaining 5% to 10% of patients, **with atypical AVNRT**, the antegrade conduction is down the fast pathway and retrograde via the slow pathway. The cycle length is thus dependent on the conduction velocity of the slow pathway, because the fast pathway generally has rapid conduction. Termination of the tachycardia is often the result of a block in the slow pathway. AV dissociation may develop during the

tachycardia because the ventricles are not involved in the reentry circuit. This does not affect the rate of tachycardia nor does the development of bundle branch block.

3. **(3) Laboratory features and diagnosis.** P-waves are generally hidden within the QRS complex or at the terminal portion of the QRS in typical AVNRT. This may be visible as a small pseudo-R′ in lead V_1 or small negative deflections in the inferior leads, as depolarization of the atria occurs simultaneously with ventricular depolarization. The RP segment is generally <100 ms. AVNRT is often induced abruptly by a PAC, and its termination, which also tends to be abrupt, is often followed by a retrograde P-wave. The termination may be followed by a brief period of asystole or bradycardia before the SN recovers from its tachycardia-induced suppression. The cycle length may vary, especially at the beginning and at the end of the tachycardia. This variation reflects the variable antegrade AV nodal conduction time. Vagal maneuvers may slow or terminate this tachycardia.

4. **(4) Therapy.** Presently, the success and safety of percutaneous catheter ablation have allowed this approach to be considered equally with medical therapy as first-line therapy for long-term management of AVNRT. The decision about treatment approach should be individualized according to the characteristics of each patient and his or her arrhythmic patterns.

RFA has the advantage of curing the arrhythmia in the majority of instances and eliminating the need for long-term suppressive therapy with medications. Cure rates with catheter ablation for AVNRT are in excess of 95%.

Medical therapy. Medications that suppress AV nodal conduction such as β-blockers, calcium channel blockers, digoxin, and adenosine all slow or block conduction in the antegrade slow pathway, whereas class IA and class IC antiarrhythmic drugs slow the conduction in the retrograde fast pathway. Adenosine may be considered as first-line drug therapy for acute termination of AVNRT. This medication is available in an intravenous form only and has a very short half-life of about 9 seconds. The use of intravenous or oral β-blockers or calcium channel blockers is an alternative if adenosine is unsuccessful. The onset of action of digoxin limits its usefulness in terminating these arrhythmias, although it may be useful to prevent recurrences. Recurrences may be prevented in patients with frequent sustained episodes with any of the above-mentioned agents except adenosine. Antiarrhythmic drug therapy is not routinely necessary or desirable for AVNRT, given the high success rates and low complication rates for catheter ablation. DCC should be considered for patients whose disease is unstable or highly symptomatic. Low energies of 10 to 50 J are usually sufficient to terminate AVNRT.

d. Atrioventricular reentrant tachycardia (AVRT)

1. **(1) Clinical presentation.** Similar to AVNRT, this is another example of an AV nodal–dependent SVT. AVRT usually has a narrow QRS with ventricular rates similar to those of AVNRT, although it more often tends to have a ventricular rate >200 beats/min. The clinical features are very similar to those of AVNRT but are distinct on an EP basis.

2. **(2) Pathophysiology.** The mechanism in AVRT relies on the presence of an accessory pathway as one portion of the circuit and the AV node as the other portion. The atrium and the ventricle on the same side as the accessory pathway are necessary components of the circuit. AVRT may be orthodromic or antidromic. Orthodromic AVRT usually has a narrow complex that uses the AV node as the antegrade limb and the accessory pathway as the retrograde limb of the circuit. Antidromic AVRT has a wide complex that is the opposite of the orthodromic variety, such that the accessory pathway serves as the antegrade limb and the AV node as the retrograde limb of the circuit. AVRT is most often of the orthodromic type. Accessory pathways may be “concealed” (inapparent by ECG) because of having only retrograde (V to A) conduction properties or

"manifest" (apparent on ECG as delta waves, i.e., Wolff–Parkinson–White [WPW] pattern). **Unlike AVNRT, the AVRT circuit must involve one of the ventricles; therefore, the development of bundle branch block on the side ipsilateral to the accessory pathway can prolong the ventricular to atrial conduction time and often the cycle length of the tachycardia.** Bundle branch block, particularly left bundle branch block (LBBB), occurs more commonly in AVRT than in AVNRT. AVRT can be distinguished from AVNRT by EP study. The presence of AV or ventriculoatrial (VA) block with continuation of the tachycardia should exclude the presence of an accessory AV pathway.

3. **(3) Laboratory features and diagnosis.** The P-waves of AVRT are frequently inscribed on the ST-segment or T-wave, because the atrial depolarization and ventricular depolarization are in series rather than in parallel. The RP segment is generally >100 ms. Orthodromic AVRT is more common, accounting for about 95% of all AVRTs, whereas antidromic AVRT accounts for only about 5%. Orthodromic AVRT is usually characterized by a narrow QRS complex as opposed to antidromic AVRT, which is characterized by a wide QRS complex.
4. **(4) Therapy.** See the discussion of therapy for WPW syndrome.

PREEXCITATION SYNDROMES. Preexcitation was originally used to describe the premature activation of ventricle in patients with WPW. The term has broadened to include all conditions in which antegrade ventricular activation or retrograde atrial activation occurs partially or totally via an anomalous pathway distinct from the normal cardiac conduction system. The incidence of preexcitation on ECG is approximately 1.5 per 1,000 cases, most of which occur in otherwise healthy subjects without organic heart disease. About 7% to 10% of these patients have associated **Ebstein anomaly and are thus more likely to have multiple accessory pathways**. There is a higher rate of preexcitation in males, with the **prevalence** decreasing with age, although the **frequency** of paroxysmal tachycardia increases with age.

Clinical presentation. Approximately 50% to 60% of patients with preexcitation report symptoms such as **palpitations, anxiety, dyspnea, chest pain or tightness, and syncope**. In approximately 25% of the cases, the disease will become asymptomatic over time. Those patients older than 40 years whose disease has been asymptomatic are likely to remain symptom free. The absence of preexcitation on ECG despite the discovery of accessory pathways in patients with asymptomatic disease likely identifies a group of patients at low risk for developing symptoms.

Pathophysiology. Patients with preexcitation generally have an accessory pathway(s) that alters the conduction between the atria and the ventricles. These accessory pathways are likely congenital, because relatives of subjects with preexcitation have an increased incidence of preexcitation. AVRT is the most common mechanism associated with preexcitation (80% to 85%), with permanent junctional reciprocating tachycardia, Mahaim fiber tachycardia, and Lown–Ganong–Levine (LGL) syndrome accounting for the remainder.

WPW syndrome. The basic abnormality lies in the existence of an accessory pathway of conducting tissue, outside of the normal conducting system, which connects the atria and the ventricles. This accessory pathway permits the atrial impulse to bypass the normal pathway through the AV node to the ventricles. In the past, these accessory pathways have been referred to as "bundles of Kent." An impulse from the atria can be conducted down both the accessory pathway and the AV node, arriving at the ventricle at nearly the same

time. This results in preexcitation of the ventricle, which is really a fusion beat, as a portion of the ventricle is activated via the accessory pathway (giving rise to the delta wave; Fig. 21.3) and the remainder of the ventricle is activated by the normal activation pathway. If antegrade conduction occurs exclusively via the accessory pathway, the resultant QRS is maximally preexcited and is a wide complex. These accessory pathways may conduct rapidly, but frequently have longer refractory periods than the AV node. The inciting event for AVRT is frequently a PAC that is blocked in the accessory pathway and that conducts to the ventricles via the AV node, which has recovered more rapidly. The resultant QRS complex in this instance is normal in appearance. After the QRS complex, the accessory pathway has had sufficient time to recover excitability, and the impulse thus conducts retrogradely to the atria. A small but significant percentage (5% to 10%) of patients have multiple accessory pathways.

Permanent junctional reciprocating tachycardia is a variant of AVRT. It is often an incessant supraventricular tachyarrhythmia with an unusual accessory pathway. Here, the accessory pathway behaves like the AV node in that it displays decremental retrograde conduction properties. Thus, the faster the stimulation of such an accessory pathway, the slower the conduction through the pathway. The accessory pathway is most often located in the posteroseptal region and acts as the retrograde limb of the reentrant circuit. The VA conduction is slowed by the decremental nature of the accessory pathway. Because of the incessant nature of this tachycardia, a tachycardia-induced cardiomyopathy may result and ablation is the therapy of choice when this occurs.

Mahaim fiber tachycardias are another variant of reentrant tachycardia. The two most common varieties that are recognized are **atriofascicular and fasciculoventricular**. In the former, the accessory pathway is located within the right atrium and inserts into the right bundle branch. The reentrant tachycardia conducts antegrade via the accessory pathway, resulting in a typical LBBB morphology with left-axis deviation. The retrograde circuit is via the AV node. In the second form of Mahaim reentry, the accessory pathway arises in the His-Purkinje fibers and allows bypass of the distal conducting system. This second type is not associated with a clinical tachycardia syndrome and further therapy is not needed.

LGL syndrome is diagnosed by the presence of a short PR interval and a normal QRS complex on the surface ECG. LGL syndrome likely represents one end (enhanced) of the normal spectrum of AV nodal conduction properties, but in some cases it is impossible to exclude a distinct perinodal accessory pathway or an abnormality in conduction characteristics of the AV node. It is uncertain if this abnormality in AV conduction is itself associated with arrhythmias.

FIGURE 21.3 Wolff–Parkinson–White syndrome, with widespread delta waves seen at the upstroke of the QRS complexes.

Diagnostic testing

EKG. The following electrocardiographic criteria are suggestive of an accessory pathway consistent with a WPW pattern. **The WPW syndrome occurs in the setting of the WPW pattern and SVT.**

The ***PR interval is short, typically <120 ms***.

The QRS complex exceeds 120 ms, with some leads showing the characteristic slurred upstroke known as a delta wave (Fig. 21.3) and a normal terminal QRS portion.

The ST-T–segment is directed opposite to the major delta and QRS vectors. The most commonly seen tachycardia in WPW syndrome is characterized by a normal QRS with a regular rate of 150 to 250 beats/min. Onset and termination are abrupt.

Localization of accessory pathway. The **surface ECG** may provide information that allows localization of the accessory pathway. Using the initial 20 ms of the delta wave in leads I, II, aVF, and V_1 [classified as positive (+), negative (–), or isoelectric (±)] and the ratio of R- and S-wave amplitudes in leads III and V_1 (classified as $R \geq S$ or $R < S$) is used in the **Arruda criteria**. Step 1 uses leads I and V_1. If lead I is isoelectric or negative or if $R > S$ in lead V_1, it is a left-sided pathway. Using aVF will then help determine if the pathway is anterolateral, lateral, or posterior. Step 2 uses lead II. If lead II is negative, the pathway is located in a branch of the coronary sinus. Step 3 uses lead V_1. If V_1 is isoelectric or negative, the pathway is septal. Again using lead aVF and QRS vector will help determine if the pathway is anterior, middle, or posteroseptal. Step 4 locates all others on the right side. Leads aVF and II will then help to differentiate anterior, lateral, or posterior locations. The **most precise localization method is EP study** with ventricular pacing or during orthodromic AVRT (the latter condition is especially helpful because there is VA conduction purely through the accessory pathway, and fusion with VA conduction through the AV node is, therefore, avoided).

Risk stratification should be considered for patients with WPW pattern or ventricular preexcitation according to ECG findings. The appearance or disappearance of preexcitation on **serial ECGs is of no predictive value**. However, **the intermittent loss or appearance of preexcitation on a beat-to-beat basis is indicative of lower risk**. This may be assessed with ambulatory Holter monitoring during usual activities or with formal exercise stress testing. Such intermittent preexcitation suggests a pathway without the ability for rapid AV conduction and, therefore, lower risk of sudden cardiac death (SCD). However, the reverse is not necessarily true in that most patients with persistent preexcitation may still be at low risk for SCD, but these patients cannot be distinguished from those at risk. Because the greatest danger to patients with preexcitation may be the development of AF, **the induction of AF may be most useful in risk stratification**. This can be done via transesophageal pacing; however, EP study is the procedure of choice for risk stratification in patients with persistent ventricular preexcitation.

Therapy

. **Emergency management of acute tachycardia episodes.** A patient ***demonstrating hemodynamic instability or extreme symptomatology should be cardioverted rapidly***. Stable patients may be treated medically.

a. **Normal QRS width.** Both types of AVRT (orthodromic and antidromic) are AV node–dependent and thus respond to AV nodal blocking therapies. Although it is reasonable to use vagal maneuvers and AV nodal blocking medications acutely in patients presenting with a narrow QRS (immediate synchronized DCC should be available should the rhythm degenerate), it is not safe in patients when they present with a wide QRS. Atrial pacing, either transvenous or transesophageal, is also quite efficacious for terminating these types of tachycardias. Adenosine, although effective in treating orthodromic and antidromic AVRTs, may induce AF in up to 15% of cases and should, therefore, be used with caution. In patients with WPW syndrome, AF is a

potentially life-threatening arrhythmia, especially when the accessory pathway has a short antegrade refractory period capable of rapid ventricular conduction.

b. Wide QRS width. Patients with accessory pathways can present with wide QRS complex resulting from **(1)** orthodromic AVRT with aberrant conduction; **(2)** antidromic AVRT; or, **most importantly**, **(3)** atrial arrhythmias (atrial tachycardia/atrial flutter/AF) with antegrade conduction down an accessory pathway. Because it is often initially impossible to determine the mechanism of a wide QRS complex in patients with an accessory pathway, they should be treated with agents that slow conduction in the accessory pathways preferentially (procainamide). Because atrial arrhythmias with antegrade accessory pathway conduction are **not** AV node–dependent, AV nodal blocking therapies are ineffective and potentially very dangerous. **β-Blockers, calcium channel blockers, digoxin, and adenosine should be avoided in patients presenting with wide complex tachycardias (WCTs),** because they may encourage preferential conduction down accessory pathways and accelerate ventricular rates, precipitating ventricular fibrillation (VF). **If the tachycardia persists, synchronized DCC** is the treatment of choice. Energies of at least 200 J are likely to be required.

If the patient develops AF, it has been observed that **definitive therapy for the AV reentrant circuit, such as ablation of the accessory pathway, often results in the decrease or even prevention of future episodes of AF**.

Long-term management

. Priority of therapy. Patients whose disease is asymptomatic at diagnosis are at low risk for sudden death. As such, it may not be justified to pursue medical or ablative therapy in these patients unless there is a family history of sudden death or the patients are competitive athletes or are in a high-risk occupation. Patients whose disease is symptomatic or who have a history of AF or aborted sudden death may be at higher risk, and such patients warrant further study.

a. Medical therapy. Medical therapy may be **appropriate for those with increased risk but no prior symptoms, those with accessory pathways located near the normal conduction pathway that might develop AV block with RFA**, or those at increased risk from invasive procedures. Single-drug therapy may be attempted with **amiodarone, sotalol, flecainide, or propafenone**. These drugs work to slow conduction in both the accessory pathway and the AV node.

b. Combination therapy can be accomplished with drugs that work on the AV node (calcium channel blockers, β-blockers) and with drugs that work exclusively on the accessory pathway (class IA antiarrhythmics).

c. Percutaneous therapy. RFA is effective 85% to 98% of the time, depending on the location of the accessory pathway. Recurrence rates are approximately 5% to 8%. Catheter ablation should be considered for any patient at high risk, patients with symptoms or tachycardias refractory to medical therapy, those who have intolerance to medical therapy, and those with high-risk occupations such as pilots.

ATRIAL PREMATURE DEPOLARIZATIONS (APDs). APDs are premature depolarizations that arise from a region other than the SN. The P-wave morphology and PR interval may be different from the sinus P-wave and normal P interval, depending on the location and timing of the APD.

Clinical presentation. APDs are usually asymptomatic and in isolation are considered to be benign. Some patients may feel palpitations or skipped beats. If there is atrial bigeminy with each APD causing AV block, patients may develop symptoms of bradycardia. APDs

may trigger SVT (AVNRT, AVRT, and atrial tachycardia) or AF in patients with the electrical and structural substrate for these arrhythmias. APDs increase in frequency as patients age and may be more frequent in patients with mitral valve disease, LV dysfunction, hypertrophic cardiomyopathy (HCM), mitral stenosis, pulmonary disease, and renal failure. Stress, alcohol and caffeine consumption, and smoking can promote APDs. However, APDs also occur in healthy individuals with structurally normal hearts and without significant external exposures (caffeine, alcohol, and stress). Although one study showed a correlation between the frequency of APDs within a 24-hour period and the risk of stroke in men, it is unclear what percentage of these men developed AF. Furthermore, in the Atherosclerosis Risk in Communities (ARIC) study which followed patients with APDs and ventricular premature depolarizations (VPDs), only patients with APDs did not have increased incidence of SCD.

Pathophysiology. APDs may be caused by a variety of mechanisms, including reentry, triggered activity, and increased automaticity. Reentry is thought to be the most common mechanism.

Therapy. Asymptomatic individuals do not need treatment for APDs. For symptomatic patients, β-blockers and class IA, class IC, and class III antiarrhythmic drugs may be considered, although no randomized controlled trials have been performed in this patient population.

VENTRICULAR TACHYARRHYTHMIAS. Ventricular tachyarrhythmias, including monomorphic VT, polymorphic VT, and VF, account for up to 80% of SCD.

Ventricular tachycardia. VT is defined as three or more consecutive QRS complexes of ventricular origin at a rate exceeding 100 beats/min.

Clinical presentation. The presentation is variable and depends on the clinical setting, the heart rate, the presence of underlying heart disease, and other medical conditions. Some patients have no or minimal symptoms, whereas others may present with syncope or sudden death. The loss of normal AV synchrony may cause symptoms in patients with decreased cardiac function at baseline. Heart rates <150 beats/min can be surprisingly well tolerated in the short term, even in the most compromised individuals. Exposure to these rates for more than a few hours is likely to be associated with heart failure in patients with poor ventricular function, whereas those with normal ventricular function may tolerate prolonged periods at such rates. The range of 150 to 200 beats/min is tolerated variably, according to the factors noted previously. Once the rate reaches and exceeds 200 beats/min, there are symptoms in virtually all patients. **Nonsustained ventricular tachycardia** (NSVT) is generally defined as a VT of duration <30 seconds. VT is **generally regular in rate and appearance**, although it can be polymorphic in appearance, slightly irregular with respect to rate, and may have capture and/or fusion beats within it.

Differential diagnosis. VT needs to be distinguished from **supraventricular tachyarrhythmia with aberrant intraventricular conduction, bundle branch block, and morphologic changes of the QRS complex secondary to metabolic derangement or pacing**.

Brugada criteria. Distinguishing VT from **supraventricular tachyarrhythmia with aberrancy** can be challenging. Various criteria have been proposed. A good rule of thumb **is that any WCT in a patient with ischemic heart disease is VT until proven otherwise**. Some have reported that >80% of WCTs in such patients are VTs. The **algorithm proposed**

by Brugada may be helpful in making this distinction, and the algorithm is both sensitive (99%) **and specific** (96.5%) in patients without a preexisting bundle branch block. As shown in Figure 21.4, a stepwise approach is applied. In the first step, the precordial leads are examined for the presence or absence of an RS complex. If an RS is uniformly absent, VT is established. If an RS is present in at least one precordial lead, one moves to the second step, which is measuring the interval from the onset of the QRS complex to the nadir of the S-wave. If this distance is >100 ms in at least one precordial lead, then the diagnosis of VT is made. If there is no RS interval >100 ms, the third step is used. In the third step, one looks for evidence of AV dissociation. If there are more QRS complexes than P-waves, then the diagnosis is VT. If not, then one moves to the fourth step, which involves examining the morphology of the QRS in the precordial leads V_1 and V_6. If the morphology criteria for VT (Fig. 21.5) are present in these leads, then the diagnosis of VT is established. If not, the diagnosis is supraventricular tachyarrhythmia with aberrant intraventricular conduction.

The Brugada criteria have been further refined to distinguish between VT and supraventricular tachyarrhythmia with antegrade conduction over an accessory pathway. After applying the preceding criteria, a second stepwise algorithm is applied (Fig. 21.6). This **second algorithm has a sensitivity of 75% and a specificity of 100% to diagnose VT and exclude preexcited tachycardia**. In the first step, leads V_4 to V_6 are examined to see if the QRS is predominantly negative. If so, then VT is favored. If not, then the second step, examining leads V_2 to V_6 for the presence of a QR complex in one or more of these leads, is applied. If there is a QR complex in any of these leads, then the diagnosis is VT. The third criterion, presence of AV dissociation, is 100% specific for VT. If there is no AV dissociation, then supraventricular tachyarrhythmia with antegrade accessory pathway conduction is favored.

FIGURE 21.4 Brugada criteria for differentiating ventricular tachycardia from supraventricular tachycardia with aberrant intraventricular conduction. VT, ventricular tachycardia; SVT, supraventricular tachycardia. **FIGURE 21.5** Classic morphology criteria for ventricular tachycardia. AV, atrioventricular; LBBB, left bundle branch block; RBBB, right bundle branch block. **FIGURE 21.6** Brugada criteria for differentiating ventricular tachycardia from antidromic tachycardia over an accessory pathway. AV, atrioventricular; VT, ventricular tachycardia.

A new criterion for differentiating VT from SVT was published in 2008 by Vereckei et al., which boasts a >90% accuracy in their cohort (Fig. 21.7). The rationale to use the new method was to simplify the approach by using one electrocardiographic lead (aVR) in a four-step, tree-like model. The method starts with identifying the presence of an initial R-wave in aVR. If present, VT is diagnosed. If not, then the next step is to assess the presence of an initial R- or Q-wave >40 ms, and if present, VT is present. If this criterion is not satisfied, then the presence of a notch on the descending limb of a negative onset and predominantly negative QRS gives the diagnosis of VT. If this is not present, then one should compare the voltage of the initial 40 ms (V_i) with the voltage of the terminal 40 ms (V_t) of the QRS complex. If $V_i/V_t \leq 1$, then it is VT. If none of these criteria are satisfied, then SVT is diagnosed.

Therapy

. **General management.** The treatment of VT may involve DCC, discontinuation of offending proarrhythmic drugs, specific antiarrhythmic therapy with drugs, correction of electrolyte imbalances, implantable devices, ablation, revascularization, and surgery. The appropriate selection of the preceding therapies is aided by the assessment of the patient, an understanding of the etiology and mechanism of the VT, knowledge of any exacerbating medical conditions contributing to the VT, and the risk-to-benefit ratio of the available therapies.

a. Priority of therapy. A patient who has no hemodynamic compromise can be treated medically, at least initially. As with most types of tachyarrhythmias, **the treatment of any unstable patient with VT is rapid DCC**. The treatment for pulseless VT is asynchronous DCC with a starting energy of 200 to 360 J. If the patient is conscious but has unstable vital signs or is extremely symptomatic, **synchronized DCC** is recommended. The most recent Advanced Cardiac Life Support guidelines (AHA) currently emphasize the delivery of high-quality cardiopulmonary resuscitation (CPR): effective chest compressions (at least 100/min and compression depth of 2 in.) with minimal interruptions, rescue breaths given over 1 second with visible chest rise while avoiding hyperventilation (30:2 ratio before an advanced airway and 10 asynchronous breaths/min after airway is secured), and a **single** shock to attempt to defibrillate pulseless VT patients followed by immediate continuation of CPR.

FIGURE 21.7 aVR criteria for diagnosing ventricular tachycardia. V_i, vertical excursion (mV) during initial (V_i) and terminal (V_t) 40 ms of the QRS complex. SVT, supraventricular tachycardia; VT, ventricular tachycardia.

b. Acute medical therapy. Intravenous amiodarone, lidocaine, procainamide, β-blockers, and other oral agents may be given initially depending on the clinical scenario. Amiodarone is the agent of choice for resistant VT causing repeated episodes and also for pulseless VT/cardiac arrest. Amiodarone and lidocaine are the preferred agents in patients with LV dysfunction (left-ventricular ejection fraction [LVEF] < 40%). Lidocaine is effective when VT is thought to be ischemic in nature. Procainamide is reasonable as the initial treatment in patients with stable monomorphic VT, because it more effectively provides early rate slowing and conversion than amiodarone. β-Blockers may be preferred for acute coronary syndrome.

Magnesium (2 g over 5 minutes) should be administered for torsades de pointes. Whenever possible, a **reversible cause for VT**should be sought. Elimination of **ischemia** and correction of **electrolyte abnormalities** are recommended. **Bradycardia** may cause frequent premature ventricular contractions or VT. Maneuvers including temporary pacing and agents that increase heart rate should be used. **Hypotension** should be promptly corrected. Therapy for CHF should be optimized with the agents known to promote survival in this disorder. **Offending agents** should be stopped whenever possible, and **antidotes** should be administered in the case of overdosage and poisoning.

c. Prevention and prophylactic treatment. All antiarrhythmic agents to date, except β-blockers, have not been shown in randomized clinical trials to be effective as the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of SCD. Since the Cardiac Arrhythmia Suppression Trial (CAST) data have become available, there has been a shift away from the use of class I agents and toward the **use of class III agents and β-blockers for prophylactic maintenance therapy** of VT. The development of **curative catheter-based therapies and surgical procedures** has somewhat reduced the role of antiarrhythmics in the prevention of recurrence, especially for VT occurring in normal hearts,

which has very high cure rates with catheter ablation. However, antiarrhythmic drug therapy remains the first-line treatment for VT, particularly for patients with cardiomyopathy. The greatest impact on survival in sudden death has been made by the **implantable cardioverter–defibrillator (ICD)**. Data from the Multicenter Unsustained Tachycardia Trial investigations have shown that **patients with CAD, an ejection fraction (EF) <40%, and NSVT who have inducible sustained VT on testing are at substantially increased risk** over those who do not have inducible VT.

d. Medical therapy. Although drug therapy continues to have a role in the prevention of VT and sudden death, this role has become more limited because there has been no decrease in mortality with the use of antiarrhythmic drugs. The Electrophysiologic Studies Versus Electrocardiographic Monitoring trial studied the efficacy of seven antiarrhythmics (imipramine, mexiletine, pirmenol, procainamide, propafenone, quinidine, and sotalol) in preventing the recurrence of sustained VT. Sotalol was seen to be the most effective, although even with sotalol, the recurrence rate was disappointing. The European Myocardial Infarct Amiodarone Trial and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) investigations were designed to study the effectiveness of empiric amiodarone for the prevention of VT after MI. Although both of these trials showed a decrease in arrhythmic deaths, no survival benefit was recorded.

e. Combination therapy. Drug therapy is becoming **an adjunct to ICD therapy** in this high-risk population. At present, fully half of those with ICDs remain on antiarrhythmic therapy. The rationale for this combined therapy includes preventing atrial tachyarrhythmias and reducing the frequency of VT and thus the frequency of ICD discharge.

Calcium channel blockers are used primarily in the management of supraventricular tachyarrhythmia. However, some of the idiopathic monomorphic VTs, (the VTs originating in the right ventricular outflow tract [RVOT]), fascicular VT, and the VTs of digitalis toxicity are responsive to calcium channel blocking agents such as verapamil and diltiazem (because of the underlying mechanism of calcium-dependent triggered activity). RFA is potentially curative for idiopathic VTs and should be considered despite effective termination with calcium channel blockers.

β-Blockers may be effective, particularly for outflow tract VT. Idiopathic left VT may respond to calcium channel blockers.

f. Percutaneous therapy

1. **(1) ICDs.** Two large trials comparing ICDs with amiodarone in high-risk patients with prior infarction, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Antiarrhythmics Versus Implantable Defibrillator (AVID) trial, have been completed. High risk implies either an EF of 35% or less or the presence of inducible sustained VT at EP study. Both trials showed a **decided advantage for ICDs**, with 30% to 50% reductions in mortality with ICDs. In fact, the AVID trial found no survival benefit from amiodarone, β-blockers, or any other antiarrhythmic agent. Newer ICDs often have antitachycardia pacing (ATP) capabilities, can recognize monomorphic ventricular rhythms with rates <200 beats/min, and can rapidly pace the ventricles to restore sinus rhythm, aborting the need for countershock. In the Primary Prevention Parameters Evaluation study which evaluated the effects of ICD programming in a patient population receiving ICDs for primary prevention, using ATP as first-line therapy for fast VT (≥182 and <250 beats/min), including a monitoring zone at 167 beats/min, and applying SVT versus VT discriminators for rates <200 beats/min helped in reducing shocks without negatively

affecting the mortality. Data from MADIT II have shown that in patients with a prior MI and an EF < 30%, the implantation of a defibrillator is associated with a significant improvement in survival. Data from the MADIT-RIT trial showed decreased inappropriate therapy and all-cause mortality with higher rate or longer detection intervals as compared with conventional programming in primary prevention patients. Programmed high-rate therapy (with a 2.5-second delay before the initiation of therapy at a heart rate of ≥200 beats/min) or delayed therapy (with a 60-second delay at 170 to 199 beats/min, a 12-second delay at 200 to 249 beats/min, and a 2.5-second delay at ≥250 beats/min) was associated with a decrease in the number of patients with a first occurrence of inappropriate ATP or shocks, and all-cause mortality, as compared with conventional programming (with a 2.5-second delay at 170 to 199 beats/min and a 1.0-second delay at ≥200 beats/min).

2. **(2) Catheter-based therapy.** RFA may be effective for reducing the incidence of VT. The success rate depends on the type of VT, with the highest success rates (>90%) in structurally normal hearts. VT associated with underlying cardiomyopathy has lower success rates with ablation, particularly those with arrhythmogenic right ventricular (RV) cardiomyopathy and ischemic cardiomyopathy. However, catheter ablation still remains an effective and feasible approach, even for these types of VTs. Presently, catheter ablation of VT does not obviate the need for an ICD in a patient with an indication for one. The role of ablation is to target the source in focal VT or the critical isthmus is reentrant VT. The VISTA trial compared targeted ablation (ablation of the critical isthmus of the reentrant circuit) versus a substrate-based ablation (ablation of all abnormal electrograms located within scar) in patients with ischemic cardiomyopathy and stable VT. The substrate-based approach resulted in fewer VT recurrences and less antiarrhythmic drug use at 1 year.

Diagnostic evaluation of a patient with VT. Once the diagnosis of VT has been established and the patient has been acutely managed with either DCC or medical therapy, further management depends on the underlying cardiac pathology. In broad terms, the substrate can be divided into two categories: the structurally normal heart and the structurally abnormal heart. Various modalities are available to determine the cardiac structure and function, which include electrocardiography, cardiac catheterization, echocardiography, nuclear imaging, and magnetic resonance imaging.

VT in a structurally normal heart. About 10% of VT in the United States occurs in structurally normal hearts, the so-called idiopathic VT. These patients have no significant CAD, no family history of arrhythmia or sudden death, and normal surface ECGs. They can be **focal VTs or reentry VTs**. Focal VTs are a result of triggered activity, abnormal automaticity, or reentry within the Purkinje fibers.

. **Focal VT**

1. **(1) Mechanism.** Focal VTs most commonly arise from the RVOT and account for up to 70% of idiopathic VTs. They may be caused by cyclic adenosine monophosphate (cAMP)-mediated EADs. Of particular importance in the diagnosis of a patient who presents with LBBB VT is to be cognizant of the possibility of arrhythmogenic right ventricular dysplasia (ARVD), which falls into the category of VT/PVCs in the structurally abnormal heart. The clinician should investigate for RV structural abnormalities (fatty infiltration), ask about a family history of ARVD, and review the electrogram for the presence of T-wave inversion across the right precordial leads, and/or epsilon waves (Fig. 21.10). A cardiac magnetic resonance imaging or cardiac positron emission tomography scan may also be useful to rule out the presence of cardiac sarcoidosis, which also would fall into the category of the structurally abnormal heart.

2. **(2) ECG.** The surface ECG usually demonstrates an LBBB and inferior axis with very positive QRS voltage in inferior leads. Other locations of focal VTs may include the LV outflow tract, aortic cusps, pulmonary artery, mitral and tricuspid annuli, papillary muscles, and epicardium.
3. **(3) Treatment.** In general focal VTs are benign, carrying a very low risk of SCD. Therefore, the treatment is predominantly guided by symptoms. Given the role of cAMP in inducing this form of VT, adenosine may be effective at acute termination. For longer term therapy in the symptomatic patient, β-blockers are typically the first-line agents and can be effective in up to 50% of patients. The nondihydropyridine calcium channel blockers may also be effective in 25% to 50% of patients. Very effective medications are sotalol and amiodarone, with up to 90% success rate in eliminating symptoms, but potential side effects may limit their use. Patients who wish to potentially avoid lifelong medications or who are refractory to medical therapy can be considered for ablation, which has variable success rate depending on the location. RVOT VT ablation success rate may be as high as 90%. Ablation procedures, although generally safe, may be associated with infrequent but life-threatening complications, including cardiac perforation and tamponade.

a. **Fascicular VTs.** Fascicular VT involves reentry using the tissue of the LV septum as the antegrade limb and usually the posterior fascicle in the retrograde limb.

1. **(1) ECG.** This typically produced a right bundle branch block (RBBB) with left-axis deviation pattern. Less commonly, the QRS pattern is an RBBB with right-axis deviation (left anterior fascicular VT).
2. **(2) Treatment.** This subtype of VT may be verapamil-sensitive, but catheter ablation can be considered in patients who want to avoid long-term medication or in whom medical therapy is ineffective.

VT/VF associated with channelopathies. Various cardiac ion channel disturbances can predispose to ventricular arrhythmias. Patients with these channelopathies have no overt structural heart disease. They are genetically heterogeneous and have variable penetrance. They include LQTS, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic VT.

. **Long QT syndrome**

1. **(1) Pathology and presentation.** This channelopathy is characterized by prolonged cellular repolarization resulting in an increase of the QT interval. Clinical presentation includes syncope or sudden death as a result of torsade de pointes, and usually an autosomal dominant transmission pattern.

Whereas at least 12 mutations have been identified, the most common subtypes of LQTS are LQT1, LQT2, and LQT3, which are characterized by mutations in the I_{Ks}, I_{Kr}, and I_{Na} channels, respectively. Interestingly, a minority of patients with the genetic mutation may actually have "normal" QT intervals. LQT1 and LQT2 mutations result in decreased outward potassium current, whereas LQT3 mutation results in increased inward sodium current, both of which result in prolonged cellular repolarization. The Jervell and Lange-Nielsen syndrome, a clinical syndrome with a constellation of a prolonged QT and sensorineural deafness, is transmitted in an autosomal recessive pattern, and thus far has been localized to the LQT1 or LQT5 mutations.

LQT1 patients typically have broad-based T-waves and exercise-induced arrhythmias, especially during swimming. LQT2 syndrome is characterized by low-amplitude or notched T-waves and auditory triggers such as sudden loud sounds like alarm clocks or strong emotion, and LQT3 is characterized by a long isoelectric ST-segment and arrhythmias during sleep.

2. **(2) Treatment.** In patients with LQTS, risk stratification involves assessment of age, gender, clinical history, and possibly the QT interval and genetic mutation. Whereas β-blockers have a

variable efficacy depending on the type of LQT mutation, typically high doses of propranolol or nadolol are used to prevent clinical symptoms. β-Blockers are recommended as first-line therapy for all LQTS patients. For the LQT3 patients, there may be a role for sodium channel blockers (flecainide) as add-on therapy if the QTc is >500 ms and acute dosing results in a >40 ms shortening of the QTc. Patients should be advised against high-intensity sports and should be educated regarding avoidance of QT-prolonging drugs. Patient with syncope despite β-blocker therapy or history of aborted sudden death should undergo ICD implantation. Left cardiac sympathetic denervation can be used as an adjunctive therapy to reduce recurrence of arrhythmias.

a. Short QT syndrome. This syndrome is characterized by gain-of-function mutations in the I_{Ks}, I_{Kr}, and I_{K1} potassium channels or CACNA1 and CACNB2 L-type calcium channel mutations. ICD therapy is the primary treatment modality (class I) in patients with aborted SCD or VT. However, particular attention needs to be given to the prevention of inappropriate shocks, because patients may have T-wave oversensing (tall T-waves) and a high incidence of AF. Quinidine can be considered (class IIb) in asymptomatic patients with a family history of SCD.

b. Brugada syndrome. Brugada syndrome is a condition associated with SCD in the setting of a structurally normal heart, characterized by an electrocardiographic pattern of RBBB and ST-segment elevation in leads V_1 to V_3 (Fig. 21.8). It is inherited in an autosomal dominant pattern with a male predominance. It is a genetically heterogeneous disease with many mutations linked to the gene *SCN5A*, which encodes for a cardiac sodium channel, leading to unopposed I_{to} potassium current in the RV epicardium. The diagnosis can be difficult because of the variable expression of the ECGs at baseline, changes in the ECG over time induced by a host of factors (fever, heart rate, autonomic tone, and medications), and the wide range of clinical manifestations. The diagnosis should be considered in patients who have documented VF, self-terminating polymorphic VT, family members with ST-segment elevation, syncope, or family history of sudden death in the setting of the electrocardiographic findings noted previously. Currently, no medication has proved effective in preventing SCD in these patients, but quinidine, which blocks the I_{to} channel, may be used as an adjunctive therapy to reduce the likelihood of arrhythmias. ICDs are currently the only available treatment and are recommended in patients with previous cardiac arrest or VT (class I), and syncope felt to be from arrhythmia with spontaneous ECG pattern (class IIa), or induced VF during EP study (IIb). It is generally recommended to implant an ICD in **symptomatic** patients and clinically follow **asymptomatic** patients with an abnormal ECG only on pharmacologic provocation and no inducible ventricular arrhythmias.

FIGURE 21.8 Leads V_1 through V_3, demonstrating type 1 Brugada pattern.

c. Catecholaminergic polymorphic VT. This arrhythmia is more common in adolescents and children and may present with SCD or stress-induced syncope. Although usually familial, it can also occur because of de novo mutations. Triggers often include emotional or physical stress, and the arrhythmia can be polymorphic, bidirectional, and less commonly, VF. Two culprit genes have been identified thus far: calsequestrin 2 (autosomal recessive pattern) and cardiac ryanodine receptor (autosomal dominant pattern). ICDs are indicated in patients with this syndrome and syncope and/or VT. β-Blockers can reduce the incidence of arrhythmias as well. Flecainide may be useful (class IIa), and sympathetic denervation can be considered (class IIb) in patients who have recurrent arrhythmia despite β-blocker therapy.

VT in the structurally abnormal heart

. **Ischemic VT. Patients with ischemic VT may have acute ischemia leading to MI or a history of ischemic heart disease with scar.** Patients who have VF/VT within 48 hours of an acute MI have a relatively high in hospital and 30-day mortality compared with patients who do not have VF/VT.

1. **(1) Etiology and pathophysiology.** At the cellular level, ischemia may alter action potentials, prolong refractoriness of cells, and uncouple the cell-to-cell propagation of depolarization. The biochemical milieu in which the cells exist with respect to ion concentrations, acid–base balance, and so forth can be altered. Also, the myocardial damage as a result of infarction is structurally heterogeneous. Therefore, scar tissue and healthy tissue are admixed in the region of the infarction. As described before, a reentrant circuit requires two functionally distinct pathways with unidirectional block in one pathway and slowed conduction down a second pathway. The changes associated with ischemia provide the anatomic substrate for reentry. The VT in the setting of ischemia tends to be **polymorphic**, whereas VT in the setting of established myocardial scar tends to be **monomorphic**. Ischemia has been shown to prolong the QT interval in some subjects, often with associated T-wave inversion. The **QT interval in ischemic-mediated polymorphic VT is not as prolonged** as that in torsade de pointes, another polymorphic VT. Ischemia is by far the **most common cause of polymorphic VT with normal QT interval**.
2. **(2) Predictors of VT.** As might be expected, **larger infarcts with greater resultant impairment of LV systolic function** are more likely to be associated with VT. In fact, LV systolic function is the single most important predictor of sudden death because of arrhythmia. Similarly, the presence of an **open artery appears to reduce the occurrence of VT and other arrhythmias**. Other proposed predictors include syncope, abnormal signal-averaged electrocardiogram (SAECG) result, NSVT, absence of heart rate variability, abnormal EP study outcome, and T-wave alternans (TWA); however, currently, the LVEF remains the most accurate predictor of sudden death.
3. **(3) Laboratory examination and diagnostic testing.** The various tests for risk stratification (EP study, SAECG, heart rate variability, TWA, and so forth) have shown poor specificity and positive predictive value for VT **and thus should not be used alone to guide therapy but in combination with the rest of the clinical information**.
4. **(4) Role for ICD.** In patients who present with a VF/VT arrest in the setting of an acute MI (within 24 to 48 hours of infarction), revascularization should be the primary initial treatment. Given the fact that acute ischemia is considered a "transient or potentially correctable cause" of VF/VT, and such patients were excluded from the AVID trial, based on current guidelines, an ICD would be indicated 90 days after revascularization if the LVEF is ≤35% or after 40 days if no revascularization was performed, but treatment should be guided on a patient-to-patient basis. Of note, patients in the AVID registry who were excluded from the AVID trial because of a "transient or potentially correctable cause" had a high mortality risk in follow-up. Of the 278 patients studied, 183 patients were determined to have ischemic causes. Of these, 161 were categorized as new MI and 22 were categorized as transient ischemia. Other causes included electrolyte abnormalities, antiarrhythmic drug interaction, and "other (illicit drug use, sepsis, hypoxia, electrocution, drowning)." For patients who are post-MI and are deemed to be at high risk for SCD during the waiting period of 40 to 90 days, a wearable cardioverter–defibrillator (WCD) may provide protection against cardiac arrest, but no randomized clinical trials comparing WCDs with medical therapy in this post-MI period have been completed to date. Patients with late VT/VF (i.e., >48 hours after acute MI) are deemed to be particularly high risk for recurrent VT/VF and therefore typically receive ICDs before hospital discharge. These patients are considered to meet secondary prevention indications for ICDs.

a. Accelerated idioventricular rhythm (Fig. 21.9) is a form of VT seen almost exclusively in ischemic heart disease, particularly during an MI and especially after reperfusion of an occluded territory. It may be seen with digitalis toxicity, but can also be present in healthy adults and children with no structural heart disease.

1. **(1)** The **EKG** features include regular or slightly irregular ventricular rhythm, a rate of 60 to 110 beats/min, a QRS morphology resembling that of PVCs, and, often, AV dissociation as well as fusion beats and capture beats.

FIGURE 21.9 Accelerated idioventricular rhythm (beats 3 through 5), interspersed with normal sinus rhythm (beats 1 and 2), lead IV.

2. **(2) Pathophysiology.** The ectopic ventricular pacing focus competes with the SN and takes control of the ventricular rate when the sinus rate slows or when sinoatrial or AV block occurs. Enhanced automaticity is the likely underlying mechanism.

Accelerating the sinus rhythm with atropine or atrial pacing can be useful to suppress the accelerated idioventricular rhythm.

3. **(3) Therapy is rarely necessary, unless** the loss of AV synchrony results in hemodynamic compromise, a more rapid VT intervenes, the accelerated idioventricular rhythm falling on the T-wave of the preceding beat (R-on-T phenomenon), the ventricular rate being rapid enough to produce symptoms, or occurrence of VF.

b. Dilated cardiomyopathy (DCM). Risk stratification is particularly difficult in patients with DCM because SAECG, microvolt TWA, and an EP study are not reliable predictors in this population, and asymptomatic ventricular arrhythmias are common. The **Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation** and Sudden Cardiac Death in Heart Failure Trial have influenced the current guidelines for implanting ICDs in patients with DCM. ICDs are recommended for patients who manifest life-threatening arrhythmias or syncope and for primary prevention in patients who have an LVEF <35% and are New York Heart Association classes I to III (less evidence exists for class I). All patients should be receiving chronic optimal medical therapy and have a life expectancy >1 year. Bundle branch reentrant tachycardia occurs most commonly in patients with DCM for which EP testing is helpful in diagnosing and guiding ablative treatment. Although ablation may be curative if bundle branch reentry is the mechanism, such patients should still be considered for ICD implantation.

c. Hypertrophic cardiomyopathy. Supraventricular tachyarrhythmia and AF are particularly poorly tolerated by these patients, as is ischemia, and may lead to VT. No prospective randomized trials regarding ICD therapy have been carried out to date in this patient population. Consequently, the precise risk stratification is debated. **ICDs are recommended for patients who have sustained VT or VF, or both, and for primary prevention in patients who have either one of the preceding life-threatening arrhythmias or one or more of other major risk factors for SCD (nonsustained spontaneous VT, family history of premature SCD, unexplained syncope, LV thickness ≥30 mm, or abnormal exercise blood pressure).** Again, all patients should be receiving chronic optimal medical therapy and have a life expectancy >1 year. EP study may be helpful in stratifying risk for VT and sudden death. Patients at low risk for HCM include those with infrequent or brief episodes that are asymptomatic or mildly symptomatic. Although **amiodarone** may be beneficial in this population, an ICD is increasingly used in those considered to be at high risk.

d. Muscular dystrophies, particularly Duchenne muscular dystrophy and myotonic dystrophy, have been associated with frequent defects in the conduction system. Heart block and bundle branch block as well as sudden death because of ventricular tachyarrhythmias are well-recognized complications of these muscular disorders.

e. Congenital heart disease. Structural abnormalities such as **repaired tetralogy of Fallot and mitral valve prolapse** have been associated with increased risk of VT and sudden death. In tetralogy of Fallot, the VT often originates in the RVOT, at the site of a previous repair. Risk of VT and sudden death in this population has been associated with QRS width (and rate of QRS width increase) as well as severity of pulmonary insufficiency. Mitral valve prolapse has been uncommonly linked to sudden death, although ventricular arrhythmias are not uncommon. **The prognosis with respect to VT is quite good in mitral valve prolapse.**

f. Arrhythmogenic right ventricular cardiomyopathy is a cardiomyopathy that begins in the right ventricle and often progresses to involve the left ventricle. It results in RV dilation with resultant poor contractile function. The RV muscle becomes increasingly replaced by adipose and fibrous tissues as the disease progresses. VT arising in the right ventricle is often an early manifestation of this disorder. The **VT is a reentrant type and has an LBBB morphology**, although in sinus rhythm, there is often inversion of the T-waves in the anterior precordial leads and a slurring of the terminal portion of the QRS complex, known as an epsilon wave (Fig. 21.10). These patients frequently have a positive SAECG for late potentials. The combination of the scarring and the late potentials provides the anatomic substrate for reentry. During EP study, it may be possible to elicit VT of varying morphologies, because of the prolific scarring of the myocardium. The **risk of VT correlates with the extent of myocardial involvement**. Therapy with sotalol or high-dose amiodarone may be somewhat successful. Ablation via catheters is often successful, but only temporizing, because the generalized involvement tends to give rise to arrhythmias at a different locus later in the disease course. ICDs are often the only reliable therapy to prevent sudden death in this disorder. Patients are advised against intense exercise, because this may promote the incidence and progression of arrhythmias.

g. Several inflammatory or infectious conditions have been associated with VT.

Sarcoidosis is frequently cited as a cause of heart block and may also cause VT and VF. **Amiodarone** and **sotalol** are the most efficacious agents in this disorder, although an ICD may be necessary in addition to the drug therapy. Catheter ablation may be considered for recurrent arrhythmia.

Acute myocarditis has been associated with both polymorphic and monomorphic VTs. It may be intractable in giant cell myocarditis. **Antiarrhythmic therapy and anti-inflammatory therapy** are generally combined in the treatment of these patients.

Chagas disease, caused by the parasite *Trypanosoma cruzi*, is a well-known cause of cardiomyopathy, particularly in South and Central America. VT and other arrhythmias because of conduction system involvement are common complications. Therapy involves antiparasitic treatment, standard therapy for CHF, antiarrhythmics, and pacemaker or ICD implantation, as appropriate. Some patients require catheter ablation of refractory VT, which sometimes must be performed epicardially.

h. Coronary anomalies. Anomalous aortic origin of the coronary artery is recognized as a cause of sudden death and/or exercise-induced death in young individuals. In an autopsy study of over 200 patients conducted by the Armed Forces Institute of Pathology, the most common coronary anomalies included the right coronary artery and left main coronary artery arising from

the left sinus, the left main and right coronary arteries arising from the right sinus, single coronary artery from the aorta, and the left main or left anterior descending artery arising from the pulmonary artery. Patients whose coronary arteries take an interarterial course (between the pulmonary artery and the aorta) may develop exercise-induced ischemia and/or sudden death. Surgical revascularization in patients with symptomatic coronary anomalies has been well described. Surgical treatment for patients with high-risk coronary anomalies who are asymptomatic is controversial.

FIGURE 21.10 Epsilon wave in a patient with arrhythmogenic right ventricular dysplasia.

i. **Drug-induced VT.** Drugs are a well-known cause of VT, both polymorphic and monomorphic VTs. This is particularly true in ischemic or infarcted hearts. Phenothiazines, tricyclic antidepressants, digitalis, epinephrine, cocaine, nicotine, alcohol, and glue (inhaled) are some of the wide variety of drugs that have been implicated in the development of monomorphic VT. The CAST and other trials of the late 1980s showed an increase in mortality resulting from the use of class I antiarrhythmic agents employed to suppress asymptomatic ventricular ectopy after MI. NSVT and depressed LV function remain risk factors for sudden death, and the agents studied in CAST did decrease the occurrence of ventricular ectopy; however, it is believed that these drugs (flecainide, encainide, and moricizine) generated VT, causing sudden death in recipients. These agents all have in common their sodium channel blocking activities. Other drugs in this class, including procainamide, quinidine, disopyramide, lidocaine, tocainide, and mexiletine, have all been shown either experimentally or clinically to be associated with increased mortality compared with controls in the peri-infarction period. The results of CAST caused a major shift away from the sodium channel blocking agents (class I antiarrhythmics) in the peri-infarction period.

Digitalis toxicity can propagate DADs, which generate action potentials, leading to VT. The VT of digitalis toxicity is typically monomorphic and often responds to calcium channel blockers. Rarely, digitalis toxicity manifests as a bidirectional VT, meaning that it has a regular rhythm with an axis that alternates from −60° to −90° to +120° to +130°, with a ventricular rate from 140 to 200 beats/min. Because digitalis toxicity may have a narrow QRS complex and may respond to calcium channel blockers, it may be confused with supraventricular tachyarrhythmia. This type of VT is best managed by removing the offending agent, digoxin, with its binding antibody. The treatment for digitalis toxicity is the same in the face of bidirectional VT.

j. **Torsade de pointes** is a type of polymorphic VT associated with delayed myocardial repolarization, most often manifested as a prolonged QT interval. Although the duration of torsade de pointes is typically brief (<20 seconds), it can be sustained and can degenerate into VF. It generally has an irregular ventricular rate (>200 beats/min) and displays a polymorphic structure with an undulating appearance. The QRS complexes appear to twist around an isoelectric axis. Characteristics that distinguish torsade de pointes from other forms of VT include (1) prolonged QT interval, (2) initiation with a short–long–short sequence, and (3) typical "twisting of the points" appearance of the VT.

1. **(1) Etiology.** QT prolongation can be congenital or acquired.

The **congenital** forms are seen in the LQTS, discussed in Chapter 23.

The **acquired forms are most often drug induced**, although polymorphic VT with a prolonged QT can be caused by electrolyte abnormalities, hypothyroidism, cerebrovascular events,

MI or ischemia, starvation diets, organophosphate poisoning, myocarditis, severe CHF, and mitral valve prolapse.

The **most commonly implicated drugs have been the class IA drugs**, although less frequent occurrences have been reported with all subclasses of class I antiarrhythmics. The class III drugs, such as sotalol, dofetilide, and, less commonly, amiodarone, have been implicated. The incidence of torsade de pointes with sotalol is in the range of 2% to 5% and with dofetilide it is ~1%. Ibutilide is an antiarrhythmic agent for supraventricular tachyarrhythmias that is associated with an incidence of torsade de pointes at least as high as that of sotalol. Other drugs implicated include the phenothiazines, haloperidol, and the tricyclic antidepressants. Antibiotics, including erythromycin and other macrolides, as well as trimethoprim–sulfamethoxazole combinations, have been implicated. The macrolides are particularly prone to cause torsade de pointes when combined with certain antihistamines such as astemizole and terfenadine. These antihistamines have also been found to cause torsade de pointes when combined with certain azole antifungal agents such as ketoconazole. Ionic contrast and promotility agents such as cisapride have also been associated with torsade de pointes. Medications associated with increasing QT interval are listed on the following website: www.torsades.org. It is maintained by the University of Arizona Center for Education and Research on Therapeutics.

Bradycardia can promote torsade de pointes in patients with prolonged QT intervals, although it is not clear if bradycardia by itself predisposes to torsade de pointes. Specifically, pause-dependent VT occurs in the setting of bradycardia and a prolonged QT interval. Usually a long RR interval followed by a short RR interval followed by another long RR interval initiates the VT.

Electrolyte disorders. Hypokalemia is the electrolyte disorder most reliably linked to torsade de pointes. **Hypomagnesemia**has been proposed as a logical cause, because the administration of magnesium frequently terminates torsade de pointes. However, there is scant evidence to confirm this. Likewise, although **hypocalcemia** is associated with prolongation of the QT interval, there are only rare reports of torsade de pointes associated with hypocalcemia.

Short coupled VT. Polymorphic VT is initiated <400 ms following the preceding QRS complex.

R-on-T phenomenon occurs when a defibrillation or pacing current or spike is delivered simultaneously with occurrence of the electrocardiographic T-wave resulting in polymorphic VT.

A variety of **cerebrovascular events** have been associated with torsade de pointes, most notably subarachnoid hemorrhage. The prolongation of the QT interval sometimes seen with intracranial bleeding is usually transient, resolving within weeks.

2. **(2) Therapy.** Acute management is aimed at terminating the arrhythmia.

If torsade de pointes is sustained or associated with hemodynamic compromise, prompt DCC should be carried out. Starting voltages are generally 50 to 100 J and can be advanced to 360 J if necessary.

Correction of hypokalemia, hypomagnesemia, and hypocalcemia should be undertaken promptly. Magnesium can be given in a bolus form at a dose of 1 to 2 g, with a total dose of 2 to 4 g given over 10 to 15 minutes. This successfully terminates torsade de pointes within 5 minutes in up to 75% of patients and within 15 minutes in virtually all patients.

Bradycardia can be corrected with either isoproterenol infusion or temporary transvenous pacing. Pacing may be preferable when readily available, because of the potential complications of isoproterenol therapy (worsened ischemia and hypertension). Offending agents should be discontinued.

k. Miscellaneous

Commotio cordis. Commotio cordis is the sudden ventricular arrhythmia occurring as a result of a blunt, nonpenetrating impact to the precordial region, which is most commonly observed in young healthy persons during participation in sports. The blow likely falls within a small 10- to 30-ms window of ventricular vulnerability just prior to the peak of the T-wave that results in polymorphic VT and sudden death. A 2002 case series of 128 individuals showed that only 16% of patients survived an episode of commotio cordis, with most returning to a baseline level of function. Prompt CPR/defibrillation was the only identifiable factor associated with a favorable outcome.

Ventricular fibrillation. VF is a **chaotic ventricular rhythm that reflects no organized electrical activity and hence no cardiac output** from the ventricle. It is devoid of the distinct elements that make up the usual electrical complex of ventricular activity. It is a **rapidly fatal rhythm, and if resuscitation is not begun within 5 to 7 minutes, death is virtually certain**. VF is often preceded by VT. Virtually all of the risk factors and conditions discussed for VT are applicable to VF. It may arise without any inciting cardiac rhythm or event.

Course of disease. Of patients who experience an out-of-hospital cardiac arrest, 75% have VF as their initial cardiac rhythm. Of those successfully resuscitated, 75% have significant CAD and 20% to 30% have a transmural infarction. Patients without an ischemic etiology have an increased risk of further episodes of sudden death, whereas those who have an MI associated with sudden death have a 1-year recurrence rate of 2%. Anterior MI complicated by VF represents a subgroup at high risk for recurrence of sudden death. Predictors of SCD include evidence of ischemia, decreased LV systolic function, 10 or more PVCs per hour on telemetry, inducible or spontaneous VT, hypertension and LV hypertrophy, smoking, male sex, obesity, elevated cholesterol, advanced age, and excessive alcohol use.

Therapy. As noted previously, VF is a rapidly fatal rhythm, which virtually never terminates spontaneously. CPR must be initiated promptly and rapid, asynchronous DCC performed as soon as possible. A **single** shock of 200 to 360 J (biphasic devices, 200 J; monophasic devices, 360 J) should be given initially followed by immediate resumption of CPR for 2 minutes before checking for a pulse. If VF/pulseless VT persists, an immediate **second** shock (biphasic devices, ≥200 J; monophasic devices, 360 J) should be given followed by a vasopressor (1 mg of epinephrine every 3 to 5 minutes; single dose of 40 units of vasopressin may replace first or second dose of epinephrine). If VF/pulseless VT persists after two or three shocks, CPR, and a vasopressor, administration of an antiarrhythmic should be considered (amiodarone is preferred and lidocaine as an alternative). The emphasis should be on performing high-quality CPR with interruptions in chest compressions **only** for ventilation (until an advanced airway is established), rhythm checks (pulse checks only if an organized rhythm is observed), and shocks.

See Chapter 23 for a discussion about the long-term treatment of survivors of VF.

Ventricular premature depolarizations and NSVT. VPDs are common in patients with both structurally normal and structurally abnormal hearts. They are usually not hemodynamically significant, except in patients with depressed EF or in patients with frequent VPDs and/or bradycardia. Whether or not VPDs increase risk of subsequent cardiovascular events depends on the study. In the ARIC study, after controlling for cardiovascular risk factors, patients with a single VPD on a 2-minute Holter had over a

twofold incidence of dying of CAD over a 10-year follow-up period compared with patients who had no VPDs. However, in the Baltimore Longitudinal Study on Aging which evaluated ambulatory ECGs on apparently healthy subjects ≥60 years of age, VPDs on ambulatory ECG monitoring did not predict the development of coronary events. One main difference between the ARIC study and the Baltimore Longitudinal Study was that in the latter, inclusion criteria were more strict, requiring a normal exercise stress test, and therefore, likely had less patients with subclinical CAD.

Therapy

. **VPDs.** Although patients post-MI with VPDs have a higher mortality than patients post-MI without VPDs, suppression of VPDs with antiarrhythmic medication is associated with increased mortality. For patients with symptomatic VPDs, β-blockers or calcium channel blockers should be the first-line agents. If this fails and the patient has no structural heart disease, class IC agents may be effective; however, potential risks and benefits of the antiarrhythmic drug should be explained to the patient. Sotalol has been shown to reduce the frequency of VPDs by 70% to 80%. In CAMIAT, amiodarone reduced VPDs and arrhythmic deaths, but did not reduce overall mortality. **A very high burden of VPDs (>20,000/d) may be associated with reduced EF, although it may be difficult to determine if the VPDs caused the cardiomyopathy or vice versa.** However, in some patients with a high burden of VPDs and idiopathic DCM, treating the VPDs either with medication or with catheter ablation may improve the LVEF. Ablation can be an alternative approach to treatment in patients with very symptomatic VPDs refractory to medical therapy and/or patients with reduced EF thought to be a result of the VPDs.

a. **NSVT** is defined as VT of duration <30 seconds. It can occur in up to 4% of healthy adults and increases in frequency as people age, and NSVT during exercise is not associated with a poor cardiovascular prognosis. The approach to NSVT is based on the cardiac substrate. However, patients with frequent polymorphic NSVT should undergo an evaluation for LQTS and catecholaminergic VT. One should also be mindful of repetitive monomorphic NSVT that may be of LBBB morphology in patients who have a family history of arrhythmias or sudden death, which may suggest ARVD. Monomorphic NSVT may also be a part of the spectrum of the outflow tract VTs.

In patients in whom **structural heart disease has been excluded, NSVT does not carry prognostic significance**. Treatment should therefore only be guided by symptoms. A similar approach to NSVT with regard to medication choices is used as with symptomatic VPDs.

b. **NSVT in structural heart disease.** In patients with MI, NSVT within the first 24 to 48 hours has little prognostic significance. However, NSVT >48 hours after acute MI may increase the risk of sudden death by almost twofold, and the risk is even higher in patients with reduced LV function. **Patients with CAD, an EF <40%, and NSVT who have inducible sustained VT on testing are at substantially increased risk** over those who do not have inducible VT. In patients with HCM, NSVT on Holter monitoring is one of the major risk factors of SCD. Patients with mitral valve prolapse and aortic stenosis who have NSVT are not at increased risk for SCD compared with those without NSVT. In patients with nonischemic DCM, NSVT is not an independent predictor of sudden death.

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CHAPTER 22

Bradyarrhythmias, Atrioventricular Block, Asystole, and Pulseless Electrical Activity

Erich L. Kiehl

I. INTRODUCTION. Bradyarrhythmias and **conduction blocks** are common electrocardiographic findings. Many of these arrhythmias are asymptomatic and do not require specific therapy, whereas others can be life threatening, requiring rapid intervention.

II. ANATOMY

A. Sinoatrial node. The normal sinus beat originates in the **sinoatrial (SA) node**, a focus of automatic cells near the junction of the superior vena cava and right atrium.

1. The blood supply to the SA node is from the **sinus node artery**, which arises from the proximal **right coronary artery** (RCA) in 55% of the population (Fig. 22.1) and the **left circumflex artery** (LCx) in 35%. The SA node receives a dual supply of blood from both the RCA and the LCx in 10% of the population.
2. The automaticity of the SA node is affected by both the parasympathetic and sympathetic nervous systems. If the SA node fails to generate an impulse, other foci in the atrium, atrioventricular (AV) node, or ventricle can act as "backup" pacemaker sites.

B. AV node. The AV node is located in the anteromedial portion of the right atrium just anterior to the coronary sinus.

1. The impulse generated by the SA node progresses through the atrium to the AV node. The AV node is also innervated by both the parasympathetic and sympathetic nervous systems.
2. The AV node receives its blood supply from the **AV node artery**, which arises from the **posterior descending artery (PDA)** in 80% of the population (Fig. 22.1), from the LCx in 10%, and from both arteries in 10%.
3. Collateral blood supply from the **left anterior descending artery (LAD)** makes the AV node somewhat less prone to ischemic damage than the SA node.

C. His bundle and bundle branches

1. After a normal delay of <200 ms in the AV node, the electrical impulse is propagated down the His bundle to the right and left bundle branches. The **left bundle branch splits further into anterior and posterior fascicles**. The autonomic nervous system does not have a major effect on conduction below the AV node.
2. The **His bundle and right bundle branch** receive their blood supply from the AV nodal artery and from septal perforating branches of the LAD. The **anterior fascicle of the left bundle branch** receives blood from the septal perforating branches of the

LAD alone. The **posterior fascicle of the left bundle branch** has a dual blood supply from the septal perforating branches of the LAD and branches of the PDA.

III.SINUS NODE DYSFUNCTION. Sinus node dysfunction encompasses any dysfunction of the sinus node and includes **inappropriate sinus bradycardia**, SA **exit block**, SA **arrest, and tachycardia–bradycardia syndrome**.

FIGURE 22.1 Diagrammatic representation of the conduction system and its blood supply. AVN, atrioventricular node; LAD, left anterior descending; LCx, left circumflex artery; LLB, left lateral branch; PDA, patent ductus arteriosus; RBB, right bundle branch; RCA, right coronary artery; SAN, sinoatrial node.

A. Clinical presentation. There is a wide range of presentations, and some patients' disease may be asymptomatic.

1. **Syncope** and **presyncope** are the most dramatic presenting symptoms. **Fatigue, angina, and shortness of breath** are more subtle consequences of sinus node dysfunction.
2. In the tachycardia–bradycardia syndrome, the primary complaint may be palpitations. Documentation of the symptomatic tachyarrhythmia may be difficult because of the sporadic and fleeting nature of the problem.

B. Etiology. The intrinsic and extrinsic causes of sinus node dysfunction are listed in Table 22.1. **Idiopathic degenerative disease** is the most common cause of intrinsic sinus node dysfunction, and the incidence increases with age. **Acute coronary syndromes** are another common cause of bradyarrhythmias, occurring in 25% to 30% of patients with myocardial infarction (MI) (Table 22.2).

C. Electrocardiographic findings

1. Inappropriate sinus bradycardia, also known as "**chronotropic incompetence**," is defined as a sinus rate of <60 beats/min that does not increase appropriately with exercise. Inappropriate sinus bradycardia must be differentiated from a low resting heart rate, which may be normal in athletes and sleeping individuals.
2. Sinus arrest, or a sinus pause, occurs when the sinus node fails to depolarize on time. Pauses of <3 seconds may be seen on Holter monitoring in up to 11% of normal adults (especially athletes) and are not a cause for concern. However, **pauses lasting longer than 3 seconds are generally considered abnormal and are suggestive of underlying pathology**, especially if the patient is awake when they occur.
3. SA exit block, although similar to sinus arrest on the electrocardiographic tracing, may be distinguished by the fact that the **duration of the pause is a multiple of the sinus PP** interval. High-grade SA exit block cannot be differentiated from prolonged sinus arrest and is treated in the same manner.

TABLE 22.1 Etiologies of Sinus Node Dysfunction

Intrinsic Causes
Idiopathic degenerative disease
Coronary artery disease
Cardiomyopathy

TABLE 22.1 Etiologies of Sinus Node Dysfunction

Hypertension
Infiltrative disorders (amyloidosis, hemochromatosis, and tumors)
Collagen vascular disease (scleroderma and systemic lupus erythematosus)
Inflammatory processes (myocarditis and pericarditis)
Surgical trauma (valve surgery and transplantation)
Musculoskeletal disorders (myotonic dystrophy and Friedreich ataxia)
Congenital heart disease (postoperative or in the absence of surgical correction)
Extrinsic Causes
Drug effects
β-Blocking agents
Calcium channel blocking agents
Digoxin
Sympatholytic antihypertensives (clonidine, methyldopa, and reserpine)
Antiarrhythmic drugs
Type Ia (quinidine, procainamide, and disopyramide)
Type Ic (flecainide and propafenone)
Type III (sotalol and amiodarone)
Others (lithium, cimetidine, amitriptyline, and phenytoin)
Autonomic influences
Excessive vagal tone
Carotid sinus syndrome
Vasovagal syncope
Well-trained athletes (normal variant and not dysfunction)
Electrolyte abnormalities
Hyperkalemia
Hypercarbia
Endocrine disorders—hypothyroidism
Increased intracranial pressure

TABLE 22.1 Etiologies of Sinus Node Dysfunction
Hypothermia
Sepsis

4. Reprinted with permission from Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Lippincott–Raven.

5. Tachycardia–bradycardia syndrome, also referred to as "sick sinus syndrome," is characterized by episodes of sinus or junctional bradycardia interspersed with an atrial tachyarrhythmia, usually paroxysmal atrial fibrillation.

D. Diagnostic testing. Invasive testing is used when noninvasive methods have failed to yield a diagnosis and sinus node dysfunction is still strongly suspected.

TABLE 22.2 Incidence of Bradyarrhythmia in the Setting of Acute Myocardial Infarction	
Rhythm	
Sinus bradycardia	2
Junctional escape rhythm	2
Idioventricular escape rhythm	1
First-degree AV block	1
Second-degree, Mobitz type I AV block	1
Second-degree, Mobitz type II AV block	4
Third-degree AV block	1
Right bundle branch block	7
Left bundle branch block	5
Left anterior fascicular block	8
Left posterior fascicular block	0

E. AV, atrioventricular.

1. **Noninvasive testing**

a. Electrocardiogram (ECG). In evaluating sinus node dysfunction, the initial workup should include a 12-lead ECG, followed by ambulatory ECG monitoring. In most cases, 24 to 48 hours of monitoring (Holter) is sufficient, but frequently, extended monitoring for 2 to 4 weeks (event recorder) is required for diagnosis. Rarely, in more paroxysmal cases, prolonged monitoring for months to years via implantable loop recorders is indicated. Use of a diary during the recording period can help correlate symptoms with the cardiac rhythm. Stress testing can help document the severity of chronotropic incompetence.

b. Autonomic testing includes physical maneuvers, such as carotid sinus massage and tilt table testing, as well as pharmacologic interventions to test the autonomic reflexes.

1. **(1)** Carotid sinus massage distinguishes intrinsic sinus arrest from a pause because of **carotid sinus hypersensitivity**, which is a 3-second or longer pause and/or a ≥50 mm Hg or greater drop in blood pressure that occurs with massage of the carotid sinus (firm pressure applied to one carotid sinus at a time for 5 seconds). **Carotid sinus massage should not normally precipitate sinus arrest**, although it will decrease the rate of depolarization of the SA node and slow conduction in the AV node. Carotid sinus hypersensitivity is relatively common in older patients with atherosclerotic disease and can be provoked by neck motion, shaving, or a tight shirt collar. When carotid sinus hypersensitivity is accompanied by syncope or presyncope, it constitutes **carotid sinus syndrome** and may warrant permanent pacing for nonvasodepressive subtypes (Table 22.3).
2. **(2)** Tilt table testing may help differentiate between syncope caused by sinus node dysfunction and that because of autonomic dysfunction (**neurocardiogenic syncope**). **Bradycardic episodes precipitated by tilt table testing are usually caused by autonomic dysfunction and not by sinus node dysfunction**.
3. **(3)** Pharmacologic testing may be used to differentiate between sinus node dysfunction and autonomic dysfunction. Total autonomic blockade is achieved after administration of atropine 0.04 mg/kg and propranolol 0.2 mg/kg. The resulting intrinsic heart rate represents the sinus node rate, devoid of autonomic influences. Assuming that the normal intrinsic heart rate (in beats/min) is defined by the formula:

$$\text{Intrinsic heart rate} = 118.1 - (0.57 \times \text{age})$$

then (a) an intrinsic heart rate lower than predicted using this formula is consistent with sinus node dysfunction and (b) an intrinsic heart rate close to the predicted rate with a clinical presentation similar to sinus node dysfunction is suggestive of autonomic dysfunction as the cause of bradyarrhythmia.

TABLE 22.3 Indications for Permanent Pacing

Indication	Class I	Class II	Class
SND	1. SND documented in association with symptomatic bradycardia and because of factors that are irreversible or because of essential drug therapy 2. Symptomatic chronotropic incompetence	IIa. No clear association between SND with heart rate <40 beats/min and symptoms can be documented IIb. In minimally symptomatic patients, chronic heart rate <40 beats/min while awake	1. bra *ass* be the 2. SN sug are as hea 3. bra no
Acquired AV block	1. Third-degree or advanced second-degree (Mobitz II) AV block at any anatomic level, associated with any	IIa 1. Asymptomatic third-degree AV block with average ventricular	1. A blo 2. A

TABLE 22.3 Indications for Permanent Pacing

	one of the following conditions: a. Bradycardia with symptoms presumed to be due to AV block b. Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia c. Documented periods of asystole ≥ 3.0 s, or an escape rhythm below the AV node, or any escape rate <40 beats/min in awake, symptom-free individuals in sinus rhythm d. Documented pauses >5 s in awake, symptom-free patients who are in atrial fibrillation e. After catheter ablation of the AV junction f. Postoperative AV block that is not expected to resolve g. Neuromuscular diseases with AV block such as myotonic muscular dystrophy, Kearns–Sayre syndrome, Erb dystrophy (limb girdle), and peroneal muscular dystrophy, with or without symptoms h. Asymptomatic persistent AV block at any anatomic site with average awake ventricular rates of 40 beats/min or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node i. Present during exercise in the absence of myocardial ischemia	rates ≥40 beats/min without cardiomegaly 2. Asymptomatic type II second-degree AV block with narrow QRS. Becomes class I recommendation when wide non-RBBB QRS. 3. Asymptomatic second-degree AV block at intra-His or infra-His levels found at EP study 4. First- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise IIb 1. Neuromuscular diseases with *any* degree of AV block (including first-degree) with or without symptoms 2. AV block in the setting of drug use or toxicity when the block is expected to recur even after drug withdrawal	de at or or 3. A an tox
Postacute MI	1. Persistent second-degree AV block in the His-Purkinje system with alternating bundle branch block or third-degree AV block within or below the His-Purkinje system after acute ST-elevation acute MI 2. Transient advanced (second- or third-degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an EP study	IIa. None IIb 1. Persistent second- or third-degree AV block at the AV node level, even in the absence of symptoms	1. T int de 2. T pre fas 3. Ne blo blo firs

TABLE 22.3 Indications for Permanent Pacing

	may be necessary 3. Persistent and symptomatic second- or third-degree AV block		pre
Chronic bifascicular blocks	1. Intermittent advanced second- or third-degree AV block Type II second-degree AV block Alternating bundle branch block	IIa 1. Syncope not proved to be due to AV block when other likely causes have been excluded, specifically ventricular tachycardia 2. HV interval >100 ms on EP study in asymptomatic patients 3. Pacing-induced infra-His block on EP study that is nonphysiologic IIb 1. Neuromuscular disorders with any fascicular or bifascicular block with or without symptoms	1. F blo 2. F deg syn
Carotid sinus hypersensitivity and neurocardiogenic syncope	1. Recurrent syncope caused by spontaneous carotid sinus stimulation inducing ventricular asystole >3 s	IIa 1. Syncope without clear, provocative events and with a hypersensitive cardioinhibitory response of >3 s IIb 1. Significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at time of tilt table testing	1. res stir cle 2. Si in eff

s I: Conditions for which there is evidence and/or general agreement that pacing is beneficial, useful, and tive.

s II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the ulness/efficacy of pacing.

s IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

s IIb: Usefulness/efficacy is less well established by evidence/opinion.

s III: Conditions for which there is evidence and/or general agreement that pacing is not useful/effective and in e cases may be harmful.

atrioventricular; EP, electrophysiologic; HV, half-value; LV, left ventricular; MI, myocardial infarction; RBBB, bundle branch block; SND, sinus node dysfunction.

oted from Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based apy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for antation of cardiac pacemakers and antiarrhythmia devices). *J Am Coll Cardiol*. 2008;51:2085–2105; Epstein Darbar D, DiMarco JP, et al. ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy rdiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task e on practice guidelines and the Heart Rhythm Society. *Circulation*. 2012;126:1784–1800.

2. **Invasive testing.** Electrophysiologic study (EPS) is rarely used in modern practice for the diagnosis of sinus node dysfunction. However, when performed, the two most common tests use indirect measurements of SA node function, as direct measurement of SA node function is laborious.

a. Sinus node recovery time (SNRT) is the time it takes the SA node to recover following paced overdrive suppression of the node.

1. (1) **A delay of longer than 1,400 ms is considered abnormal.** This measurement may be corrected by subtracting the intrinsic sinus cycle length (in milliseconds) from the recovery time. **A corrected SNRT >550 ms is suggestive of sinus node dysfunction.**

2. (2) The limitations of this test are as follows:

1. (a) It is an indirect measurement of SA node function and reflects both sinoatrial node conduction time (SACT) and automaticity.

2. (b) It may be falsely shortened by an SA node entrance block during atrial pacing (because of failure of the paced impulse to reset the sinus node) or falsely prolonged by an SA node exit block (the sinus node is normal but the impulse cannot leave the node), which affects its specificity.

3. (c) The SNRT is not prolonged in all patients with sinus node dysfunction, which affects its sensitivity.

b. Sinoatrial node conduction time

3. (1) The steady-state atrial rate is determined (A_1–A_1 interval or the time between P-waves). Then, premature atrial **extra stimuli** (A_2) are introduced by pacing high in the right atrium, starting in late diastole at progressively shorter intervals until atrial refractoriness is found (i.e., A_2 does not result in a P-wave). The duration before the next spontaneous atrial impulse (A_3) is measured and the baseline rate is subtracted.

$$\text{SACT} = (A_2 - A_3 \text{ interval}) - (A_1 - A_1 \text{ interval})$$

4. (2) The test assumes that SA node automaticity is not affected by pacing, that conduction time into the node is equal to conduction time out of the node, and that there is no shift in the principal pacemaker site.

Therapy. Treatment for symptomatic sinus node dysfunction may be pharmacologic, pacing, or a combination of both.

Indications for pacing in sinus node dysfunction are largely determined by symptoms (e.g., correlation with a documented arrhythmia; Table 22.3).

Pacing may also be indicated when essential drug therapy that causes sinus node dysfunction cannot be stopped or changed.

For patients with **tachycardia–bradycardia syndrome**, a pacemaker is often placed for management of the bradyarrhythmia, and antiarrhythmic or rate-controlling drugs are added for treatment of the tachycardia episodes.

Acute treatment for patients with **symptomatic sinus node dysfunction** includes the following:

. Atropine (0.04 mg/kg intravenous [IV] bolus)

a. Isoproterenol (starting at 1 µg/min intravenously), which may be used as a bridge to pacemaker placement. Isoproterenol is not indicated in most patients with cardiac arrest

b. Temporary pacing for patients whose conditions fail to respond to drug therapy

For patients requiring permanent pacing for sinus node dysfunction, a dual-chamber (right atrium and ventricle) pacemaker should be implanted and programmed to DDD or AAI modes, which have been shown to be superior to VVI mode with respect to subsequent incidence of atrial fibrillation, heart failure, pacemaker syndrome, and pacing-induced systolic cardiomyopathy. Subsequent AV block occurs in up to 35% of patients with sinus node dysfunction over extended follow-up, and thus single-chamber AAI pacing is typically used in younger patient populations.

AV CONDUCTION DISTURBANCES. These disturbances are classified as first-, second-, or third-degree block, depending on the severity of the conduction abnormality.

Classification

First-degree AV block is characterized by prolongation of the PR interval beyond 200 milliseconds. This finding may occur as a normal variant in 0.5% of asymptomatic young adults without overt heart disease. In older individuals, it is most often caused by idiopathic degenerative disease of the conducting system.

Second-degree AV block

. Second-degree AV block is characterized by **a failure of one or more, but not all, atrial impulses to conduct to the ventricles**. The block may be at any level of the AV conduction system.

a. When more than one atrial impulse is present for each ventricular complex, the rhythm may be described as a ratio of the number of atrial impulses to the number of ventricular complexes (for two P-waves preceding each QRS complex, 2:1 second-degree AV block is present).

1. **(1)** Lesser degrees of AV block (i.e., 4:3 or 3:2) with a prolonging PR interval prior to a nonconducted atrial impulse are described as **Mobitz type I AV block** (also known as **Wenckebach** block).

1. **(a)** The conducted impulse of a **Mobitz type I block** will generally be narrow, and the site of block is often in the AV node above the His bundle.

2. **(b)** A Mobitz type I block with a bundle branch block is still likely to be above the His bundle, but a His bundle electrogram is needed to confirm the level of block.

2. **(2)** High-grade AV block (3:1, 4:1, or greater) is typically described as **Mobitz type II AV block**. The conducted impulses will generally be preceded by constant PR intervals and have a wide QRS morphology (right bundle branch block [RBBB] or left bundle branch block [LBBB] pattern). The site of block is often below the AV node. A **Mobitz type II block** is usually intra-Hisian or infra-Hisian and has a greater propensity for progressing to **third-degree AV block**.

3. **(3)** Pure 2:1 conduction patterns cannot be reliably classified as Mobitz type I or type II by ECG alone, and if diagnostic maneuvers (such as exercise) are not able to elucidate one type of second-degree block versus the other, an EPS may be warranted.

Third-degree AV block, or **complete heart block**, may be acquired or congenital and is characterized by AV electrical dissociation.

. A total of 60% to 90% of cases of **congenital complete heart block** result from neonatal lupus. The vast remainder occur concurrently with congenital structural heart defects.

a. Acquired AV block occurs most commonly (~50%) because of progressive degeneration of the conduction system, but the differential includes a myriad of reversible and irreversible, iatrogenic and noniatrogenic causes (Table 22.4).

Clinical presentation

Signs and symptoms

. First-degree AV block is generally not a cause of symptoms.

a. Second-degree AV block *may* result in symptoms; however, high-grade second-degree AV block may progress to third-degree AV block, which can frequently cause symptoms.

b. Depending on the escape rate, patients with **third-degree AV block** may experience **fatigue** or **syncope**.

Physical findings. The amplitude of the arterial pulse and venous waveform varies, depending on the timing of atrial filling of the ventricles.

. Second-degree AV block is associated with a periodic change in amplitude. In patients with **third-degree AV block**, amplitude is constantly changing, with periodic appearance of **cannon a-waves** (large-amplitude waves in the venous pulsations seen in the neck when the atria contracts against a closed tricuspid valve).

a. Heart sounds are similarly affected by the change in filling duration of the ventricles.

TABLE 22.4 Causes of Atrioventricular Block

Drug effects
Digoxin
β-Blockers
Certain calcium channel blockers (nondihydropyridines)
Membrane-active antiarrhythmic drugs
Ischemic heart disease
Acute myocardial infarction
Chronic coronary artery disease
Idiopathic fibrosis of the conduction system
Lenegre disease
Lev disease
Congenital heart disease
Congenital complete heart block
Ostium primum atrial septal defect
Transposition of the great vessels

TABLE 22.4 Causes of Atrioventricular Block

Maternal systemic lupus erythematosus
Calcific valvular disease
Cardiomyopathy
Infiltrative disease
Amyloidosis
Sarcoidosis
Hemochromatosis
Infectious/inflammatory diseases
Endocarditis
Myocarditis (Chagas disease, Lyme disease, rheumatic fever, tuberculosis, measles, and mumps)
Collagen vascular diseases (scleroderma, rheumatoid arthritis, Reiter syndrome, systemic lupus erythe and polymyositis)
Metabolic
Hyperkalemia
Hypermagnesemia
Endocrine—Addison disease
Trauma
Cardiac surgery
Radiation
Catheter trauma
Catheter ablation
Tumors
Mesothelioma
Hodgkin disease
Malignant melanoma
Rhabdomyosarcoma
Neurally mediated
Carotid sinus syndrome

TABLE 22.4 Causes of Atrioventricular Block
Vasovagal syncope
Neuromyopathic disorders
Myotonic muscular dystrophy
Slowly progressive X-linked muscular dystrophy

b. Reprinted with permission from Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Lippincott–Raven; 1998.

1. **(1) The first heart sound** (S_1) becomes softer as the PR interval is prolonged, resulting in a soft S_1 in first-degree AV block, a progressive softening of S_1 in type I second-degree AV block, and a constantly changing S_1 in third-degree AV block.
2. **(2)** Third-degree AV block may also result in a functional systolic ejection murmur.

Etiology. The causes of AV block are listed in Table 22.4; the most common cause is **idiopathic degenerative fibrosis. Acute MI** results in AV block in 14% of patients with inferior infarction and 2% of those with anterior infarction, usually within the first 24 hours.

Diagnostic testing

First-degree AV block. Measuring a PR interval longer than 200 ms in adults and 180 ms in children makes the diagnosis. A P-wave precedes each QRS, and both the P and the QRS are morphologically normal.

Second-degree AV block

. The diagnosis of **Mobitz type I** is made when the following criteria are met on the ECG:

1. **(1)** Sequential and gradual prolongation of the PR interval terminated by a nonconducted P-wave
2. **(2)** Prolongation of the PR interval occurring in progressively shorter increments in "typical" Wenckebach, which results in progressive shortening of the RR intervals prior to the nonconducted atrial impulse
3. **(3)** Duration of the pause following the nonconducted P-wave is less than the sum of any two consecutively conducted beats.
4. **(4)** Decreased PR interval following the pause when compared with the prepause PR interval
5. **(5)** "Grouped beating," a pattern of repeated groups of QRS complexes characteristic of Wenckebach block

a. Mobitz type II second-degree AV block is less common than type I.

1. **(1)** The PR and PP intervals are constant with a sudden nonconducted P-wave (Fig. 22.2), in contrast to nonconducted (blocked) premature atrial contractions that have varying PR and PP intervals.
2. **(2)** Each QRS complex may have multiple P-waves, which are designated by the number of P-waves before each conducted QRS (3:1, 4:1, etc.). The QRS complex is typically not narrow (a narrow QRS complex is suggestive of a Mobitz type I block). It is often difficult to distinguish between 2:1 Mobitz I versus Mobitz II patterns by ECG alone, particularly if the QRS complex is narrow. A commonly used discrimination tool in this scenario is exercise ECG testing. Exercise improves (decreases) AV nodal conduction time but *not* infranodal conduction time, and thus may *improve* block from 2:1 to 3:2 in Mobitz I, whereas block should be unchanged to *worsened* (2:1 to 3:1) in Mobitz II.

Third-degree AV block (Fig. 22.3)

. Third-degree AV block is characterized by the identification of **complete dissociation of the atrial and ventricular electrical activities** (no temporal relationship exists between the P-waves and the QRS complexes), with atrial activity more rapid than ventricular activity. Using calipers, it is possible to march out the progression of the P-waves to determine the atrial rate.

a. Third-degree AV block is only one cause of AV dissociation; **not all AV dissociation is third-degree AV block.** For example, conditions where the ventricles are depolarizing faster than the atria—such as accelerated junctional rhythm or ventricular tachycardia—also result in AV dissociation if there is a lack of retrograde conduction over the AV node.

FIGURE 22.2 Mobitz type II second-degree atrioventricular block with 3:1 conduction.
FIGURE 22.3 Third-degree atrioventricular block with sinus tachycardia and right bundle branch block.

Therapy. Patients with first-degree AV block and Mobitz type I AV block usually do *not* require therapy. Permanent pacing is indicated for Mobitz type II AV block and third-degree AV block without reversible cause. (See Table 22.3 for complete indications for pacing.)

Medical therapy may be used as a bridge to pacing, but it has no role in long-term treatment.

. The principal drug used as a bridge to pacing is **atropine**:

1. **(1)** It reduces heart block because of hypervagotonia but not because of AV nodal ischemia.
2. **(2)** It is more useful for AV block in inferior MI than anterior MI.
3. **(3)** It does not increase infranodal conduction (will not improve second-or third-degree AV block that is below the AV node).
4. **(4)** It is ineffective in the denervated hearts of transplant patients.
5. **(5)** It is used with caution (if at all) in Mobitz type II AV block because of a possible paradoxical decrease in heart rate (as atrial rate increases, AV conduction decreases, and a 2:1 block with an atrial rate of 80 beats/min and a ventricular rate of 40 beats/min may be converted to a 3:1 block with an atrial rate of 90 beats/min and a ventricular rate of 30 beats/min).

a. Targeted medical therapy ± temporary pacing is indicated for potential reversible causes prior to permanent pacemaker implantation. For example, cardiac Lyme should receive appropriate antibiotic therapy. Overmedication with AV nodal blocking agents should receive adequate time for drug metabolism/clearance ± administration of reversal agents (e.g., glucagon, IV calcium). Digoxin-specific Fab fragments may be used to treat patients with symptomatic AV blocks related to the use of digitalis.

Pacing

. Third-degree AV block as a complication of **inferior MI** is usually temporary and thus usually only requires **temporary pacing**. However, complete heart block as a result of **anterior MI** often requires **permanent pacing** (Table 22.3).

a. Acquired third-degree AV block usually requires pacing, but patients with congenital third-degree AV block often have a sufficiently rapid escape rhythm to prevent symptoms and avoid permanent pacemaker implantation.

b. For irreversible third-degree AV block *without* permanent atrial tachyarrhythmia, a permanent dual-chamber pacemaker should be implanted and programmed to DDD mode. However, if the preimplant ejection fraction is ≤50%, implantation of a biventricular pacemaker (cardiac resynchronization therapy [CRT]) should be considered, due to lower composite rates of

mortality, heart failure, and adverse left ventricular remodeling with CRT in this patient population (BLOCK-HF).

c. The location of the right ventricular permanent pacing lead, whether apical or nonapical, did not affect clinical outcomes or left ventricular remodeling in PROTECT-PACE, a recent prospective randomized control trial (RCT).

JUNCTIONAL RHYTHMS. Junctional rhythms arise from the area surrounding the AV node, including the supranodal fibers, the node itself, and the bundle of His. This area has an intrinsic rate of 30 to 60 beats/min and serves as a faster escape mechanism that supersedes the automaticity of ventricular myocardium (0 to 40 beats/min) in the case of complete AV block. Junctional rhythm that is faster than the sinus rhythm is referred to as **accelerated junctional rhythm**.

Clinical presentation. Patients usually do not develop symptoms that are directly attributable to accelerated junctional rhythm. The **physical findings of AV dissociation may be noted** and are the same as those seen in third-degree AV block.

Etiology

Accelerated junctional rhythm is seen in approximately **10% of patients with acute MI**. More than one-half of these patients have inferior and about one-third have anterior MI.

Digitalis toxicity by itself does not seem to cause accelerated junctional rhythm, as evidenced in persons with normal hearts who take accidental overdoses of digoxin. **Concomitant heart disease** is required to develop accelerated junctional rhythm.

Other causes of accelerated junctional rhythm are valve surgery, acute rheumatic fever, direct current cardioversion, cardiac catheterization, serious infection, chronic obstructive pulmonary disease, systemic amyloidosis, and uremia with hyperkalemia.

ECG findings

Accelerated junctional rhythm

. **Unless the junctional rhythm causes retrograde activation of the atria**, the P-wave is normal in morphologic characteristics. The QRS complex has a normal duration, unless there is concomitant bundle branch block. The distinguishing characteristic of accelerated junctional rhythm is the AV dissociation and changing PR interval (Fig. 22.4).

a. The difference between accelerated junctional rhythm and third-degree AV block is the fact that the ventricular rate is faster than the atrial rate in accelerated junctional rhythm and slower than the atrial rate in third-degree AV block.

Junctional rhythm. In the absence of a sinus beat, the AV node can act as a backup pacemaker. The ECG findings are classically an absence of P-waves (or retrograde P-waves with negative axis in inferior leads immediately before or after the QRS complex with short PR/RP intervals, respectively), a narrow QRS complex, and a rate of 30 to 60 beats/min.

Therapy

Therapy for junctional rhythm secondary to SA node failure or AV block is as previously outlined for AV conduction disturbances.

Patients with accelerated junctional rhythm do not usually require therapy for the arrhythmia, although management of the underlying cause is indicated.

Suppression of accelerated junctional rhythm may be achieved by **increasing the atrial rate with drugs** (e.g., atropine and adrenergics) or **pacing**.

Digoxin-induced accelerated junctional rhythm is an indication to stop digoxin, but it does not usually require administration of digoxin-specific Fab fragments.

INTRAVENTRICULAR CONDUCTION DISTURBANCES. Conduction disturbances because of blockage below the AV node are classified on the basis of the intraventricular conduction system. An intraventricular conduction disturbance (IVCD) does not itself cause bradyarrhythmia, but it may be associated with any of the other rhythms that cause bradycardia. When associated with an acute MI, an IVCD predicts a worse outcome.

Etiology

The causes of IVCDs are similar to those that cause AV block (Table 22.4); **idiopathic degenerative conduction disease** and **acute ischemic syndromes** are the most common causes.

IVCDs increase with age and affect up to 2% of individuals older than 60 years.

The incidence of IVCDs is increased in persons with structural heart disease, especially those with coronary artery disease.

ECG findings

The ECG findings of IVCDs are summarized in Table 22.5 and examples are presented in Figures 22.5 to 22.8. As shown, **IVCDs may be further classified by the number of fascicles they affect**.

Fascicular blocks

. Unifascicular block affects only one of the three fascicles. Examples are RBBB, left anterior fascicular block (LAFB), and left posterior fascicular block (LPFB).

FIGURE 22.4 Accelerated junctional rhythm.

TABLE 22.5 Electrocardiographic Features for the Fascicular and Bifascicular Blocks

ECG Finding	LBBB	LAFB	LPFB	RBBB
QRS axis		≥ −45°	+90° to +120°	
QRS duration leads I/aVL	≥120 ms broad monophasic R	Normal qR	Normal rS	≥120 ms qRS with wide terminal S
Leads II, III, and aVF		rS	qR	
Leads V_1 and V_2	rS or QS			rsR′ or rSR′
Leads V_5 and V_6		S	no Q	qRS

ECG, electrocardiogram; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; RBBB, right bundle branch block.

a. Bifascicular block is present when conduction disturbances affect two of the fascicles, most commonly the right bundle branch and the left anterior fascicle. Approximately, 6% of these patients progress to complete heart block. RBBB with LPFB is less common, but the progression to complete heart block is more common.

b. "Trifascicular block" is said to be present when there is a combination of bifascicular block and first-degree AV block (Fig. 22.8).

FIGURE 22.5 Left anterior hemiblock. **FIGURE 22.6** Left posterior hemiblock.

FIGURE 22.7 Left bundle branch block. **FIGURE 22.8** First-degree atrioventricular block with right bundle branch block and left anterior hemiblock.

Therapy. Pacing is indicated in patients with bifascicular block who have advanced AV block (Mobitz II or complete heart block) or alternating bundle branch block. Whereas an EPS is not routinely performed in this setting, pacing may also be indicated in asymptomatic patients if a prolonged HV interval >100 ms or nonphysiologic infra-Hisian block is found (Table 22.3).

POSTPROCEDURAL BRADYARRHYTHMIAS

Etiology. Bradyarrhythmias following cardiac surgery and endovascular procedures are not uncommon.

Cardiac surgery, in particular valvular surgery and myectomy, can cause mechanical damage to the conduction system, leading to new AV block and IVCD that are variably reversible. The estimated incidence of persistent high-grade AV block requiring permanent pacemaker implantation following cardiac surgery is 2% to 7%. The risk following transcatheter aortic valve replacement appears to be much greater, ranging from 10% to 40% and highly manufacturer specific. The risk of permanent high-grade AV block following nonurgent, coronary-exclusive interventions (coronary artery bypass grafting or percutaneous coronary intervention) is comparably low.

Prolonged ischemic time during cardiac surgery, most commonly cardiac transplantation, can similarly lead to sinus node dysfunction (SND) and subsequent permanent pacing requirement (up to 10% of posttransplant patients).

Therapy. Because postprocedural bradyarrhythmias are frequently temporary and resolve with time postprocedure, temporary pacing should be utilized initially, with the decision to proceed to permanent pacing made only after extended surveillance (institution and procedure-dependent, ranging from 5 to 14 days). The same criteria listed in Table 22.3 are used to determine the indications for permanent pacing postprocedure.

PULSELESS ELECTRICAL ACTIVITY AND ASYSTOLE

Pulseless electrical activity (**PEA**) is defined as the absence of a pulse or blood pressure, yet with the continued presence of electrical activity of the heart. Asystole is defined as the absence of *both* cardiac electrical (e.g., flat line) and mechanical activity. PEA and asystole exist on the same spectrum, classified by advanced cardiac life support (ACLS) as "nonshockable" rhythms and carry exceedingly poor prognoses, with survival 2% after out-of-hospital and 20% to 30% after in-hospital PEA/asystolic arrest.

Etiology

PEA results from electromechanical dissociation, a condition where cardiac electrical activation is ongoing (although not necessarily functioning normally) but produces inadequate (or absent) mechanical contraction/cardiac output. PEA can occur in a variety of **rhythm disturbances**, ranging from idioventricular escape rhythm to sinus tachycardia, although classically excluding ventricular tachycardia and ventricular fibrillation (VF) according to ACLS algorithms. PEA may degenerate to asystole, or asystole may occur directly.

A variety of potentially reversible clinical situations are classically associated with PEA and asystole, abbreviated as the H's and T's (Table 22.6).

Therapy

Rapid management targeted at the suspected underlying cause is most likely to result in favorable outcome. The differential of PEA/asystolic arrest should always include the "H's and T's": **H**ypovolemia, **H**ypothermia, **H**ypoxia, **H**ypoglycemia, **H**yperkalemia, acidosis ("**H**ydrogen ions"), **T**ension pneumothorax, **T**hrombosis (coronary or pulmonary), **T**amponade, **T**oxins, and **T**rauma (Table 22.6).

Emergency resuscitation should be initiated at once as per ACLS protocols:

. Effective, uninterrupted cardiopulmonary resuscitation (CPR) prioritized over advanced airway management

a. Epinephrine, 1 mg IV push every 3 to 5 minutes

b. One-time IV push of 40 IU of vasopressin may be considered as an alternative to epinephrine during the first or second round of ACLS.

c. Atropine is no longer recommended for routine ACLS administration during PEA/asystole, nor is routine defibrillation for potential coarse VF masquerading as asystole, nor routine cardiac pacing for bradycardic rhythms or asystole.

TABLE 22.6 Conditions That Cause Pulseless Electrical Activity

Condition	Clues	Management
Hypovolemia	History of poor oral intake and/or increased blood volume/GI/insensible losses, flat neck veins and poor skin turgor on physical examination, preceding sinus tachycardia, collapsible IVC on ultrasound	Volume infusion (+ transfu
Hypothermia	History of exposure to cold, central body temperature, and ECG findings (bradycardia, Osborn waves)	Gradual warming
Hypoxia	Baseline pulmonary pathology, cyanosis, increasing A–a gradient, airway concerns	Increase oxygen delivery intubation)
Hypoglycemia	History of diabetes (particularly insulin-requiring), fingerstick blood glucose, recent NPO status, acute kidney injury/renal failure	Dextrose administration
Hyperkalemia	History of renal failure, ischemic presentation, uncontrolled diabetes, ECG findings (peaked T-waves, QRS prolongation, sine wave)	(Immediate for electr chloride/gluconate, com sodium bicarbonate, a (long term for potassium or dialysis
Hydrogen ions (acidosis)	History of renal failure, medical comorbidity predisposing to hypercapnia (COPD), acidosis or hypercapnia on arterial blood gas	Sodium bicarbonate, hype
Tension pneumothorax	History (asthma, ventilator, COPD, recent procedure or trauma), no pulse with CPR, neck vein distention, tracheal deviation, absent breath sounds	Needle decompression

TABLE 22.6 Conditions That Cause Pulseless Electrical Activity

Thrombosis (MI)	CAD history, ischemic symptoms, ST-changes on ECG, elevated cardiac enzymes, ventricular arrhythmia preceding or subsequent to PEA arrest	Urgent revascularization
Thrombosis (pulmonary embolism)	Predisposing history (high Wells' score), preceding hypoxia or elevated A–a gradient without clear alternative pulmonary pathology, ECG findings (sinus tachycardia, S1Q3T3, new RBBB, RV strain)	(Periarrest): consider t suspicion and not contr diagnosis via CT or V/Q
Tamponade (cardiac)	History (recent cardiac procedure or trauma, renal failure, malignancy), vein distention; impending tamponade—tachycardia, hypotension, low pulse pressure with pulsus paradoxus, electrical alternans on ECG	Urgent pericardiocentesis
Toxins (drug overdose)	History of ingestion, empty pill bottles at the scene, pupils, skin, and neurologic examination. ECG findings (brady- or tachycardia, PR + QRS + QTc intervals, aVR elevation)	Toxicology consultation administration, drug (intubation)
Trauma	History of recent trauma, physical examination findings (absent breath sounds, overt fractures, ecchymoses, pupil asymmetry), FAST ultrasound findings, profound anemia	Aggressive volume resus trauma surgery consulta

d. A–a, alveolar–arterial; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; CT, computed tomography; ECG, electrocardiogram; FAST, focused assessment with sonography in trauma; GI, gastrointestinal; IV, intravenous; IVC, inferior vena cava; MI, myocardial infarction; NPO, nil per os; PEA, pulseless electrical activity; RBBB, right bundle branch block; RV, right ventricle/ventricular.

e. Although not yet integrated into ACLS guidelines, 20 IU vasopressin + 1 mg ephinephrine for up to first 5 CPR cycles *and* 40 mg methylprednisolone during the first CPR cycle followed by stress-dose hydrocortisone with taper after return of spontaneous circulation demonstrated improved survival and neurologic outcomes after in-hospital PEA/asystolic arrest in a prospective RCT.

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LANDMARK ARTICLES

Curtis AB, Worley SJ, Adamson PB, et al; for the BLOCK HF trial investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med*. 2013;368:1585–1593.

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CHAPTER 23

Sudden Cardiac Death

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I. DEFINITION AND EPIDEMIOLOGY. Sudden cardiac death (SCD) is defined as death following cardiac arrest in a patient with or without known preexisting heart disease in whom the mode and time of death were unexpected. If the person survives the circulatory arrest with return of spontaneous circulation, whether from cardiopulmonary resuscitation (CPR), defibrillation, or spontaneously, the event is deemed a sudden cardiac arrest (SCA). The incidence of SCD in the United States is estimated at 359,800 out of hospital cases per annum, with 209,000 in-hospital cases, accounting for 10% to 15% of all deaths from natural causes and about 50% of all cardiac deaths. SCD exhibits a bimodal age distribution with peaks between birth and 6 months of age and then rises steadily from age 30. A male preponderance is observed in all age groups, narrowing after age 65, and is attributable to an increased incidence of coronary artery disease (CAD). Whereas the absolute risk of SCD is greater among high-risk populations, most SCDs occur in patients who have not been identified as being at risk, being the first presentation of cardiovascular disease in approximately 25% of patients.

It is postulated that most cases of SCA present with ventricular fibrillation (VF) or ventricular tachycardia (VT). As the time from onset of arrest and rhythm identification increases, the proportion of VF decreases. This suggests that asystole and pulseless electrical activity (PEA) are frequently the result of prolonged VT or VF and resultant ischemia and hypoxia. Bradyarrhythmias and pump failure are also responsible for a significant proportion of SCA, especially in patients with advanced heart failure.

II. CAUSES OF SCD

A. CAD accounts for 80% or more episodes of SCD in western societies, and SCD is the first presentation of CAD in 20% to 25% of patients. However, the extent to which acute ischemia plays a role in initiating a trigger for SCD is less clear. On autopsy, 40% to 70% of SCD patients have evidence of remote coronary infarction, whereas only 15% to 20% have evidence of acute occlusive coronary thrombus. Therefore, the majority of SCD episodes in patients with CAD are considered to be primary (i.e., no precipitating factor can be identified), whereas secondary causes such as acute myocardial ischemia/myocardial infarction (MI), drug toxicity or proarrhythmic agents, decompensated heart failure, or electrolyte imbalance can be identified in the minority. Patients with reduced left ventricular ejection fraction (LVEF) and frequent premature ventricular contractions (PVCs) are identified as a particularly high-risk subgroup. A study of patients implanted with a loop

recorder with recent MI and ejection fraction (EF) ≤40% found that the terminal rhythm was VF in 86% of all sudden deaths.

B. Cardiomyopathies

1. **Dilated cardiomyopathy (DCM).** Patients with DCM represent the second largest group of patients who experience SCD, after those with CAD, accounting for approximately 10% of cases. The annual mortality from DCM is 11% to 15%, with SCD accounting for about 30% of all deaths in this population. The presence of reduced LVEF and syncope are high-risk markers for SCA in these patients. There is also a higher incidence of sudden deaths related to bradyarrhythmias and PEA in patients with advanced disease.
2. **Hypertrophic cardiomyopathy (HCM).** The incidence of SCD in patients with *HCM* is 2% to 4% per year in adults and 4% to 6% per year in children and adolescents. Risk factors for SCD in this population include prior SCA, family history of SCD, sustained or nonsustained VT (NSVT), syncope, a drop in blood pressure with exercise, and septal hypertrophy ≥30 mm. Myocardial scar, detected by late gadolinium enhancement on magnetic resonance imaging (MRI), is also emerging as a predictor of risk. SCD usually results from ventricular arrhythmias, but occasionally may be precipitated by atrial fibrillation (AF), bradyarrhythmias, or myocardial ischemia.
3. **Arrhythmogenic right ventricular dysplasia (ARVD).** *ARVD* is a rare genetic disorder characterized by heart failure, ventricular arrhythmias, and SCD. Mutations involving the desmosome result in fibrofatty infiltration of the right ventricle. The incidence of SCD is approximately 2% per year and is mainly due to ventricular tachyarrhythmia. Electrocardiogram (ECG) characteristics of *ARVD* include right bundle branch block (RBBB), T-wave inversion in V_1 through V_3, and epsilon waves. On echo or MRI, there is regional right ventricular akinesia, dyskinesia, or aneurysm, and the diagnosis may be confirmed by endomyocardial biopsy.
4. **Other inherited cardiomyopathies.** Several other cardiomyopathies also present increased risk of SCA. These include *Pompe disease*(GAA), *Danon disease* (LAMP2), *left ventricular hypertrophy with Wolff–Parkinson–White (WPW) syndrome* (PRKAG2), *Fabry disease*(GLA), and *familial amyloidosis* (TTR).

C. The channelopathies

1. **The congenital long QT syndrome (LQTS).** *LQTS* is a familial disease with a prevalence of about 1:2,000, characterized by an abnormally long QT interval, leading to the development of early after-depolarizations and torsades de pointes. It is the most common cardiac channelopathy. The two variants of the syndrome include the more common autosomal dominant form (Romano–Ward syndrome) and the less common recessive form (Jervell and Lange-Nielsen syndrome), which is associated with congenital deafness. At least 15 mutations at different LQTS susceptibility genes have been identified. The most common form is LQT1, accounting for 35% of cases. LQT1 arises from a mutation in *KCNQ1*, which encodes the α-subunit of the potassium channel conducting the slow delayed rectifier current (I_{Ks}). Clinically, LQT1 is characterized by broad-based T-waves and exercise-induced arrhythmic events, especially during swimming. LQT2, accounting for 30% of cases, is caused by mutations in the *KCNH2* gene encoding the HERG protein (I_{Kr}current) and presents with low-amplitude, notched T-waves and auditory arrhythmogenic triggers. LQT2 is also associated with postpartum SCD. LQT3 is caused by a gain-of-function mutation in the

sodium channel gene *SCN5A* and manifests a long, isoelectric ST-segment and SCD events during sleep.

The mortality rate for LQTS is estimated to be about 1% per year. High-risk patients include those with a corrected QT interval >500 ms, a history of syncope or SCA, male sex in children and female sex in adults (especially after menopause), and the LQT2 or LQT3 genotype. It has been postulated that 11% to 13% of sudden infant death syndrome cases may be caused by LQTS. All patients are treated with β-blocker therapy; however, genotype-specific and individualized therapies are evolving. Symptomatic patients who are either refractory to or intolerant of medical therapy or who have other high-risk markers for SCD should be considered for implantable cardioverter–defibrillator (ICD) implantation and left cardiac sympathetic denervation. It seems increasingly likely that many patients who suffer cardiac events because of drug-induced or other acquired QT prolongation have a *forme fruste* of LQTS.

2. **Short QT syndrome** presents with QT interval <350ms, with a predisposition for supraventricular arrhythmias. It is caused by mutations in genes encoding the potassium channel, resulting in shortening of the action potential duration and increasing vulnerability to VF.
3. **Brugada syndrome** is characterized by ECG finding of incomplete RBBB with coved ST-elevation >0.2 mV in >1 right precordial leads. Although traditionally caused by mutations in the *SCN5A* gene encoding the cardiac sodium channel, which disposes to polymorphic VT or VF, more than 17 mutations in other genes have been identified to cause the characteristic ECG changes. Making the diagnosis can be challenging, as these ST-elevations are often transient, occurring during stress, fever, or provocation by class I antiarrhythmic drugs, with normalized ECG during other times. The risk of SCA is up to 30% at 3 years in untreated symptomatic patients. AF and conduction abnormalities are frequently associated. Symptomatic patients (syncope or SCA) should undergo ICD implantation. Risk stratification for asymptomatic patients is controversial.
4. **Catecholaminergic polymorphic ventricular tachycardia (CPVT)** is due to mutations in the ryanodine receptor and calsequestrin and results in a malignant phenotype of bidirectional VT during emotional or physical stress. Treatment is with β-blockers and ICD, and recent evidence suggests an emerging role for flecainide.

D. Other causes of SCD. The risk of SCD is also higher in patients with ***WPW syndrome***, especially if they have rapidly conducting accessory pathways. AF can be associated with very rapid ventricular rates and degeneration to VF. An RR interval ≤220 ms during spontaneous AF indicates a higher risk. The incidence of SCD is 0.05% to 0.1% per year and is higher in males in their second and third decades, but the phenomenon is easily identifiable and manageable. When no cause of SCA can be found, the label *idiopathic VF* is applied. In some cases, VF is triggered by a PVC which is amenable to catheter ablation. *Early repolarization* on ECG may denote a higher risk of SCD in the presence of proarrhythmic triggers, and the clinical implications of this are still being clarified. Refer to Table 23.1 for other cardiac and noncardiac causes of SCD.

III. DIAGNOSTIC AND PROGNOSTIC TESTING. Survivors of SCA should have a detailed cardiovascular evaluation. Reversible precipitating factors must be identified and corrected. Underlying diseases must be identified and managed, and the risk of recurrent

SCA must be determined. Diagnostic and prognostic testing appropriate for the survivor of SCA includes the following:

A. **ECG** for the evidence of MI or ischemia, intraventricular conduction delay, accessory pathway (WPW syndrome), prolonged QT interval, epsilon waves, Brugada pattern, and left ventricular hypertrophy

B. **Laboratory data** to rule out reversible causes, such as cardiac biomarkers, abnormal electrolytes, antiarrhythmic drug levels for toxicity, and urine screening for illicit drugs such as cocaine

C. **ECG monitoring** to assess frequency, duration, and symptomatology of arrhythmias

D. **Twenty-four-hour ambulatory electrocardiography** during normal activities can be useful in predicting the risk of recurrent SCA

E. **Echocardiography** for the assessment of left ventricular function, valvular disease, cardiomyopathy, and hypertrophy. Nuclear or angiographic determinations of left ventricular function may be used but do not provide as much information as echocardiography. LVEF continues to be the most potent predictor of SCD, behaving as a continuous variable with markedly increased risk when LVEF is lower than 40%. However, nonsudden death also increases with declining EF, meaning that the likely mode of death cannot be predicted.

F. **Coronary angiography** for the assessment of CAD or coronary anomalies

G. **Exercise or pharmacologic stress testing** with radionuclide imaging or echocardiography if CAD is present and myocardial ischemia and/or viability is in question

H. **Electrophysiologic (EP) testing** has a limited role in assessing the survivor of SCA. Given its low sensitivity, a negative test does not exclude recurrent SCA, and almost all patients who survive SCA are in any case candidates for an ICD. Although EP testing may be performed to guide programming of the ICD, this is rarely done in practice. Voltage mapping has been used to corroborate a diagnosis of ARVD, and mapping and ablation are essential in the management of patients with WPW and selected patients with cardiomyopathy and VT. Emerging applications of ablation in ARVD and Brugada syndrome require further study.

I. **Cardiac MRI.** Cardiac MRI may be useful for evaluating arrhythmogenic right ventricular cardiomyopathy and to investigate evidence of scar, inflammation, or left ventricular hypertrophy.

J. **Drug challenge** with flecainide, procainamide, or ajmaline to provoke the Brugada pattern should be considered in all SCA survivors where the above tests do not reveal a cause. Epinephrine infusion or exercise testing has been used to diagnose LQT1 and CPVT.

K. **Genetic testing** for the channelopathies, HCM, and ARVD is becoming increasingly comprehensive; however, many as-yet unidentified mutations are postulated to exist. At present, only 21% of patients with Brugada syndrome and 52% with ARVD have an identifiable causative mutation. Testing in cases where a clear phenotype has not been established, or is not suggestive of a genetic disorder, is discouraged, because many variants are of uncertain significance. A positive genetic test is useful and facilitates family screening, but a negative test is not.

TABLE 23.1 Some Other Conditions with an Increased Risk of Sudden Cardiac Death

Cardiac	Noncardia
Cardiovascular	Neurologic
Coronary artery anomalies	Epilepsy
Coronary artery embolism	Hereditary
Coronary arteritis (polyarteritis nodosa and Kawasaki syndrome)	Friedreich
Coronary artery dissection	Central ne
Coronary spasm	Respiratory
Myocardial bridging	Asthma
Valvular and great vessels	Obstructiv
Severe aortic stenosis	Massive p
Severe mitral regurgitation	Pulmonary
Prosthetic valvular obstruction or dehiscence	Endocrine a
Ruptured sinus of Valsalva aneurysm	Diabetes r
Aortic dissection	Acromega
Electrophysiologic	Electrolyte
Progressive cardiac conduction disease (Lev–Lenegre disease)	Acid–base
Myocardial	Renal
Left ventricular hypertrophy	Chronic ki
Infiltrative disease (sarcoid and amyloid)	Hemodialy
Apical ballooning syndrome	Psychiatric/
Myocarditis	Depressio
Congenital	Anxiety
Eisenmenger physiology	Anorexia r
Late after surgical repair, especially of tetralogy of Fallot	Intense en
Trauma	Situational
Cardiac tamponade	Intense ex
Commotio cordis	Drugs
	Antiarrhyth
	Typical an
	Other QT-
	Drug–drug
	Cigarette s
	Cocaine

IV. THERAPY

A. Acute therapy for SCA

1. Cardiopulmonary resuscitation. Early response is crucial. The two most critical components of out-of-hospital cardiac resuscitation are the availability of a rapid response system and bystander CPR. Survivors of SCA are more likely to be discharged from the hospital if the arrest is witnessed and they receive early CPR from bystanders. There is an increasing effort to train police personnel, students, and the general public in resuscitation techniques, focusing on high-quality, uninterrupted chest compressions.

2. **Automated external defibrillator (AED) and public access defibrillation.** An AED is designed to be used by emergency personnel and lay rescuers with minimal or no training for victims of out-of-hospital SCA. The device monitors the patient's ECG via self-adhesive defibrillation electrode pads applied to the chest wall and is programmed with a VF detection algorithm. When the device detects VF, an alarm is emitted, followed by delivery of a defibrillation shock or an indicator for the rescuer to press a button to deliver the shock. Availability of these devices results in more rapid delivery of defibrillation and improved survival to hospital discharge in several large trials. Provision of AEDs for public access defibrillation in airports, sporting facilities, and shopping malls has the potential to have a significant impact on survival of out-of-hospital SCA. Home AEDs have not been shown to increase survival.

3. **Advanced cardiac life support (ACLS).** Unlike AEDs, incorporation of ACLS techniques into prehospital care has not been shown to improve survival in out-of-hospital SCA. Continuous refinements in ACLS algorithms continue to be made, including an emphasis on high-quality CPR with minimal interruption.

4. **Postcardiac arrest hospital care.** Initial management is focused on establishing and maintaining hemodynamic stability and supportive care. Amiodarone or lidocaine (especially if ischemia is suspected as the trigger) is often used to prevent further ventricular tachyarrhythmias. Therapeutic hypothermia for patients who remain unconscious after resuscitation confers a modest improvement in neurologic outcome. Immediate coronary angiography, with revascularization if indicated, may improve survival in patients in whom an ischemic etiology is suspected. Further diagnostic testing is described above.

B. Primary prevention of SCD

1. **Identifying individuals at risk for SCD.** No single factor has been identified that accurately predicts the occurrence of SCD, although combinations of factors have been more useful. In general, the specificity and positive predictive value of these tests are poor, whereas the negative predictive value is much better (particularly for combinations of tests). Overall, the most potent predictor of survival continues to be LVEF, but other factors may aid prognostication and guide subsequent therapy. Other tools for predicting the risk of SCD, such as EP testing, ambulatory electrocardiography, signal-averaged electrocardiography (SAECG), baroreflex sensitivity, heart rate variability (HRV), and T-wave alternans, have been used to identify high-risk groups, but none have been shown to be of convincing value. Although a combination of different tests can improve sensitivity and specificity, the positive predictive value remains modest.

2. **Pharmacologic agents and surgical/percutaneous revascularization.** Because the majority of episodes of SCD occur in patients with CAD, agents that reduce myocardial ischemia (β-blockers), prevent or limit the extent of MI, and alter ventricular remodeling after MI (angiotensin converting enzyme inhibitors and aldosterone antagonists) have all been shown to reduce the incidence of SCD. Although there is no direct evidence of a role for antiplatelet agents or statins in reducing SCD, such an effect is likely, given the reduction in mortality in several broad populations. Early studies of surgical myocardial revascularization showed a reduction in SCD for patients with triple-vessel CAD and left ventricular dysfunction compared with those patients treated medically. Fibrinolysis and percutaneous coronary intervention also reduce SCD in patients with MI.

Catheter ablation of VT has a role in select patient populations, particularly in patients with incessant arrhythmias, despite antiarrhythmic drug and/or implantable device therapy.

More than 40 years ago, complex ventricular ectopy in survivors of MI was recognized as a risk factor for SCD. Suppression of ventricular ectopy with antiarrhythmic drugs in such patients was, therefore, thought to be beneficial. However, the Cardiac Arrhythmia Suppression Trial demonstrated that the proarrhythmic effects of class Ic antiarrhythmic drugs are greater than the benefit achieved through ectopy suppression in the post-MI population, resulting in a 2.6-fold increased mortality. Excess mortality was also demonstrated in survivors of MI with poor left ventricular function taking the class II/III agent sotalol in the Survival With Oral *d*-Sotalol study and with mexiletine.

To date, of all the antiarrhythmic drugs, only amiodarone has been shown to reduce SCD in some populations. Initial small trials of amiodarone therapy for survivors of MI, and meta-analyses of these trials, suggested reduced SCD mortality and the larger but unblinded Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina study appeared to corroborate this finding. However, several prospective, placebo-controlled trials did not. The Survival Trial of Amiodarone in Patients with Congestive Heart Failure failed to demonstrate a significant reduction in either SCD or all-cause mortality in a largely male population with heart failure, EF $\leq$ 40%, and frequent PVCs. Although the European Myocardial Infarct Amiodarone Trial demonstrated a 35% reduction in arrhythmic deaths in a population with recent MI, there was no difference in all-cause mortality. The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) similarly reported a reduction in resuscitated VF or arrhythmic death in survivors of MI with frequent ventricular ectopy, but no difference in all-cause mortality. Lastly, there was no difference in the primary end point of all-cause mortality between amiodarone and placebo in the medical treatment arm of the large Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). The newer benzofuran derivative, dronedarone, also reduced SCD in the pivotal ATHENA trial of patients with AF and additional risk factors, but increased all-cause mortality in patients with severe heart failure in the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease. Mexiletine showed a trend toward increased mortality, and dofetilide and azimilide had no effect on all-cause mortality or SCD in patients with recent MI in large controlled studies.

In summary, amiodarone reduces SCD but not all-cause mortality in patients with heart failure or recent MI, and several other antiarrhythmics, including class Ic agents, mexiletine, dronedarone, and sotalol, may increase mortality in this population.

3. **Implantable devices.** In light of the inefficacy and even hazards of antiarrhythmic drugs for the prevention of SCD, attention has shifted to the ICD. Since its introduction by Mirowski in 1980, technical refinements have paralleled a series of clinical trials which extended indications to primary prevention in select populations. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) demonstrated a 54% relative risk reduction in all-cause death versus usual care in 196 patients with prior MI, New York Heart Association (NYHA) class I–III heart failure, EF $\leq$ 35%, NSVT, and inducible, nonsuppressible, ventricular arrhythmia during EP study (EPS). The Multicenter Unsustained Tachycardia Trial (MUSTT) randomized patients with CAD, EF $\leq$ 40%, NSVT, and inducible VT/VF to receive EP-guided antiarrhythmic drug therapy, with or without an ICD, or no therapy. The 27% reduction in arrhythmic death or cardiac arrest in the EP-guided drug

therapy arm was entirely driven by a 76% reduction in patients with ICDs, with no difference between drug therapy and no therapy. Given the modest predictive value of EPS, MADIT II dispensed with inducible VT as an inclusion criterion and enrolled patients with prior MI on the basis of an EF ≤ 30%. This randomized comparison of ICD with usual care demonstrated a 31% relative risk reduction in all-cause mortality over an average follow-up of 20 months. MADIT, MUSTT, and MADIT II all enrolled patients with prior MI. Whereas the underpowered Amiodarone Versus Implantable Cardioverter-Defibrillator and Cardiomyopathy Trial failed to show a benefit of ICDs over medical therapy in patients with nonischemic cardiomyopathy (NICM), the results of the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation trial extended primary prevention ICD therapy to these patients. In patients with NICM, heart failure, EF ≤ 35%, and NSVT or frequent PVCs, a nonsignificant reduction in all-cause mortality was observed, with a significant reduction in SCD. The larger SCD-HeFT randomized 2,521 patients with ischemic cardiomyopathy (52%) or NICM (48%), EF ≤ 35%, and NYHA functional class II or III heart failure to receive conventional therapy plus placebo, amiodarone, or a single lead ICD. ICD therapy reduced all-cause mortality by 23% compared with placebo, whereas amiodarone was not associated with any benefit. These trials, and SCD-HeFT in particular, ushered in the current era of primary prevention ICDs for patients risk-stratified largely on the basis of EF.

The limitations of ICDs have also been defined by clinical trials. The Coronary Artery Bypass Graft (CABG) Patch Trial demonstrated that primary prevention ICD implantation at the time of CABG in patients with preoperative left ventricular dysfunction (EF ≤ 35%) and an abnormal SAECG did not improve the overall survival, despite reducing arrhythmic deaths. The lower event rates in the CABG Patch Trial were consistent with earlier evidence that CABG reduces the risk of SCD in this population, negating the protective effect of the ICD.

MADIT, MUSTT, and MADIT II studied patients with remote (>3 weeks) ischemic events. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) assessed whether the benefits of ICD therapy would also be seen early after MI. The trial enrolled patients 6 to 40 days post-MI with EF <35% and impaired HRV or elevated average 24-hour heart rate and randomized them to receive an ICD or no ICD. Although ICD therapy reduced arrhythmic death, this was offset by an increase in nonarrhythmic death in the ICD group, so there was no difference in all-cause mortality over 30 months of follow-up. These results were confirmed by the larger Immediate Risk Stratification Improves Survival (IRIS) trial, which enrolled a similar population. Taken together, IRIS and DINAMIT suggest that whereas ICDs prevent SCD in high-risk patients early post-MI, this merely changes the mode of death to nonsudden death, without affecting the overall survival. This is supported by a secondary analysis of DINAMIT, which showed that the risk of nonsudden death in the ICD group was 4.8-fold higher in those who had received an appropriate shock. The above findings have been incorporated into the Centers for Medicare and Medicaid Services coverage determination for ICDs, which excludes patients with MI within 40 days and surgical or percutaneous revascularization within 3 months of ICD implantation. A wearable defibrillator is available for temporary use, while diagnostic testing is ongoing, or during periods of transient elevated risk.

4. **Cardiac resynchronization therapy (CRT).** Approximately 30% of patients with advanced heart failure (EF ≤ 35%) have an associated ventricular conduction delay resulting in a QRS duration ≥120 ms and are candidates for CRT. The strongest data for

CRT therapy exist for individuals with left bundle branch block (LBBB) and QRS duration >150 ms with LVEF of 35% or less and at least class II NYHA symptoms. Biventricular pacing has been shown to improve survival, quality of life, exercise capacity, and EF in patients with advanced CHF. Extended follow-up data from the Cardiac Resynchronization in Heart Failure trial also reported a significant 46% reduction in SCD in patients with CRT without a defibrillator when compared with no CRT. However, a significant number of SCDs occurred in the CRT group, some of which might conceivably have been prevented by a defibrillator. The only large randomized trial comparing CRT with a defibrillator (CRT-D), CRT without defibrillator (CRT-P), and no device was the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial. Although not powered to detect a difference between CRT-D and CRT-P, a nonsignificant 50% decrease in SCD was seen with CRT-D in patients with NYHA class III or IV CHF, EF ≤ 35%, and a QRS duration ≥ 120 ms. These data suggest that CRT-D should be considered for most patients eligible for biventricular pacing. See Chapter 52 in this book for in-depth discussion of CRT.

C. Secondary prevention

1. **Pharmacologic agents.** As with primary prevention of SCD, the disappointing efficacy and safety of class I antiarrhythmic drugs shifted attention to other antiarrhythmic drugs for the secondary prevention of SCD. In the Cardiac Arrest in Seattle Conventional Versus Amiodarone Drug Evaluation study, amiodarone reduced cardiac death, arrest, and ICD shocks compared with conventional class I antiarrhythmic drugs in a secondary prevention population. In addition, the Electrophysiologic Study Versus Electrocardiographic Monitoring trial demonstrated that the class II/III antiarrhythmic drug sotalol was superior to six class I agents guided by EP testing or Holter monitoring in preventing all-cause, cardiac, and arrhythmic mortality in patients with a history of VT/VF, SCA, or syncope. However, emergence of the ICD led to randomized trials comparing the efficacy of best medical therapy and ICDs for the secondary prevention of SCD.
2. **Implantable devices.** The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial studied the efficacy of ICD therapy versus the antiarrhythmic drugs amiodarone or sotalol for the secondary prevention of SCD in patients with resuscitated VF or sustained VT plus either syncope or EF ≤ 40% and hemodynamic compromise during VT. Inducible arrhythmias were not required for inclusion, and only sotalol therapy was guided by EP testing (only 2.6% of patients randomized to antiarrhythmic drug therapy were discharged on sotalol). ICDs reduced all-cause mortality by 31% at 3 years of follow-up.

   Two other large trials of ICDs for secondary prevention of SCD that ran concurrently with AVID reported similar results. The Cardiac Arrest Study Hamburg found that ICDs conferred a nonsignificant 23% reduction in all-cause mortality when compared with amiodarone or metoprolol in patients with resuscitated cardiac arrest because of documented VT/VF. The propafenone arm of the study was terminated early after an interim analysis showed excess mortality compared with the ICD group. The Canadian Implantable Defibrillator Study enrolled a similar population as the AVID trial, randomizing patients with resuscitated VF, sustained VT with syncope or hemodynamic compromise and EF ≤35%, or unmonitored syncope with subsequent spontaneous or induced VT to ICD or amiodarone therapy. Over a mean follow-up period of 3 years, a nonsignificant 19.7% relative risk reduction in all-cause mortality was observed, as well as a nonsignificant 32.8% reduction in SCD. Each of the above studies excluded patients with a transient or reversible cause of ventricular arrhythmias,

such as MI within 72 hours, or electrolyte imbalances. A meta-analysis of these three trials confirmed a significant 28% reduction in the relative risk of death with the ICD, which was due largely to a 50% reduction in SCD.

Of considerable interest is evidence that patients screened for the AVID trial but thought to have a transient or reversible cause of SCA, and who were not entered in the trial but followed in a registry, had poor long-term survival similar to those patients who were also ineligible for the trial but known to be at high risk for SCD. These data emphasize the need for meticulous evaluation of every SCA survivor and careful consideration of whether SCA was due to a cause that was not only transient and reversible but also preventable in the future.

D. Summary: Antiarrhythmic drugs versus ICDs. Current guidelines for ICD therapy are summarized in Table 23.2. From the available data, there is good evidence that many antiarrhythmic drugs are not efficacious and may be harmful in the primary prevention of SCD, and antiarrhythmic drugs (apart from β-blockers) are not indicated for this purpose. ICD therapy has proven to be highly effective in the termination of malignant ventricular arrhythmias and is more effective than antiarrhythmic medications for the prevention of SCD in patients with ischemic or nonischemic heart failure and an EF ≤35%. Patients with prolonged QRS duration, especially with LBBB, should also be considered for CRT. The most powerful predictor of SCD risk in this population remains LVEF, and other methods such as EP testing and SAECG may give additional information but are neither sensitive nor specific enough to select patients for ICD therapy. Specific antiarrhythmics may have niche uses in high-risk patients with genetic diseases predisposing to SCD, such as HCM, ARVD, Brugada syndrome, and LQTS, and an ICD is also indicated in select patients. The bradyarrhythmias respond well to pacemaker therapy. Radiofrequency catheter ablation is the therapy of first choice in patients with WPW syndrome and is an effective synergistic therapy in patients with VT who have recurrent ICD shocks.

TABLE 23.2 Indications for Implantable Cardioverter–Defibrillator Therapy

Class I

1. Survivors of cardiac arrest because of VF or hemodynamically unstable sustained VT after evalua and to exclude any completely reversible causes
2. Structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unsta
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT
4. LVEF ≤35% because of prior MI, at least 40 d post-MI, and NYHA class II or III
5. Nonischemic DCM, LVEF ≤35%, and NYHA class II or III
6. LV dysfunction because of prior MI, at least 40 d post-MI, LVEF ≤30%, and NYHA class I
7. NSVT because of prior MI, LVEF ≤40%, and inducible VF or sustained VT during EPS
8. Symptomatic sustained VT in association with congenital heart disease after hemodynamic and EP

Class IIa

1. Unexplained syncope, significant LV dysfunction, and nonischemic DCM
2. Sustained VT and normal or near-normal ventricular function
3. HCM with one or more major risk factors for SCD
4. ARVD/C with one or more risk factors for SCD
5. LQTS with syncope and/or VT while receiving β-blockers
6. Nonhospitalized patients awaiting heart transplantation

TABLE 23.2 Indications for Implantable Cardioverter–Defibrillator Therapy

7. Brugada syndrome with syncope
8. Brugada syndrome with documented VT that has not resulted in cardiac arrest
9. Catecholaminergic polymorphic VT with syncope and/or documented sustained VT while receiving
10. Cardiac sarcoidosis, giant cell myocarditis, or Chagas disease
11. Congenital heart disease with recurrent syncope of undetermined origin in the presence of eithe ventricular arrhythmias during EP study

Class IIb

1. Nonischemic heart disease, LVEF ≤ 35%, and NYHA class I
2. LQTS with risk factors for SCD
3. Syncope and advanced structural heart disease where thorough invasive and noninvasive investig
4. Familial cardiomyopathy associated with sudden death
5. LV noncompaction
6. Recurrent syncope associated with complex congenital heart disease and advanced systemic ve invasive and noninvasive investigations have failed to define a cause

Class III

1. Patients who do not have a reasonable expectation of survival with an acceptable functional status
2. Incessant VT or VF
3. Patients with significant psychiatric illnesses that may be aggravated by device implantation or that
4. NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for car
5. Syncope of undetermined cause without inducible ventricular tachyarrhythmias and without structu
6. VF or VT that is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease)
7. Ventricular tachyarrhythmias because of a completely reversible disorder in the absence of stru imbalance, drugs, or trauma)

E. ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; CRT-D, cardiac resynchronization therapy with a defibrillator; DCM, Dilated cardiomyopathy; EP, electrophysiologic; EPS, electrophysiologic study; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter–defibrillator; LQTS, long QT syndrome; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; RV, right ventricle; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff–Parkinson–White.

F. Adapted from the 2008 ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities; American Heart Association, Inc.

G. Evidence from several recent randomized trials demonstrates the superiority of the ICD over antiarrhythmic drugs for the population requiring secondary prophylaxis. Antiarrhythmic drugs such as amiodarone, sotalol, and mexiletine may be of use in those patients who experience frequent ICD shocks.

V.PROGNOSIS

A. VF and pulseless VT ("shockable rhythms") are the initial rhythm in approximately one-quarter of SCA victims and are associated with more favorable outcomes than asystole or PEA. VT/VF incidence declines by ~10% with each minute after

the onset of cardiac arrest; therefore, witnessed SCA and prompt recognition and defibrillation are associated with improved survival. Only one-third of SCA victims receive bystander CPR. A recent large study of cardiac arrest incidence and outcomes in North America found that of the 60% of patients in whom resuscitation was attempted, 10.6% survived to hospital discharge, with wide regional variation. This proportion rose to 31.4% if the initial rhythm was VF. A number of factors have been identified to aid prognostication post arrest, including preexisting comorbidities, absent pupillary and corneal reflexes, extensor or no motor response to pain on day 3, and myoclonus status epilepticus; however, none are definitive.

VI. FUTURE. Large population studies are needed to better define the incidence of SCD across ethnic/racial groups and elucidate the mechanisms. Discovery of risk markers of SCD in the general population, such as clinical, molecular, and genetic factors, will facilitate targeting of evaluation and therapy to those who need it. CAD and its consequences account for 80% of SCD, often occurring as the first presentation of CAD. Given the difficulty in identifying those with subclinical disease who are ostensibly at low risk, focus has recently moved to primordial prevention—the prevention of the development of risk factors for CAD. This will likely have the most impact on SCD at the population level, but its effects are difficult to measure. In those at established risk, improved risk markers that refine the current LVEF-based approach will allow better targeting of ICD therapy.

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WEB SITES

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QT Drug Lists. Arizona Center for Education and Research on Therapeutics, The Critical Path Institute, Tucson, AZ and Rockville, MD. https://crediblemeds.org/

CHAPTER 24

Atrial Fibrillation

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I. INTRODUCTION. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is characterized by the degeneration of organized atrial electrical activity into a rapid, chaotic pattern. AF accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances. An estimated 3 million people in the United States and 6 million people in Europe have AF. The prevalence of AF is higher in men and increases with age. AF is associated with an increased risk of stroke, heart failure, and mortality.

A. Classification. AF can be classified as **new-onset** or **recurrent** (at least two episodes). AF can also be classified according to its pattern as **paroxysmal** (self-limiting), **persistent** (sustained >7 days), **long-standing persistent** (sustained >12 months), and **permanent** (no longer pursuing restoration of sinus rhythm). It is important to distinguish **nonvalvular** from **valvular AF** (rheumatic mitral stenosis, prosthetic heart valve, or mitral valve repair) because this impacts antithrombotic choice. Many of the clinical trials of the new oral anticoagulants excluded patients with prosthetic heart valves, mitral stenosis, and severe valvular disease who were likely to require imminent valve surgery. The term **lone AF** has been used to describe patients without structural heart disease and should only be used in patients at very low risk for complications of AF such as thromboembolism.

B. Pathophysiology. Multiple disease pathways contribute to AF, and these mechanisms are incompletely understood. **The role of the pulmonary veins as a source for triggers of AF is increasingly appreciated.** A previous model proposed by Moe et al. in 1962 described multiple reentrant wavelets within the atrial tissue that contributed to the maintenance of AF. More recent data support a focal mechanism involving both increased automaticity and multiple reentrant wavelets that occur predominantly in the left atrium around the pulmonary veins. A new model incorporates these mechanisms of initiation of AF and additional atrial substrate conditions for AF maintenance. In turn, this may be affected by various modulating factors such as autonomic tone, medications, atrial pressure, and catecholamine levels. AF is a very complex arrhythmia, and this mechanistic model simply serves as a conceptual framework on which to build.

C. Risk factors. AF is most commonly associated with advanced age, hypertension, valvular heart disease, congestive heart failure, and coronary artery disease. AF has also been associated with physiologic stress, drugs, pulmonary embolism, chronic lung disease, hyperthyroidism, caffeine, infectious processes, and various metabolic disturbances. AF has

also been linked with obesity and obstructive sleep apnea. This phenomenon seems to be mediated by left atrial dilation. Other less common cardiac associations include preexcitation syndromes, pericarditis, and cardiomyopathies. Surgery, particularly cardiac surgery, is associated with a high risk of AF. Persistence of AF has been correlated with elevated C-reactive protein levels, which raises the possibility of a role for inflammation in this condition.

D. Clinical presentation. The clinical presentation of AF can vary widely. Some patients may be **asymptomatic** whereas others can present with severe hemodynamic instability such as those with ventricular preexcitation. The most common symptoms are **palpitations, fatigue,**and **dyspnea**. Some patients may present with **chest discomfort** or **syncope**. AF is also commonly found in patients admitted with **stroke**.

E. Diagnostic testing. The initial evaluation of a patient with new-onset AF includes a detailed history and physical examination to define the clinical type of AF (pattern, frequency, and duration) and to characterize the nature of symptoms associated with AF. Additional evaluation should include the following:

1. Laboratory evaluation should include a complete blood count, comprehensive metabolic panel, magnesium level, and **thyroid function tests**. Hyperthyroidism should always be considered, especially when the ventricular rate is difficult to control.

2. 12-Lead electrocardiogram (ECG) should be obtained to verify AF and determine the ventricular response rate. P-waves are absent and replaced by **fibrillatory (f) waves**. The atrial electrical activity is disorganized, and the ventricular response rate is usually **irregularly irregular**. The atrial rate is generally in the range of 400 to 700 beats/min whereas the ventricular response rate is generally in the range of 120 to 180 beats/min in the absence of drug therapy. Special attention should be paid to signs of underlying left ventricular hypertrophy, ventricular preexcitation, and ischemic heart disease because these features can affect management. The ECG may also be used to measure and follow PR, QRS, and QT intervals during treatment with antiarrhythmic agents.

3. Transthoracic echocardiography is usually performed to identify the presence of structural heart disease, to assess atrial and ventricular size and function, and to document coexistent pulmonary hypertension.

4. Additional investigation in selected patients with AF may include ambulatory ECG monitoring or a 6-minute treadmill walk test to document heart rate response to exercise. An evaluation for sleep apnea should be considered in obese patients or if the index of suspicion is otherwise high.

II. THROMBOEMBOLIC RISK AND TREATMENT.

Patients with AF are at increased risk of systemic thromboembolism compared with the general population, and antithrombotic therapy should be considered in all patients. Decisions regarding antithrombotic therapy should be individualized after careful consideration of the risks of stroke and bleeding as well as patient preferences.

A. Anticoagulation strategy with cardioversion. Electrical, pharmacologic, and spontaneous cardioversion carries an increased risk of thromboembolism with most events occurring in the 10 days following restoration of sinus rhythm. Therefore, several factors should be considered when deciding upon an anticoagulation strategy with cardioversion.

1. Duration of AF

a. Patients with AF **longer than 48-hour duration** represent a particularly high-risk population. These patients merit transesophageal echocardiography (TEE) to rule out left atrial thrombus or 3 weeks of therapeutic anticoagulation prior to cardioversion **regardless of CHA_2DS_2-VASc score**.

b. For patients with AF **less than 48-hour duration** that are high risk for thromboembolism, anticoagulation is recommended as soon as possible before or immediately after cardioversion. For patients who are low risk for thromboembolism, either anticoagulation or no anticoagulation may be considered.

c. **Duration of anticoagulation.** For patients requiring anticoagulation, they should continue therapy **for at least 4 weeks after cardioversion**. Decisions regarding long-term anticoagulation should be made after careful consideration of the risks and benefits of therapy.

d. **Choice of anticoagulant.** For patients with nonvalvular AF, anticoagulation with intravenous heparin, low-molecular-weight heparin (LMWH), warfarin, and new oral anticoagulants may be considered. For those with mitral stenosis and AF, warfarin is the only proven oral anticoagulant to date. Recent American College of Cardiology/American Heart Association guidelines support the use of noncoumadin anticoagulants in other forms of valve disease associated with AF based on registry data from multiple clinical trials.

B. Long-term anticoagulation. The decision for long-term anticoagulation in patients with nonvalvular AF should be individualized after taking into account the risks, benefits, and patient preferences.

1. **Thromboembolic risk.** Current guidelines recommend the use of the **CHA_2DS_2-VASc risk stratification score** for the assessment of stroke risk in patients with nonvalvular AF (see Table 24.1). The pattern of AF (paroxysmal, persistent, long-standing persistent, or permanent) should not be considered.

2. **Bleeding risk.** Multiple tools exist to predict bleeding risk; however, their clinical application is limited by imprecise bleeding estimates. The **HAS-BLED bleeding risk score** (hypertension, abnormal renal and liver function, stroke, bleeding tendency, labile international normalized ratio, elderly, and drugs/alcohol concomitant use) is the most commonly used score, but its routine use is not included in current guidelines. Intracerebral hemorrhage is the most feared bleeding complication and has been reported to occur between 0.2% and 0.4% per year in patients taking warfarin.

TABLE 24.1 CHA_2DS_2-VASc Risk Stratification Score for Patients with Nonvalvular AF

Risk Factor	Score
Congestive heart failure[a]	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Systemic thromboembolism (including TIA)	2
Vascular disease[b]	1

TABLE 24.1 CHA_2DS_2-VASc Risk Stratification Score for Patients with Nonvalvular AF

Age 65–74 y	1
Female sex[c]	1
Maximum score	9
Ischemic Stroke Risk[d]	
CHA_2DS_2-VASc Score	**Percent per Year**
0	0.2
1	0.6
2	2.2
3	3.2
4	4.8
5	7.2
6	9.7
7	11.2
8	10.8
9	12.2
Antithrombotic Strategy[e]	
CHA_2DS_2-VASc Score	**Recommendation**
0	Reasonable to omit therapy (class IIa, LOE: B)
1	No therapy or oral anticoagulation or aspirin (c
≥2	Oral anticoagulation (class I, LOE: A)

3. AF, atrial fibrillation; LOE, level of evidence; TIA, transient ischemic attack.
4. [a]Documented moderate to severe systolic dysfunction or recent decompensated heart failure requiring hospitalization regardless of ejection fraction.
5. [b]Prior myocardial infarction, peripheral arterial disease, or aortic plaque.
6. [c]If age <65 years with no other risk factors, female sex does not independently increase risk.
7. [d]Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182,678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J.* 2012;33(12):1500–1510.

8. [e] Based on January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation.* 2014;130(23):2071–2104.

9. **Choice of oral anticoagulant.** The use of most new oral anticoagulants should also be avoided in patients with severe kidney disease. For patients with AF, the antithrombotic selection should take into account multiple factors such as comorbidity, dosing frequency, patient preference, cost, tolerability of warfarin, drug interactions, and other clinical characteristics (see Table 24.2).

10. **Nonpharmacologic stroke prevention.** For patients who have an unacceptable risk of bleeding on anticoagulation, percutaneous techniques to occlude the left atrial appendage have been shown to be effective. There are several devices available, but the **WATCHMAN device** is the most commonly used. This device was approved by the United States Federal Drug Administration in March 2015 based on the findings in two randomized trials that compared the device to warfarin therapy (PROTECT AF and PREVAIL). After left atrial appendage occlusion, patients should be treated with 6 weeks of oral anticoagulation and aspirin followed by 6 months of aspirin and clopidogrel. **Surgical closure of the left atrial appendage should be considered in all patients with AF who require cardiac surgery.**

III. RATE CONTROL.

Control of the ventricular response rate is an important strategy in the management of AF, and multiple drugs that slow conduction through the atrioventricular (AV) node can be utilized. **It is important to recognize signs of ventricular preexcitation in patients with AF** because AV nodal agents in this setting can facilitate increased conduction down the accessory pathway and lead to further hemodynamic compromise. **The ideal resting heart rate should be less than 80 beats/min** although a more lenient target of less than 110 beats/min can be used as long as left ventricular systolic function is preserved. Heart rate during exercise should also be assessed to ensure adequate control.

A. **β-Blockers** have a rapid onset of action and are available in both oral and intravenous forms. They can be used in both the inpatient and outpatient setting. Metoprolol succinate, carvedilol, and bisoprolol are the preferred agents if patients have concomitant left ventricular systolic dysfunction. β-Blockers should be used with caution in patients with bronchospastic airway disease.

B. **Nondihydropyridine calcium channel blockers** such as diltiazem and verapamil have a rapid onset of action and are available in both oral and intravenous forms. **These medications should not be used in patients with decompensated heart failure or cardiac amyloidosis.** Both diltiazem and verapamil are available in short-acting and sustained-release oral formulations.

C. **Digitalis** is available in both oral and intravenous forms. It is primarily used for rate control when contraindications exist to β-blockers and calcium channel blockers and in patients with left ventricular systolic dysfunction. It may also be used as an adjunct to β-blockers and calcium channel blockers. It is important to remember that digoxin is most effective at controlling the resting heart rate but less effective with activity. **Digitalis toxicity** is a serious complication of chronic therapy. Cardiac manifestations of digitalis

toxicity include all arrhythmias except rapidly conducted atrial tachyarrhythmias. Patients also present with gastrointestinal and neurologic complaints. Digitalis toxicity can be treated with digoxin-specific antibody fragments.

TABLE 24.2 Choices of Oral Anticoagulants

	Warfarin	Dabigatran	Rivaroxaban
Target	Factors II, VII, IX, X	Thrombin	Factor Xa
Half-life (hours)	20–60	14–17	5–9
Dosing frequency	Once daily	Twice daily	Once daily
Antidote	Vitamin K	Idarucizumab	None[a]

[a] Andexanet is currently in clinical trials.

D.

E. Antiarrhythmic medications such as **amiodarone** can also be used for rate control because of its β-blocking properties if other medications are unsuccessful. Patients must be anticoagulated, given the chance of pharmacologic cardioversion. Dronedarone should never be used for rate control in patients with permanent AF because of increased harm.

F. **AV nodal ablation with insertion of a permanent ventricular pacemaker** can be used if medical therapy is unsuccessful and should only be considered as a last resort. If possible, the device should be implanted 4 to 6 weeks before AV nodal ablation to ensure adequate pacemaker function prior to procedure. These patients should be followed closely for the development of a cardiomyopathy because of chronic right ventricular pacing in which case a referral for cardiac resynchronization therapy may be necessary.

IV. RHYTHM CONTROL. The treatment of **any unstable patient where AF is contributing to hemodynamic instability is immediate direct current cardioversion (DCCV)**. For stable patients with AF, attempts to restore and maintain sinus rhythm utilizing cardioversion, antiarrhythmic drugs, and catheter ablation are commonly used (see Fig. 24.1). Although rhythm control with antiarrhythmic drugs has not been shown to be superior to rate control with respect to mortality, restoration of sinus rhythm is associated with symptom relief and improved quality of life in many patients. Other factors such as young age, new-onset AF, and tachycardia-induced cardiomyopathy also favor a rhythm control strategy.

A. **Electrical cardioversion.** Successful restoration of sinus rhythm is most effectively accomplished with DCCV, which is successful approximately 80% of the time. Whenever possible, DCCV should be performed under sedation with appropriate hemodynamic monitoring and in the presence of personnel skilled in airway management. See Chapter 58 for more procedural details of DCCV.

B. **Pharmacologic cardioversion.** Flecainide, propafenone, dofetilide, amiodarone, and intravenous ibutilide can be used for cardioversion as long as no contraindications exist. However, the success rate is much lower than DCCV.

1. Intravenous ibutilide is a class III agent that carries a 1% to 2% risk of **torsades de pointes**, and patients should be monitored after drug administration. Because of this, the use of ibutilide for pharmacologic cardioversion has fallen.

2. As needed, **flecainide** and **propafenone** can be used for selected outpatients as long as these agents have been shown to be safe in a monitored setting. **This "pill-in-the-pocket" approach should always be used in conjunction with AV nodal blocking agents** because these class IC antiarrhythmic agents can promote 1:1 ventricular conduction in patients with atrial flutter. These agents should not be used in patients with coronary artery disease, left ventricular dysfunction, or other significant heart disease.

3. **Dofetilide should always be started in a monitored inpatient** setting because of its risk for QT prolongation and subsequent torsades de pointes.

FIGURE 24.1 Approach to rhythm control for patients with paroxysmal and persistent atrial fibrillation. CAD, coronary artery disease; LVH, left ventricular hypertrophy. (Adapted from the January CT, Wann LS, Alpert JS, et al. ACC/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;64(21):2305–2307; American Heart Association, Inc.)

C. **Drugs to maintain sinus rhythm.** A number of oral agents are available for the maintenance of sinus rhythm. It should be kept in mind that the initiation or upward dose titration of antiarrhythmic drugs should be done with caution and, in many instances, should be performed in a hospital setting with cardiac monitoring. This is particularly true for the class III agents sotalol and dofetilide. On the other hand, in patients without structural heart disease, the class IC agents flecainide and propafenone may be considered for initiation on an outpatient basis.

1. **Vaughan Williams class IA agents.** These sodium channel blockers have seen a decline in use over time primarily because of a high incidence of intolerable side effects but also because of the possibility of increased mortality in patients with structural heart disease.

a. **Procainamide** is not used frequently due to its gastrointestinal, hematologic, and immunologic (i.e., drug-induced lupus) side effects. An active metabolite of this drug, *N*-acetylprocainamide (NAPA), is cleared renally and has class III antiarrhythmic properties. Blood levels of both procainamide and NAPA need to be monitored to prevent toxicity, especially in patients with renal or hepatic insufficiency. **Procainamide is still used in stable patients with AF and evidence of ventricular preexcitation.**

b. **Quinidine** is not used frequently due to its relatively high incidence of gastrointestinal, hematologic, and neurologic side effects. Additionally, quinidine prolongs the QT interval and has significant drug–drug interactions. Quinidine has no negative inotropic effects and can be used in patients with advanced renal dysfunction when other antiarrhythmics cannot be used.

c. **Disopyramide** is not used frequently due to its powerful negative inotropic and anticholinergic effects although it is used in patients with **hypertrophic cardiomyopathy**.

2. **Vaughan Williams class IC agents. Flecainide** and **propafenone** are sodium channel blockers that have become the preferred agents for maintenance of sinus rhythm in patients without significant heart disease. The Cardiac Arrhythmia Suppression Trial found flecainide to be associated with increased mortality when used for suppression of ventricular arrhythmias in patients with left ventricular dysfunction after myocardial infarction. Furthermore, these agents are negative inotropes and can prolong QRS duration.

Therefore, **these agents should not be used in patients with coronary artery disease or structural heart disease and should be used in caution in patients with significant conduction system disease without a pacemaker**. In patients with atrial flutter, these agents can slow the atrial rate to the point where 1:1 ventricular conduction occurs; therefore, they should **always be administered in conjunction with AV nodal blocking agents**.

3. **Vaughan Williams class III agents.** These potassium channel blockers have become the preferred agents for most patients with structural heart disease. Sotalol and dofetilide should be avoided in patients with severe left ventricular hypertrophy.

a. **Sotalol** has β-blocking properties and should be used in caution in patients with heart failure. This agent also causes **QT prolongation**, and drug initiation or dose increase should be performed in a hospital setting with cardiac monitoring. The dose must be reduced in patients with renal insufficiency.

b. **Dofetilide** is an effective drug for the maintenance of sinus rhythm in patients with heart failure, coronary artery disease, and sinus node dysfunction. This agent is generally well tolerated but can cause **QT prolongation** especially in the setting of renal dysfunction. Therefore, drug initiation or dose increase should be performed in a hospital setting with cardiac monitoring. The prescription of the drug is tightly controlled, and only those certified in its use may prescribe it. Careful attention should be paid to avoid electrolyte disturbances and concomitant administration with other QT prolonging drugs, thiazide diuretics, and verapamil.

c. **Amiodarone** has properties of all four Vaughan Williams classes and has a very long half-life (up to 120 days). It is generally reserved for patients in whom other antiarrhythmic drugs are contraindicated or ineffective because of the **significant side effects that occur in the liver**, **lungs**, **thyroid**, **and eyes**. Patients should undergo periodic screening for drug toxicity. Sinus node dysfunction is also a common side effect.

d. **Dronedarone** is similar to amiodarone but has less side effects. It is contraindicated in patients with New York Heart Association classes III or IV heart failure as well as recently decompensated heart failure, especially those with left ventricular systolic dysfunction. It can cause bradycardia and QT interval prolongation and should not be used in permanent AF. There is potential for serious hepatotoxicity, and liver function tests should be monitored closely.

D. **Catheter ablation to maintain sinus rhythm.** The role of catheter ablation continues to expand rapidly and is currently used in many patients to maintain sinus rhythm. **Radiofrequency ablation** and **cryoballoon ablation** can both be utilized to isolate the pulmonary veins. When AF is resistant to at least one class I or class III antiarrhythmic agent, current guidelines recommend the use of catheter ablation in patients with symptomatic paroxysmal AF (class I, Level of Evidence: A), symptomatic persistent AF (class IIa, Level of Evidence: A), and symptomatic long-standing persistent AF (class IIb, Level of Evidence: B). Catheter ablation can be considered before a trial of antiarrhythmics in patients with recurrent symptomatic paroxysmal AF (class IIa, Level of Evidence: B) and patients with symptomatic persistent AF (class IIb, Level of Evidence: C). **Patients must be on anticoagulation during and after the procedure.** A discussion about the risks and benefits of catheter ablation should always occur. For more details about the procedure, refer to Chapter 55.

E. Surgical ablation to maintain sinus rhythm. The surgical maze procedure was first introduced in 1987 by Dr. James Cox and tested the original hypothesis that reentry is the predominant mechanism for the development and maintenance of AF. Known as the Cox-Maze procedure, the original technique used biatrial "cut-and-sew" incisions in critical locations to create barriers to the propagating wavelets that are responsible for the initiation and maintenance of AF. The technique has undergone multiple revisions over the years, and the original "cut-and-sew" technique has mostly been replaced by the Cox-Maze IV, which utilizes radiofrequency and cryothermal devices to create the lines of ablation. The Cox-Maze procedure has not had widespread acceptance as a means of treatment for AF except in patients undergoing open heart surgery. Even in these patients, the additional intraoperative time and complexity of the procedure have limited its widespread surgical application.

V.SPECIFIC POPULATIONS

A. Postoperative cardiac and thoracic surgery. AF is common postoperatively. The incidence of postoperative AF varies with the type of surgery and is highest following cardiac surgery (between 20% and 50%). It usually occurs in the first 5 days after surgery and is a major determinant of the length of stay and hospital cost.

1. Therapy. Postoperative AF is usually self-limited, and DCCV is not always needed. Patients who develop AF should be treated with β-blockers or nondihydropyridine calcium channel blockers to achieve adequate rate control. There are a variety of antiarrhythmic agents available for cardioversion in these patients. AF carries an increased risk of stroke in the postsurgical patient; therefore, anticoagulation is recommended if AF persists for longer than 48 hours. The choice of antiarrhythmic agent, AV nodal blocker, and anticoagulant depends on the patient's comorbidities and type of surgery.

2. Prevention. There is evidence supporting the prophylactic administration of certain medications to prevent the development AF in patients undergoing cardiac surgery. **Amiodarone**, when given prophylactically before or after cardiac surgery, has been found to significantly reduce the incidence of postoperative AF. **Sotalol** has also been studied, but there is conflicting evidence regarding its effectiveness. Administration of **colchicine** may also be considered in patients to reduce AF after surgery.

B. Acute coronary syndromes. The incidence of AF following acute coronary syndromes ranges between 10% and 20% at 30 days. AF is more commonly associated with acute myocardial infarction in older patients as well as those with significant left ventricular dysfunction. Patients with AF in this setting have a worse outcome at 30 days compared with those in sinus rhythm. Guidelines recommend **urgent DCCV in patients with acute myocardial infarction and AF with rapid ventricular rates and intractable ischemia**. Intravenous β-blockade is indicated for rate control to reduce myocardial oxygen consumption, and digoxin or amiodarone is an alternative for patients with significant left ventricular dysfunction and heart failure. Stroke rates are also increased in these patients, and anticoagulation is recommended for patients with a CHA_2DS_2-VASc score of at least 2.

C. Preexcitation syndromes. The most feared complication of AF in patients with ventricular preexcitation is the development of ventricular fibrillation because of rapid conduction of AF down an accessory pathway. The incidence of sudden cardiac death in patients with preexcitation syndromes is around 0.6% per year. The risk factors for sudden death include a short refractory period of an antegrade accessory pathway (<250 ms), short

R–R interval during preexcited AF, and the presence of multiple accessory pathways. Immediate electrical cardioversion is recommended for hemodynamically unstable patients. Intravenous procainamide or ibutilide should be used in hemodynamically stable patients. **It is critical to avoid AV nodal blocking agents in patients with AF and evidence of ventricular preexcitation.**

D. Pregnancy. AF occurs infrequently during pregnancy and usually has an identifiable cause such as mitral valve disease, thyroid disease, or pulmonary disease. The ventricular rate can be controlled with β-blockers, nondihydropyridine calcium channel blockers, or digoxin. Currently available antiarrhythmic medications cross the placenta and are excreted in breast milk and should therefore be avoided if possible. However, amiodarone, sotalol, and flecainide have all been used successfully during pregnancy in selected instances. Quinidine has the longest safety record of any antiarrhythmic agent in pregnancy and remains the agent of choice for pharmacologic conversion of AF. In the hemodynamically unstable patient, electrical cardioversion can be performed without any concern for fetal damage. Anticoagulation should also be given high priority during pregnancy, given the risk of thromboembolic disease during pregnancy. Only those patients with a very low risk of thromboembolism do not require anticoagulation. Warfarin is generally avoided during the first trimester of pregnancy because of its teratogenic effects and also during the last month of pregnancy because of bleeding concerns at the time of delivery. Administration of unfractionated heparin either by continuous intravenous infusion in a dose sufficient to increase the activated partial thromboplastin time (aPTT) to 1.5 to 2 times control or by intermittent subcutaneous injection of 10,000 to 20,000 units every 12 hours adjusted to prolong the mid-interval aPTT to 1.5 times control is appropriate. LMWH may also be considered during the first trimester and last month of pregnancy although there are limited data about clinical outcomes.

E. Hypertrophic cardiomyopathy. Patients with AF and hypertrophic cardiomyopathy have a high risk of systemic thromboembolism. Therefore, **these patients should be anticoagulated regardless of their CHA_2DS_2-VASc score**. Antiarrhythmic medications such as **amiodarone** and disopyramide can be used to maintain sinus rhythm and should be used in combination with a β-blocker or nondihydropyridine calcium channel blocker. Sotalol, dofetilide, and dronedarone may also be considered.

F. Pulmonary disease. AF commonly develops in patients with chronic obstructive pulmonary disease. General recommendations include the treatment of the underlying lung disease, correction of hypoxia, and correction of acid–base imbalances. Medications commonly used to treat bronchospastic airway disease such as theophylline and β-adrenergic agonists can precipitate AF and decrease the ability of medications to control the ventricular response rate. Antiarrhythmic medications with β-blocking properties such as sotalol, propafenone, and adenosine can worsen bronchospasm and are contraindicated in patients with severe bronchospastic airway disease. Ventricular rate control is usually achieved with nondihydropyridine calcium channel blockers such as verapamil and diltiazem.

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CHAPTER 25

Venous Thromboembolism and Hypercoagulable States

Donald Clark III

I. VENOUS THROMBOEMBOLISM AND HYPERCOAGULABLE STATES

A. Venous thromboembolism (VTE). Deep-vein thrombosis (DVT) and pulmonary embolism (PE) represent different manifestations of the same clinical entity referred to as VTE. It is a common, lethal disease that affects hospitalized and nonhospitalized patients, recurs frequently, is often overlooked, and can result in long-term complications, including chronic thromboembolic pulmonary hypertension and the postthrombotic syndrome (PTS).

1. Deep-vein thrombosis. The lower extremities are the most common sites for DVT, but other affected sites include the upper extremities and the mesenteric and pelvic veins. The main goal in the management of DVT is the prevention of PE and PTS. Proximal lower extremity DVTs (popliteal vein and above) have an estimated risk of PE of 50% if not treated. Approximately 25% of calf vein thrombi propagate (in the absence of treatment) to involve the popliteal vein or above.

2. Pathogenesis and risk factors. Virchow's triad still forms the best framework for understanding the pathogenesis of VTE. **The triad includes *stasis, hypercoagulability,* and *injury to the vessel wall***. There are both inherited and acquired risk factors for hypercoagulability. The most common **inherited** risk factors include **factor V Leiden** (FVL) and **prothrombin gene mutation (G20210A)**; deficiency of the natural **anticoagulant protein C (PC), protein S (PS)**, and **antithrombin (AT)**; **hyperhomocysteinemia**; and **elevated factor VIII** levels. Acquired risk factors include **immobilization, surgery**, **trauma**, **pregnancy**, use of oral **contraceptives** (OCPs) or **hormone replacement** therapy (HRT), **malignancy**, **antiphospholipid syndrome** (lupus anticoagulant and/or anticardiolipin antibodies), **heparin-induced thrombocytopenia** (HIT), **myeloproliferative** disorders, **smoking**, **obesity** (body mass index [BMI] > 30), **inflammatory bowel disease**, **central venous catheters** or **pacemakers**, and **the nephrotic syndrome**.

3. Clinical manifestations. Typical symptoms of DVT in the upper and lower extremities include pain and swelling. Signs of DVT on physical examination may include increased warmth, tenderness, edema, the presence of dilated veins (collaterals), erythema, and, in extreme situations, cyanosis or gangrene. A limb-threatening manifestation of DVT, **phlegmasia cerulea dolens**, occurs most often in the setting of malignancy, HIT, or other hypercoagulable conditions in which the thrombus completely occludes venous outflow, causing massive limb swelling, hypertension in the capillary bed, and eventually ischemia and

necrosis. Phlegmasia cerulea dolens is a vascular emergency requiring leg elevation, anticoagulation, and, in select cases, thrombolysis or surgical or catheter-based thrombectomy. Fasciotomy may also be required to relieve associated compartmental syndromes.

4. Diagnosis

a. **Clinical examination** is unreliable in the diagnosis of DVT, as symptoms and signs are often insensitive and nonspecific. Pretest probability scores improve the utility of further testing. For example, using the Wells score (Table 25.1), patients in the low pretest probability category have a 96% negative predictive value for DVT (99% if the D-dimer is negative as well), but the positive predictive value in patients with a high pretest probability is <75%, supporting the need for further diagnostic testing to identify patients with thrombosis.

b. **Venography** has been the gold standard test for the diagnosis of DVT in the past.

However, because venography is invasive and requires the use of potentially harmful contrast agents, it has largely been replaced by noninvasive tests such as duplex ultrasonography.

c. **Duplex ultrasonography** has a sensitivity and specificity of about 95% and 98%, respectively, for the detection of proximal DVT in symptomatic patients; however, it is operator dependent and is less sensitive in asymptomatic individuals and for thrombi located in the calf veins. **An inability to compress the vein with the ultrasound transducer is diagnostic for DVT.** Diagnosis of recurrent DVT is more challenging, given the high incidence of persistently noncompressible veins after an initial event. False positives may occur when pelvic masses result in isolated noncompressibility of the common femoral veins.

d. **D-Dimer.** The sensitivity and negative predictive value of this test are high. The combination of a **low pretest probability and a negative D-dimer has an extremely high negative predictive value for VTE (approximately 99%)**. A positive D-dimer, however, is nonspecific, and other diagnostic testing should be performed.

TABLE 25.1 Pretest Probability of Deep-Vein Thrombosis (Wells Score)

Clinical Feature[a]
Active cancer (treatment ongoing or within previous 6 mo of palliative treatment)
Paralysis, paresis, or recent plaster immobilization of the lower extremities
Recently bedridden for more than 3 d or major surgery, within 4 wk
Localized tenderness along the distribution of the deep venous system
Entire leg swollen
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial
Pitting edema (greater in the symptomatic leg)
Collateral superficial veins (nonvaricose)
Alternative diagnosis as likely or greater than that of DVT
Score

TABLE 25.1 Pretest Probability of Deep-Vein Thrombosis (Wells Score)
High
Moderate
Low
Modified Score (Adds One Point If There Is a Previously Documented DVT)
Likely
Unlikely

e. DVT, deep-vein thrombosis.

f. [a]In patients with symptoms in both legs, the more symptomatic leg is used.

g. Reprinted from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997;350(9094):1795 (Copyright © 1997 Elsevier. All rights reserved.); Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med*. 2003;349(13):1227. (Copyright © 2003 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

h. Other diagnostic tests less frequently used to detect DVT include magnetic resonance venous imaging and computed tomography (CT). These tests are mainly helpful in the diagnosis of DVT in the pelvic veins, inferior vena cava (IVC), or mesenteric veins.

5. Treatment

a. Anticoagulation. The main goals of treatment for DVT include relief of symptoms and prevention of PE, PTS, and recurrent VTE. Once the diagnosis of DVT is confirmed, **anticoagulation should be started immediately unless there is a contraindication**. Initial therapy should include heparin, low-molecular-weight heparin (LMWH), fondaparinux, or a direct oral anticoagulant (DOACs). Weight-based dosing of **unfractionated heparin (UFH)** (80 U/kg bolus followed by 18 U/kg/h intravenous [IV] infusion) has been shown to achieve a therapeutic activated partial thromboplastin time (aPTT) more rapidly than fixed-dose regimens. The aPTT should not be followed in patients with an abnormal baseline aPTT (e.g., in patients with lupus anticoagulant) and in patients who require unusually high doses of heparin such as in AT deficiency. In these situations, the anti-factor Xa assay should be used.

1. **(1) LMWH** is administered as a weight-based subcutaneous injection. Enoxaparin is given either as a once-daily injection (1.5 mg/kg/d) or twice per day (1 mg/kg every 12 hours). No monitoring is required except in obese, pediatric, or pregnant patients or patients with renal insufficiency. When necessary, the anti-Xa level using LMWH as a reference standard should be measured 4 hours after an injection. The therapeutic range is 0.5 to 1.0 IU/mL for the 12-hour regimen and ≥1.0 IU/mL for the daily dose.

2. **(2)** Once anticoagulation with UFH or LMWH is begun, a **VKA** may be initiated. The overlap with a VKA should be continued for a minimum of 5 days and until the international normalized ratio

(INR) is within the target range of 2.0 to 3.0 for two consecutive days to permit adequate depletion of vitamin K–dependent coagulation factors.

3. **(3) Fondaparinux**, an indirect factor Xa inhibitor, is approved as treatment for acute DVT and PE when used in combination with a VKA. Fondaparinux is administered as a once-daily subcutaneous injection of 5, 7.5, or 10 mg based on body weight (<50, 50 to 100, and >100 kg, respectively) for the treatment of DVT or PE. Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) and bacterial endocarditis.

4. **(4) Direct oral anticoagulants.** Multiple new DOACs with different mechanisms of action have been evaluated in patients with VTE. These medications include rivaroxaban, apixaban, edoxaban (direct factor Xa inhibitors), and dabigatran (direct thrombin inhibitor [DTI]). The results of these trials are summarized in Table 25.2. **Overall, DOACs have proven non-inferior to VKAs and are associated with fewer bleeding complications.** Factor Xa inhibitors rivaroxaban and apixaban have a more rapid onset of action which obviates the need for parenteral anticoagulation in the initial treatment of VTE. Additionally, because these agents have stable pharmacodynamics (unlike warfarin), routine monitoring is not required. **Current guidelines suggest DOACs over VKAs for the treatment of VTE, except in patients with active cancer in whom LMWH is the treatment of choice.**

5. **(5) Thrombolytic therapy** for DVT may be beneficial in select individuals and is preferably administered locally via a catheter-directed approach. Systemic lysis is also an option if a catheter-directed approach is not available. Both routes carry an increased risk of systemic hemorrhage compared with standard anticoagulation alone. Current guidelines recommend against routine thrombolytic use in patients with DVT, except for those patients (without contraindication) with an extensive acute proximal DVT (ileofemoral DVT) or individuals at risk for limb gangrene secondary to venous occlusion. The recently published ATTRACT trial demonstrated among patients with acute proximal DVT that catheter-directed thrombolysis did not lower the risk of PTS and resulted in higher risk of major bleeding.

TABLE 25.2 Overview of Phase III Clinical Trials with Non-vitamin K–dependent New Oral Anticoag Treatment and Standard Duration of Anticoagulation after Venous Thromboembolism

Drug	Trial	Design	Treatments and Dosage	Duration	Patients	Efficacy Outco (Resu
Dabigatran	RE-COVER	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg bid)[a] vs. enoxaparin/warfarin	6 mo	2,539 patients with acute VTE	Recurren fatal under dabiga 2.1% warfar
	RE-COVER IP	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg bid)[2] vs. enoxaparin/warfarin	6 mo	2,589 patients with acute VTE	Recurren fatal under dabiga 2.2% warfar

TABLE 25.2 Overview of Phase III Clinical Trials with Non-vitamin K–dependent New Oral Anticoag Treatment and Standard Duration of Anticoagulation after Venous Thromboembolism

Rivaroxaban	EINSTEIN-DVT	Open-label	Rivaroxaban (15 mg bid for 3 wk, then 20 mg od) vs. enoxaparin/warfarin	3, 6, or 12 mo	3,449 patients with acute DVT	Recurren fatal under rivarox 3.0% warfar
	EINSTEIN-PE	Open-label	Rivaroxaban (15 mg bid for 3 wk, then 20 mg od) vs. enoxaparin/warfarin	3, 6, or 12 mo	4,832 patients with acute PE	Recurren fatal under rivarox 1.8% warfar
Apixaban	AMPLIFY	Double-blind, double-dummy	Apixaban (10 mg bid for 7 d, then 5 mg bid) vs. enoxaparin/warfarin	6 mo	5,395 patients with acute DVT or PE	Recurren fatal under vs. 2. warfar
Edoxaban	Hokusai-VTE	Double-blind, double-dummy	LMWH/edoxaban (60 mg od; 30 mg od if creatinine clearance 30–50 mL/min or body weight <60 kg) vs. UFH or LMWH/warfarin	Variable, 3–12 mo	8,240 patients with acute DVT and/or PE	Recurren fatal under edoxa 3.5% warfar

bid, bis in die (twice daily); CRNM, clinically relevant
ajor; DVT, deep-vein thrombosis; LMWH, low-molecular-weight heparin; od, omni die (once daily); PE,
onary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

[a]Approved doses of dabigatran are 150 mg bid and 110
id.

From Konstantinides SV, Torbicki A, Agnelli G, et al. 2014
guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis
management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*.
;35(43):3033–3073. Reproduced by permission of The European Society of Cardiology.

9. **(6)** Previous small trials suggested **graduated compression stockings** (GCS) may help prevent PTS; however, a large randomized trial reported no benefit. These trials have been criticized for methodologic flaws, but the routine use of GCS for the prevention of PTS has fallen out of favor. Early ambulation as tolerated after diagnosis is safe and should be encouraged.

10. **(7) Vena caval interruption.** Current guidelines recommend against the routine insertion of IVC filters for the treatment of DVT. **Indications for placement of IVC filters are as follows: a contraindication to anticoagulation, a complication from anticoagulation, or recurrent thromboembolization despite adequate anticoagulant therapy. IVC filter alone is not an effective therapy** for DVT, and resumption of anticoagulation as soon as risk of bleed is acceptable is recommended.

b. **Duration of treatment.** The duration of treatment following the diagnosis of DVT is **dependent on the risk of recurrence**. Risk factors for recurrence include an idiopathic DVT, underlying hypercoagulable states (listed in subsequent text), and malignancy. In addition, placement of a permanent IVC filter, elevated D-dimer levels, advanced age, male sex, and increased BMI also place individuals at a higher risk for recurrence. The risk of recurrence is low while patients are on anticoagulation; however, clinicians must weigh the risk of bleeding against the risk of new thrombosis. Current guidelines **recommend 3 months of anticoagulation** for patients with a **first episode of DVT secondary to a transient cause**. Anticoagulation for at least **3 months** is recommended for patients with a **first episode of idiopathic DVT**, with consideration given for indefinite anticoagulation in patients with a first unprovoked proximal DVT who are considered to be at low or moderate bleeding risk. Long-term (indefinite) anticoagulation is also recommended in patients with malignancy for as long as the cancer remains active and in patients who have unexplained recurrent DVTs. For patients with unprovoked proximal DVT who desire to stop anticoagulation, aspirin may be considered to prevent recurrent VTE. It should be noted that **aspirin** is much less effective than anticoagulation for VTE recurrence prevention and is not considered an alternative to anticoagulation.

c. **Calf vein thrombosis.** Current guidelines recommend anticoagulation for acute isolated distal DVT if there are **severe symptoms or high-risk features for extension to the proximal veins**. Risk factors for extension that favor anticoagulation over surveillance include positive D-dimer, extensive thrombosis (>5 cm in length, multiple veins, >7 mm maximal diameter), close proximity to proximal veins, no provoking factor, active cancer, history of VTE, or inpatient status. In patients who are managed with surveillance (serial imaging once or twice weekly for 2 to 3 weeks), anticoagulation is recommended if the thrombus extends further in the distal veins or to the proximal veins. The decision for anticoagulation or surveillance should also consider bleeding risk and patient preference.

d. **Superficial venous thrombosis** frequently occurs as a complication of an IV line in an upper extremity, but may occur spontaneously in the upper or lower extremities. Anticoagulation is not routinely administered, but may be considered for those at higher risk for extension to the proximal veins (>5 cm length, <5 cm from the sapheno-femoral or sapheno-popliteal junction). **Patients with superficial venous thrombosis should undergo ultrasound to rule out DVT.**

e. **Upper extremity DVT.** Upper extremity DVT is most often related to central venous catheter placement and/or pacemaker devices. Other less common causes include thoracic outlet syndrome, Paget–von Schröetter syndrome (also referred to as effort thrombosis), and hypercoagulable conditions including malignancy. Patients may be asymptomatic but more frequently complain of arm swelling and pain. Anticoagulation is indicated if there are no contraindications. Thrombolysis should be considered in younger

patients with effort thrombosis, who have a low risk of bleeding and symptoms of acute onset. Determination of the length of anticoagulation should be decided using the same processes described for acute lower extremity DVTs.

B. Pulmonary embolism. It is difficult to approximate the true incidence of PE, but there are estimates that as many as 300,000 Americans have a fatal PE each year and as many as 34% of affected individuals present with sudden death. **The majority of patients die because of a failure in diagnosis rather than inadequate therapy.** In fact, the mortality rate for PE without treatment is approximately 30%, whereas it is only 2% to 8% with adequate treatment. PE remains the most common preventable cause of hospital death in the United States.

1. Pathophysiology and symptoms. Hemodynamic collapse related to PE results from the combination of vascular obstruction from thrombus and vasoconstriction caused by inflammatory mediators and hypoxia. Elevated pulmonary vascular resistance results in decreased right ventricular outflow, leading to a decrease in preload and cardiac output resulting in hypotension. Elevated right ventricular wall tension can lead to decreased right coronary artery flow and ischemia. Cardiopulmonary collapse from PE is more common in patients with coexisting coronary artery disease (CAD) or underlying cardiopulmonary disease.

PE may present as one of the following three syndromes: (a) **acute cor pulmonale**, (b) **pulmonary infarction**, or (c) **dyspnea**. Patients presenting with acute cor pulmonale, as manifested by the sudden development of dyspnea, cyanosis, shock, or syncope, usually have a massive PE leading to cardiovascular collapse. Patients with pulmonary infarction usually present with pleuritic chest pain, dyspnea, and hemoptysis, and an audible friction rub may be heard. The majority of patients present with generalized symptoms of chest pain, dyspnea, and malaise.

2. Diagnosis. Several pretest probability scores have also been developed for the diagnosis of PE similar to those for the diagnosis of DVT. In a validation study of the Wells clinical decision rule, only 0.5% of patients who were unlikely to have PE and had a negative D-dimer had subsequent nonfatal VTE.

a. Troponin. Cardiac troponins have been evaluated in the setting of acute PE, and elevated levels correlate with electrocardiographic and echocardiographic findings of right ventricular pressure overload. Troponin elevation can be seen in patients with and without CAD, but the overall mortality and inhospital complications are higher in patients with acute PE and elevated cardiac troponin than in patients without elevated cardiac troponin.

b. Brain natriuretic peptide elevation in the absence of renal dysfunction is also a marker of right ventricular dysfunction in patients with PE. Like elevated troponin levels, these elevated levels have also been shown to be predictors of adverse outcome in patients with acute PE.

c. Arterial blood gas. PE can result in significant hypoxia, but in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 26% of patients with angiographically proven PE had PaO_2 >80 mm Hg. Similarly, a **normal alveolar–arterial gradient does not preclude the diagnosis of PE**. Therefore, a normal PaO_2 cannot rule out PE; however, hypoxia in the absence of cardiopulmonary disease should raise the suspicion for this diagnosis. In patients with cardiopulmonary collapse, a normal PaO_2suggests that PE is an unlikely cause.

d. **Chest radiography** may be more helpful in establishing other diagnoses. When present, findings are nonspecific and include pleural effusion, atelectasis, and consolidation. The classic signs, including the Westermark sign (regional oligemia), Hampton hump (pleural-based, wedge-shaped shadow), and Palla sign (enlarged right inferior pulmonary artery), are uncommon.

e. **Electrocardiography.** Like chest radiography, the major utility of the electrocardiogram (ECG) in the diagnosis of PE is to rule out other major diagnoses, such as acute myocardial infarction (MI). The most specific finding on an ECG is the classic $S_1Q_3T_3$ pattern, but the most common findings are nonspecific ST-segment and T-wave changes. Other commonly reported findings include sinus tachycardia, atrial fibrillation, and right bundle branch block.

f. **Echocardiography.** More than 50% of hemodynamically stable patients with PE will not have evidence of right ventricular dysfunction on transthoracic echocardiography (TTE). Patients with **hemodynamic collapse, however, will generally have severe right ventricle dysfunction**, and TTE can provide rapid bedside assessment in these critically ill patients. TTE findings include right ventricular dilation, right ventricular hypokinesis, tricuspid regurgitation, septal flattening, paradoxical septal motion, diastolic left ventricular impairment secondary to septal displacement, pulmonary artery hypertension, lack of inspiratory collapse of the IVC, and, rarely, direct visualization of the thrombus. In patients with large PE, it has been observed that despite moderate or severe right ventricular free wall hypokinesis there is relative sparing of the apex. This finding is referred to as **McConnell sign** and has a specificity of 94% and a positive predictive value of 71% for PE. McConnell's sign may be useful in discriminating right ventricular dysfunction because of PE versus other causes.

g. **Ventilation–perfusion (V/Q) scanning. V/Q** scanning is now considered a second-line imaging method for the diagnosis of PE. **V/Q**scans are helpful in patients who have normal chest radiography or who are unable to have CT scanning, such as those with renal insufficiency, contrast allergy, or pregnancy. The results of PIOPED suggest that **V/Q** scanning is helpful if the scan is normal or at high probability for PE (87% of patients with high-probability scans had PE, but only 4% of patients with normal scans had PE). Intermediate-or low-probability scans are the most common finding, however, occurring in approximately 70% of patients in the PIOPED study. In addition, patients who had a high or intermediate clinical suspicion for PE but a low-probability scan still had a 40% and 16% rate, respectively, of PE diagnosed by pulmonary angiography. Hence, it is currently advised that **patients with a high or intermediate clinical suspicion for PE but a low-probability V/Q scan have additional tests to confirm or refute the diagnosis**.

h. **Computed tomography pulmonary angiography (CTPA).** Because of its wide availability and the ability to directly visualize thrombus, **CT imaging has become the standard imaging technique for the diagnosis of acute PE**. CTPA not only allows direct visualization of the thrombus but also has great value in excluding other diseases, including aortic dissection, pneumonia, or malignancy. It is especially useful in evaluating central PE (thrombus is seen as an intraluminal filling defect), and although the diagnostic yield for peripheral or subsegmental PE was low initially, the use of multidetector CTPA has greatly increased its sensitivity and specificity for the diagnosis of small peripheral or subsegmental PEs. The major disadvantages of CT are radiation exposure and the possibility of

contrast-induced nephrotoxicity. A meta-analysis of 23 studies including 4,657 patients who were suspected of having PE but had normal CT scans found that only 1.4% developed VTE and 0.51% developed fatal PE by 3 months. These rates are similar to those in other studies involving patients who had suspected PE but were found to have normal pulmonary angiograms.

i. **Pulmonary angiography** remains the gold standard diagnostic test for PE, but it is used infrequently because of the advent of CT scanning. In some situations where a lung scan shows perfusion abnormalities and is nondiagnostic for PE, selective angiography of the abnormal area may be considered so as to limit the amount of contrast needed. In experienced centers, associated morbidity and mortality are low.

j. **Magnetic resonance angiography** (MRA) may be an alternative to CT for the diagnosis of PE in patients who have contrast allergy or for whom avoidance of radiation exposure is desired. At the current time, an MRA should be considered only at those centers with experience with this modality and only for patients for whom standard tests are contraindicated.

3. **Treatment.** All patients with PE are treated with anticoagulation and supportive care. Risk stratification using a combination of hemodynamic stability, biomarkers, and echocardiographic criteria is utilized to determine the use of catheter-directed therapies and systemic lysis.

a. **Risk stratification and management algorithm.** The pulmonary embolism severity index (PESI) is a validated clinical tool to assess prognosis for patients presenting with acute PE (Table 25.3). In normotensive patients, this tool can reliably distinguish between intermediate and low risk and therefore identify patients who may require further evaluation. Additionally, there is a growing body of evidence supporting early discharge or home therapy for patients at low risk. Current guidelines incorporate risk stratification utilizing the PESI score into an algorithm for managing patients with acute PE (Fig. 25.1).

TABLE 25.3 Original and Simplified Pulmonary Embolism Severity Index

Parameter	Original Version	Simplified
Age	Age in years	1 point (if a
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥ 110 beats/min	+20 points	1 point
Systolic blood pressure < 100 mm Hg	+30 points	1 point
Respiratory rate > 30 breaths/min	+20 points	–
Temperature < 36°C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhemoglobin saturation < 90%	+20 points	1 point

TABLE 25.3 Original and Simplified Pulmonary Embolism Severity Index

	Risk Strata[a]	
	Class I: ≤65 points Very low 30-d mortality risk (0%–1.6%) **Class II: 66–85 points** Low mortality risk (1.7%–3.5%)	**0 points** ∇ (95% CI 0.
	Class III: 86–105 points Moderate mortality risk (3.2%–7.1%) **Class IV: 106–125 points** High mortality risk (4.0%–11.4%) **Class V: >125 points** Very high mortality risk (10.0%–24.5%)	**≥point(s)** (95% CI 8.

b. [a]Based on the sum of points.

c. From Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(43):3033–3073. Reproduced by permission of The European Society of Cardiology.

d. **Anticoagulation** and supportive care have remained the standard of care in the management of acute PE. **Current guidelines recommend initial treatment with anticoagulants for patients with a high clinical suspicion for PE while awaiting the results of diagnostic testing.** Traditionally, patients with acute non-massive PE have been treated with parenteral anticoagulation (IV UFH, LMWH, fondaparinux) followed by the initiation of a VKA. The advent of DOACs has revolutionized the management of VTE.

e. **DOACs** discussed previously, are outlined in Table 25.2. As with DVT, current guidelines suggest DOACs over VKAs for the treatment of VTE, except in patients with active cancer in whom LMWH is the treatment of choice.

FIGURE 25.1 Risk-adjusted management strategies in acute PE. A/C, anticoagulation; CT, computed tomographic pulmonary angiography; PE, pulmonary embolism; PESI, pulmonary embolism severity index; RV, right ventricular; sPESI, simplified pulmonary embolism severity index. [a]If echocardiography has already been performed during diagnostic work-up for PE, and RV dysfunction detected, or if the CT already performed for diagnostic work-up has shown RV enlargement (RV/left ventricular [LV] ratio ≥0.9), a cardiac troponin test should be performed except for cases in which primary reperfusion is not a therapeutic option (e.g., because of severe comorbidity or limited life expectancy of the patient). [b]Markers of myocardial injury (e.g., elevated cardiac troponin I or T concentrations in plasma) or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma). If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic work-up (e.g., in the chest pain unit) and was positive, then an echocardiogram should be considered to assess RV function, or RV size should be (re)assessed on CT. [c]Patients in the PESI class I–II, or sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests are also to be

classified into the intermediate–low-risk category. This might apply to situations in which imaging or biomarker results become available for the calculation of the clinical severity index. These patients are probably not candidates for home treatment.[d] Thrombolysis, if (and as soon as) clinical signs of hemodynamic decompensation appear; surgical pulmonary embolectomy and percutaneous catheter-directed treatment may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high.[e] Monitoring should be considered for patients with confirmed PE and a positive troponin test, even if there is no evidence of RV dysfunction on echocardiography or CT.[f] The simplified version of the PESI has not been validated in prospective home treatment trials; inclusion criteria other than the PESI were used in two single-armed (nonrandomized) management studies. From Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC).*Eur Heart J.* 2014;35(43):3033–3073. Reproduced by permission of The European Society of Cardiology.

f. **Systemic thrombolysis** for the treatment of acute PE is highly individualized, as there have been no clearly established short-term mortality effects. Because of favorable outcomes with prompt recognition and anticoagulation for PE, **thrombolysis should be reserved for hemodynamically unstable patients with acute massive PE and a low risk of bleeding**. The recent PEITHO trial investigated the role of systemic thrombolysis among patients with acute PE at intermediate risk, defined as hemodynamic stability but with positive cardiac troponin and evidence of right ventricular dysfunction by either CT or echocardiography. This double-blinded trial randomized >1,000 patients to receive IV tenecteplase single bolus (30 to 50 mg based on body weight) or placebo in addition to anticoagulation. Overall, mortality was <2% at 7 days with no significant difference between groups. The group receiving thrombolytics was less likely to develop hemodynamic decompensation; however, this was at the cost of significantly increased risk of intracranial and other major bleeding. Based on these results, **routine use of systemic thrombolysis is not recommended in normotensive patients at intermediate risk**.

g. **Catheter-based therapies** have gained interest in recent years given the significant bleeding risk associated with systemic thrombolysis. These procedures include percutaneous catheter-delivered intrapulmonary thrombolysis, mechanical fragmentation, aspiration thrombectomy, rheolytic thrombectomy, and ultrasound-assisted thrombolysis (utilizing the EKOS catheter). Data are limited to observational studies and small clinical trials with surrogate endpoints, but suggest these therapies may be an effective option with acceptable safety profile. Currently, catheter-based therapies are only recommended at experienced centers for high-risk patients with contraindications to systemic thrombolysis or failed thrombolysis.

h. **Surgical pulmonary embolectomy** was the first definitive therapy to be performed for PE. There have been no randomized trials evaluating embolectomy, and the primary use of this procedure is in patients with shock and a contraindication to thrombolysis or failed thrombolysis.

C. **VTE prophylaxis.** Although PE is the third most common cause of hospital-related death in the United States, less than half of all hospitalized patients at risk for VTE receive adequate prophylactic treatment. Most hospitalized patients have at least one or more risk factors for VTE, and **without prophylaxis, the incidence of hospital-acquired**

DVT is 10% to 20% among medical patients and even higher among surgical patients (15% to 40%).

There are two major forms of prophylaxis, **mechanical and pharmacologic**. Those who cannot receive prophylactic anticoagulation should be prescribed mechanical modalities such as intermittent pneumatic compression devices. Pharmacologic prophylaxis can be achieved by a number of agents, including UFH, LMWH, fondaparinux, a VKA, and rivaroxaban, which is approved for VTE prophylaxis after hip and knee replacement surgery. Other new oral anticoagulant agents (dabigatran and apixaban) are available outside the United States for prophylaxis and will likely be available sometime in the near future in the United States. In high-risk populations such as those with hip or knee replacement, a combination of mechanical and pharmacologic therapies should be considered. In select surgical procedures, extended prophylaxis is recommended. For example, extended prophylaxis for up to 28 to 35 days is recommended for patients who have had a hip fracture or who undergo total hip replacement surgery.

II.HYPERCOAGULABLE CONDITIONS. Conditions that predispose persons to an increased risk of thrombosis are referred to as hypercoagulable states or thrombophilia. **These conditions are being identified more frequently and may be classified as inherited or acquired. Hypercoagulability testing should be considered in individuals with idiopathic VTE, family history of clotting, a first thrombotic event before the age of 50 years, thrombosis at unusual locations, resistance to anticoagulation, and those with recurrent thromboses.**

A. Factor V Leiden and prothrombin gene mutation. The FVL mutation is more prevalent in persons of European and Scandinavian ancestry. The prothrombin gene mutation G20210A (PT G20210A) is also inherited as an autosomal dominant mutation and may lead to a higher plasma level of prothrombin. It is also more common in those of Caucasian ancestry and confers a 2.8-fold increased risk of VTE. The role of FVL and PT G20210A mutations in arterial thrombosis is unclear. There is only a modest association between inherited thrombophilias and major arterial thromboses such as MI, stroke, or peripheral arterial disease. Therefore, routine screening for these mutations is not warranted in most patients with arterial thrombosis. FVL and PT G20210A are associated with VTE during pregnancy, OCP use, and HRT. There are no clear evidence-based guidelines for managing patients with thrombosis in the setting of these thrombophilias. In general, acute thrombosis should be managed in a standard fashion, but the duration of therapy is less clear, and the benefits of long-term anticoagulation must be weighed against the risks of bleeding.

B. Defects in the natural anticoagulants (protein C, protein S, and antithrombin). Deficiency of any of the three natural anticoagulants is associated with an increased risk of venous thrombosis. All are inherited as autosomal dominant defects and are further subclassified based on reduction in their levels or defective quality of the protein. Levels of PS and PC are lower in conditions such as disseminated intravascular coagulation, inflammatory states, nephrotic syndrome, acute thrombosis, and liver disease. Pregnancy and OCP use can also decrease the levels of PS. Both PC and PS levels are lowered by warfarin therapy, and, therefore, these tests should not be assayed in patients who are receiving VKAs. Similarly, initiation of warfarin therapy without concomitant anticoagulation in the setting of acute VTE may lead to warfarin-induced skin necrosis

(manifested as painful necrosis of the skin, primarily in fatty areas including the breast, buttocks, and thighs).

C. **Homocysteine.** Hyperhomocysteinemia is a risk factor for venous and arterial thromboses. It may be inherited, and genetic defects causing a deficiency of cystathionine β-synthase or a mutation in methylenetetrahydrofolate reductase have been reported. Acquired causes include deficiencies in vitamin B_{12}, B_6, or folate; smoking; and liver or renal failure. Treatment with folate in doses between 0.5 and 5 mg is usually effective in reducing the levels of homocysteine; however, this does not reduce the risk of major cardiovascular events, symptomatic venous thrombosis, or recurrent venous thrombosis.

D. **Heparin-induced thrombocytopenia.** HIT is a common, underrecognized but potentially devastating condition in patients who receive heparin or LMWH. The reported incidence is between 3% and 5% in patients exposed to UFH and lower (<1%) in patients exposed to LMWH. The pathogenesis of HIT involves the formation of antibodies (usually immunoglobulin G [IgG]) against a heparin–platelet factor 4 (PF4) complex. The **HIT antibodies then trigger procoagulant effects** through platelet and endothelial cell activation, as well as thrombin generation **leading to both microvascular and macrovascular thromboses**. The clinical spectrum of HIT ranges from isolated thrombocytopenia without thrombosis (referred to as isolated HIT) to HIT(T), which is associated with both arterial and venous thromboses. Other manifestations of HIT may include hypotension from adrenal hemorrhage secondary to adrenal vein thrombosis and ensuing infarction, skin necrosis at injection sites, or venous limb gangrene. **HIT should be suspected in any patient who develops thrombocytopenia while receiving heparin or LMWH**; any patient who develops a >50% decline in platelet count after the initiation of either anticoagulant; or any patient who develops new thrombosis or extension of an existing thrombosis while receiving either of these agents. In patients with HIT and de novo exposure to heparin, thrombocytopenia (platelet count < 150,000 per μL) usually occurs between days 5 and 14 (with day of heparin exposure being day 0). In patients with a recent exposure to either agent (generally within the last 100 days), HIT may develop sooner and is referred to as rapid-onset HIT. This complication may also develop 9 to 40 days after heparin or LMWH has been discontinued and is known as delayed-onset HIT.

Laboratory tests to aid in the diagnosis of HIT include functional assays such as heparin-induced platelet aggregation and serotonin release assays (SRAs), and antigen assays (immunoassays) which detect IgG, IgM, or IgA antibodies that bind UFH to PF4. The SRA has the highest sensitivity and specificity for the diagnosis of HIT.

The first step in the treatment of HIT is the prompt discontinuation of all sources of heparin or LMWH, including heparin flushes, heparin-coated catheters, any intermittent use of heparin during dialysis, and total parenteral nutrition or angiography. However, approximately 20% to 53% of patients with HIT will develop thrombosis (many within the first month) when heparin is discontinued or treated with LWMH alone. Therefore, the initiation of an alternative anticoagulant, unless contraindicated, is recommended. **DTIs**, including lepirudin and argatroban (both approved by the Food and Drug Administration), may be used initially. Once platelet counts are more than 100,000 to 150,000 mm^3, warfarin may be started at a low dose (2.5 to 5 mg preferred). Early introduction or higher doses of warfarin may lead to venous limb gangrene or warfarin-induced skin necrosis. Overlapping

the DTI with the VKA should be continued for at least 5 days and not discontinued until the INR is therapeutic for two consecutive days. Argatroban falsely elevates the INR; therefore, it should not be discontinued until INR >4, as recommended by the manufacturer. After cessation of argatroban, the INR should be rechecked within a few hours to confirm that it is between 2 and 3. The duration of anticoagulation for patients with HIT is generally determined by the location and type of thrombosis. In patients without thrombosis (isolated HIT), the duration of anticoagulation is less clear, but given the high incidence of thrombosis within the first month, it is reasonable to continue anticoagulation for at least a month in the absence of contraindications.

E. Antiphospholipid antibodies are a heterogeneous group of autoantibodies that, if present in a patient with thrombosis, lead to the antiphospholipid syndrome. Antiphospholipid antibodies can be divided into three groups: (a) anticardiolipin antibodies, (b) lupus anticoagulants, and (c) β_2-glycoproteins. They are often associated with other autoimmune conditions and can cause recurrent pregnancy loss, as well as arterial or venous thrombosis. Thrombocytopenia is also an occasional feature of this syndrome. Anticardiolipin antibodies are detected and quantified using an enzyme-linked immunosorbent assay and may be IgG, IgM, or IgA. IgG titers have been correlated more often with thrombosis. Lupus anticoagulants prolong phospholipid-dependent blood clotting times, and it has been reported that there is about a fivefold increased risk of thrombosis in patients with this finding. Once a thrombotic event occurs, long-term therapy with warfarin must be considered. A higher target INR had been considered necessary in the past (approximately ≥3.0), but is no longer considered necessary as data have suggested that most patients can be maintained with a target INR of 2.0 to 3.0. In those individuals that are suspected of failing adequate therapy, one strategy is to correlate the INR to factor II and factor X levels (of ≤20% to 30%) to ensure adequate anticoagulation.

F. Malignancy. Many malignancies induce a hypercoagulable state, and in patients with idiopathic VTE, a search for age- and gender-specific malignancies may be necessary.

G. Other conditions. Elevated factor VIII levels and the dysfibrinogenemias have also been associated with thrombosis; however, the role of deficiencies of plasminogen, tissue plasminogen activator (of the fibrinolytic system), and factor XIII polymorphisms as emerging risk factors for hypercoagulability is less clear.

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CHAPTER 26

Aortic Aneurysm and Aortic Dissection

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Maran Thamilarasan

I.INTRODUCTION

A. The aorta

1. **Anatomy.** The aorta is the **principal conductance vessel** in the body and is divided into the ascending, arch, descending thoracic, and abdominal components.

a. The **ascending aorta** includes the aortic root, which contains the sinuses of Valsalva. The left and right coronary arteries arise from the left and right coronary sinuses, respectively.

b. The **aortic arch** gives rise to the great vessels of the head and arms. These include the brachiocephalic (innominate), the left common carotid, and the left subclavian arteries.

c. The **descending aorta** begins distal to left subclavian artery. The point at which aortic arch joins the descending aorta is called the **isthmus**, marked by ligamentum arteriosum. The aortic isthmus is often the site of origin of dissection tear because the aorta is relatively fixed to the thoracic cage in this region. The **descending thoracic aorta** provides the intercostal vessels as it courses through the posterior mediastinum. The vascular supply to the anterior spinal artery is included among these vessels.

d. The **abdominal aorta** begins just after the aorta crosses the diaphragm. It provides the splanchnic and renal arteries before bifurcating to become the common iliac arteries.

2. **Histology.** The aorta comprises **three layers**: the intima, the media, and the adventitia.

a. The **intima** is the internal lining layer of the aorta and is easily damaged.

b. The **media** is the main structural layer of the aorta. It consists primarily of laminar layers of elastic tissue and smooth muscle in varying amounts. This structure allows for the high tensile strength and elasticity required to withstand the pressure changes of each heartbeat throughout the life of the individual.

c. The **adventitia** is the thin outer layer that anchors the aorta within the body, in addition to providing nourishment to the outer half of the wall through the vasa vasorum.

3. **Physiology**

a. The **elasticity of the aortic wall allows it to distend** under the pressure created during ventricular systole. In this way, the kinetic energy that was developed during ventricular systole is stored as potential energy in the distended aortic wall. Then, during ventricular diastole, the potential energy is converted back to kinetic energy by elastic recoil of the wall. Therefore, forward blood flow is maintained throughout the cardiac cycle.

b. The aorta aids in the control of **systemic vascular resistance (SVR)**. Pressure receptors in the ascending aorta and aortic arch signal the vasomotor centers of the brain via the vagus nerve. When blood pressure is elevated, the reflex response is to lower heart rate and decrease SVR. The converse is true when blood pressure is decreased.

II. AORTIC DISSECTION

A. Etiology and pathology

1. **Aortic dissection classically occurs when a tear in the intima results in separation of the intima from the media (90% of cases). This aortic tear then propagates anterograde or less commonly, retrograde typically creating a false lumen in the aortic wall. Atypical variants of aortic dissection include intramural hematoma (IMH) and penetrating aortic ulcer (PAU). In either case, acute aortic dissection results from a pathologic weakening of the aortic wall because of medial necrosis, atherosclerosis, or inflammation. IMH** represents a focal hemorrhage of the aortic wall caused by rupture of the vasa vasorum within the aortic wall and may cause secondary dissection, whereas **PAU** is a focal defect in the endoluminal surface of the aortic wall produced by atherosclerotic erosion through the intima with ulceration into the media. The natural history of IMH is similar to that of classic aortic dissection. In fact, in 4% to 10% of dissections, an intimal tear is not found. Therefore, ***it is reasonable to treat IMH similar to de facto aortic dissection including surgery if located in the ascending aorta or aggressive medical therapy if in the descending aorta*** *(Level of Evidence: C)*.

   Surgery is often recommended for patients exhibiting unstable symptoms or lesions involving the ascending aorta. Otherwise, medical management and frequent radiologic follow-up for signs of progression are recommended.

   There are many risk factors for aortic dissection, although the most common is a history of systemic hypertension as evidenced in over 70% of cases. Younger patients suffering aortic dissection are more likely to have a genetic or morphologic risk factor, such as genetic syndromes associated with aortopathy, bicuspid aortic valve (BAV), or prior aortic surgery. The following list includes the most common conditions associated with aortic dissection:

a. Increased age and uncontrolled hypertension are the two most common risk factors.

   Other modifiable risk factors include tobacco use, dyslipidemia, and cocaine use.

b. **Genetic syndromes associated with aortic aneurysm and dissection.** Marfan, Ehlers–Danlos, Loeys–Dietz syndromes and familial thoracic aortic aneurysm (TAA) and dissection syndrome are associated with an increased risk of aortic dissection. **These patients require comprehensive aortic imaging at diagnosis and heightened surveillance to follow aortic diameter owing to the increased risk of complications related to aortic disease.** *Aortic imaging is recommended for first-degree relatives with TAA and/or dissection to identify those with asymptomatic disease (Level of Evidence: B).*

1. **(1) Marfan syndrome.** Marfan syndrome is a genetic disorder with high penetrance and variable expression affecting connective tissue. Marfan syndrome is associated with mutations of the *FBN1* gene, which encodes fibrillin-1, a large glycoprotein that contributes to the structure of the extracellular matrix and serves as a regulator of transforming growth factor-β (TGF-β). The principal features of Marfan syndrome involve the cardiovascular, ocular, and skeletal systems, with patients at exceedingly high risk for aortic disease. In fact, nearly all patients with Marfan syndrome demonstrate some form of aortic disease during their lifetime.
2. **(2) Loeys–Dietz syndrome.** An autosomal dominant disorder associated with a triad of arterial tortuosity and aneurysm, hypertelorism, and bifid uvula, Loeys–Dietz syndrome results from mutations in either TGF-β receptor type 1 or 2 (*TGFBR1* or *TGFBR2*). Vascular disease among these patients is highly prevalent, with 98% demonstrating aortic root aneurysms, and portends a grim prognosis. Early reports of Loeys–Dietz syndrome suggested a particularly aggressive disease process with arterial complications occurring at a mean age of 26 years. However, subsequent data have revealed less aggressive phenotypes with later presentations, and a mean age of death closer to the fifth decade among less severe phenotypes. Repair of the aortic root is recommended at lesser aorta diameters (<4.4 to 4.6 cm by computed tomography [CT] or magnetic resonance imaging [MRI]) because of the aggressive nature of this condition.
3. **(3) Ehlers–Danlos syndrome, type IV (vascular form).** The vascular form of Ehlers–Danlos syndrome is characterized by an autosomal dominant inheritance of the *COL3A1* gene mutation that encodes type III procollagen. Clinical features include easy bruising and rupture of the uterus, intestines, and arteries. Median survival is 48 years and often no aneurysms are documented. Gravid women with this condition have a particularly poor prognosis during childbirth because of the high risk of arterial and uterine rupture.
4. **(4) Familial TAA and dissection syndrome.** A significant number of patients presenting with aortic aneurysms and dissection have family history of aortic disease without identifiable clinical syndrome such as Marfan or Loeys–Dietz. Genetic analysis identified several new mutations in this group that predisposes to aortopathy. These include TGFBR2 (similar to Loeys–Dietz without other phenotypic features), ACTA2, myosin heavy chain (MYH11), myosin light chain (MYLK), and cGMP-dependent PRKG1 and SMAD3.

c. **Hereditary conditions and congenital anomalies** such as BAV and coarctation of the aorta are also established risk factors for aortic dissection. Turner syndrome is associated with BAV (10% to 25%), aortic coarctation (8%), and dilatation of the ascending aorta. Although patients with Turner syndrome require screening for aortic disease at diagnosis, requirements of surveillance for aortic dilatation follow those of other patients with BAV. *All patients with BAV should have both the aortic root and ascending aorta evaluated for evidence of aortic dilatation (Level of Evidence: B). First-degree relatives of patients with a BAV, premature onset of thoracic aortic disease with minimal risk factors, and/or a familial form of TAA or dissection should be evaluated for the presence of a BAV and asymptomatic thoracic aortic disease (Level of Evidence: C).*

1. **(1) Vasculitides** associated with large vessel inflammation and aortitis contribute to medial degeneration of the aortic wall and may increase the risk of aortic dissection. Examples of these inflammatory disorders include giant-cell arteritis, Takayasu arteritis, syphilis, and Behçet disease.
2. **(2) Aortic dissection exhibits a strong association with pregnancy.** Among cases of aortic dissection in women <40 years of age, up to half may present during the third trimester or early in the postpartum period. **Gravid women with Marfan syndrome and preexisting aortic root dilatation are at especially high risk for aortic dissection**.

3. **(3) Direct aortic trauma is associated with aortic dissection.** Blunt chest trauma, such as that occurring in a motor vehicle accident, may cause aortic transection or mural hematoma. Intravascular instrumentation during arterial catheterization, insertion of an intraaortic balloon pump, or aortic cannulation, cross-clamping, and graft insertion may also serve as a source of intimal damage and dissection.

B. Epidemiology. The incidence of aortic dissection has been estimated from 2 to 3.5 cases per 10,000 person-years, corresponding to 6,000 to 10,000 cases per year in the United States. The male-to-female ratio approaches 3:1, with the peak incidence in the sixth and seventh decades of life. The mortality for untreated acute aortic dissection is largely determined by the location of the dissection, but overall mortality is approximately 1% per hour within the first 48 hours if surgery is not performed. Approximately 65% of dissections originate in the ascending aorta (just above the right or noncoronary sinus), 20% in the descending thoracic aorta, 10% in the aortic arch, and the remainder in the abdominal aorta.

C. Classification schemes

1. **Anatomic classification schemes** used to commonly describe aortic dissection include the DeBakey and Stanford systems (see Table 26.1 and Fig. 26.1 for a description of the DeBakey and Stanford classifications). Anatomic classification refers to the portion(s) of aorta involved. The Stanford classification will be used throughout this chapter.
2. Dissections are further classified according to chronicity: acute (<2 weeks from onset) or chronic (>2 weeks from onset).

Anatomic involvement and chronicity of dissection influence the recommended treatment approach and indicate prognosis.

TABLE 26.1 Aortic Dissection Classification Systems

Classification	Pathologic Description
Stanford	
Type A	Any dissection involving the ascending aorta
Type B	Any dissections *not* involving the ascending aorta
DeBakey	
Type I	Entry point in the ascending aorta, extends to the aortic arch and often beyond
Type II	Confined entirely to the ascending aorta
Type III	Entry in the descending aorta (distal to left subclavian); extends distally (usually) or p

D. Clinical presentation

1. **Signs and symptoms**

a. Aortic dissection may present with a wide range of clinical manifestations. Proximal dissections are most commonly characterized by a sudden onset of chest pain (80%) that is severe in intensity and ripping, tearing, stabbing, or sharp in quality. Pain may radiate to the interscapular region of the back (47%) or abdomen (21%). Among descending aortic dissections, back pain (64%), chest pain (63%), and abdominal pain (43%) are most common. **Typical symptoms are less common in the elderly.**

FIGURE 26.1 Anatomic appearance of three different aortic dissection classifications.

b. Presenting clinical findings may include the murmur of severe aortic insufficiency (AI) (45%) associated with proximal aortic dissection and contributing to acute heart failure (5% to 6%), hypotension (14%) or shock (13%) associated with cardiac tamponade (5% to 10%), syncope (13%), myocardial infarction (MI) (7% to 19%) with retrograde dissection into the ostia of the coronary arteries, cerebrovascular accident (CVA) (8%) with cephalad carotid extension, paraplegia (2%) with extension into the intercostal and spinal arteries, or cardiac arrest. Dissections involving the arterial supply to the limbs may contribute to pulse deficits (26%), acute limb ischemia (10%) with distal extension, and neuropathy.

E. Diagnostic testing

1. Evaluation. Figure 26.2 provides an algorithm to aid in diagnosis. Key characteristics important in defining the extent of aortic dissection and clinical management include ascending versus descending aortic involvement, site of the intimal tear, presence or absence of AI, presence of pericardial effusion and/or tamponade, coronary involvement, and involvement of visceral arterial supply. CT, MRI, transesophageal echocardiography (TEE), and invasive aortography are common imaging modalities useful in the diagnosis of acute aortic dissection. The relative advantages and disadvantages of the four modalities are outlined in Table 26.2. **Selection of the specific imaging modality for identification or exclusion of aortic dissection should be based on clinical variables, local expertise, and clinical availability to facilitate rapid diagnosis (Level of Evidence: C).**

2. *An electrocardiogram (ECG) should be performed in all patients with suspected aortic dissection (Level of Evidence: B).* Most frequently, ECG is useful to exclude an acute coronary syndrome presenting atypically as symptoms of aortic dissection. *Because dissection-related acute MI is infrequent, ST-segment elevation on ECG should be treated as an independent coronary event without delay for aortic imaging unless the patient is at high risk for aortic dissection (Level of Evidence: B).*

3. Chest radiography may occasionally detect findings suggestive of dissection, although it is inadequately sensitive to definitively exclude the presence of acute aortic dissection. *A negative chest x-ray should not delay definitive aortic imaging in patients determined to be high risk for aortic dissection by initial screening (class III recommendation, Level of Evidence: C).*

F. Selected imaging modalities for diagnosis of acute aortic dissection

1. CT. Contrast-enhanced, cardiac-gated multidetector CT is a widely available and the most commonly used imaging modality for the detection of aortic dissection, with excellent sensitivity and specificity approaching 100%. This modality has many advantages, including rapid scan and interpretation times. Disadvantages include iodinated contrast and radiation exposure.

FIGURE 26.2 Aortic dissection diagnostic/therapeutic algorithm. CCU, coronary care unit; CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

TABLE 26.2 Comparison of Imaging Modalities in Aortic Dissection

TABLE 26.2 Comparison of Imaging Modalities in Aortic Dissection

Factor	Angiography	CT
Intimal tear definition	+ +	+ + +
False lumen thrombus +/−	+ + +	+ + +
Involvement of branch vessels	+ + +	+ +
Pericardial effusion	−	+ + +
Coronary involvement	+ + +	−
AI presence	+ + +	−
Overall sensitivity (%)	88	100
Overall specificity (%)	95	98

AI, aortic insufficiency; CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography.

Modified from Isselbacher EM, Eagle RA, DeSanctis RW. Diseases of the aorta. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 5th ed. Philadelphia, PA: WB Saunders; 1997:1546–1581. Copyright © 1997 Elsevier. With permission.

2. **MRI and magnetic resonance angiography (MRA).** Like CT, MRI provides multiplanar imaging of the thoracic aorta with high sensitivity and specificity that is very accurate for diagnosis of acute aortic disease. MRA offers unique gadolinium-enhanced and black blood imaging techniques to evaluate aortic anatomy and morphology that prove particularly useful in assessing the aortic wall. Advantages of MRI include the ability to identify anatomic variants, such as IMH or PAU, assess branch arterial involvement, and provide useful information on aortic valvular and left ventricular systolic function while avoiding exposure to iodinated contrast or radiation. MRI is well suited for chronic follow-up of aortic syndromes because ionizing radiation is not necessary. Use of MRI is limited by availability, prolonged acquisition time, and incompatibility with implanted ferromagnetic devices. MRI is not an appropriate test for patients that are hemodynamically unstable.
3. **Transthoracic echocardiography (TTE) and TEE.** TTE allows for a rapid noninvasive evaluation, primarily of the proximal aorta with overall limited sensitivity and specificity. Visualization of the proximal aorta and other critical structures using TTE may be limited by factors that reduce image quality, such as emphysema, mechanical ventilation, and obesity. With an esophageal approach, TEE overcomes many of the challenges with improved sensitivity and specificity while offering a safe and rapid assessment of acute aortic disease. A major limitation of either TTE or TEE includes the appearance of ultrasound artifacts that may mimic a dissection flap, such as that of reverberation artifact.
4. **Invasive aortography.** Aortography offers accurate information about the location of dissection, providing visualization of the false lumen or intimal flap, branch vessel involvement, and communication between true and false lumens. Invasive aortography is useful in evaluating PAU, as it is characterized by endovascular aortic contrast protruding into an atherosclerotic plaque. False negatives can occur with thrombosis of the false lumen, IMH,

or equal filling of the false lumen. Disadvantages or aortography include a low sensitivity, risks associated with any invasive procedure, contrast administration, and availability of experienced operators to perform the study.

5. Recommendations for aortic imaging techniques to determine the presence and progression of thoracic aortic disease

a. *Measurements of aortic diameter should be taken at reproducible anatomic landmarks, perpendicular to the axis of blood flow, and reported in a clear and consistent format (Level of Evidence: C).*

b. *For measurements taken by CT imaging or MRI, the external diameter should be measured perpendicular to the axis of blood flow. For aortic root measurements, the widest diameter, typically at the mid-sinus level, should be used (Level of Evidence: C).*

c. *For measurements taken by echocardiography, the internal diameter should be measured perpendicular to the axis of blood flow. For aortic root measurements, the widest diameter, typically at the mid-sinus level, should be used (Level of Evidence: C).*

d. *Abnormalities of aortic morphology should be recognized and reported separately even when aortic diameters are within normal limits (Level of Evidence: C).*

e. *The finding of aortic dissection, aneurysm, traumatic injury and/or aortic rupture should be immediately communicated to the referring physician (Level of Evidence: C).*

f. *Techniques to minimize episodic and cumulative radiation exposure should be utilized whenever possible (Level of Evidence: B).*

G. Therapy. Death in aortic dissection results from vascular compromise, tamponade, or aortic rupture. ***Management of proximal (type A) thoracic aortic dissection requires immediate open surgical treatment to resect the entire aneurysmal aortic segment and the proximal extent of dissection (Level of Evidence: C).*** Surgery greatly improves outcomes and avoids the risks associated with progression of dissection. One- and 3-year survival after surgery for type A dissection is excellent, with survival rates of 96.1% and 90.5%, respectively. Survival rates at 1 and 3 years are 88.6% and 68.7%, respectively, among those who do not receive surgery for type A dissection. ***Patients with distal (type B) thoracic and abdominal aortic dissections should be managed medically unless life-threatening complications, such as malperfusion syndromes, progression of dissection, aortic enlargement, or refractory hypertension, develop (Level of Evidence: B).*** **Percutaneous endovascular aortic repair (EVAR)** is a technically feasible and potentially effective option for nonsurgical treatment of type B aortic dissection. Table 26.3 recommends the course of treatment for various types of dissections. The 5-year survival rate for patients leaving the hospital with appropriate treatment (medical or surgical) for type B dissection ranges from 75% to 82%.

1. Priority of therapy. The initial management of patients with suspected aortic dissection is directed at **reducing aortic wall stress. Aortic wall stress is affected by the velocity of ventricular contraction (d*P*/d*t*), the rate of ventricular contraction, and blood pressure. Medical stabilization of acute aortic dissection should target the reduction of heart rate followed by lowering of blood pressure.** Invasive hemodynamic monitoring and sufficient intravenous access for volume replacement should also be

established simultaneously. An initial and aggressive treatment approach to reduce d*P*/d*t* applies to all patients regardless of the location of dissection or whether the eventual management strategy is medical or surgical. This is a critical management step because patients with aortic dissection often present and are diagnosed at smaller centers necessitating transfers to tertiary centers with expertise in aortic surgery.

TABLE 26.3 Surgical versus Medical Therapy for Aortic Dissection

Medical Therapy	Surgical Therapy	Endovasc
Uncomplicated type B dissection	Acute, type A dissection	Malperfusi B dissec
Stable, lone arch dissection	As an alternative to endovascular therapy for complicated type B dissection	Complicate
Stable, chronic type B dissection (>2 wk after onset of symptoms)	End-organ dysfunction	Possibly treatmer dissectio
	Aortic insufficiency associated with Marfan syndrome retrograde extension into the ascending aorta	

2. **Medical therapy** (see Table 26.4)

a. ***With suspicion of acute aortic dissection, β-blockers should be initiated immediately and titrated to target heart rate of <60 beats/min*** *(Level of Evidence: C). In patients who are intolerant of β-blockers, nondihydropyridine calcium channel blockers may serve as an acceptable alternative to control heart rate* (see Table 26.4) *(Level of Evidence: C). In the setting of acute aortic regurgitation, use of rate-controlling agents, such as* β*-blockers, should be used with caution because they block compensatory tachycardia (Level of Evidence: C).*

b. *Once the heart rate goal has been achieved, systolic blood pressure should be targeted to <120 mm Hg with the use of angiotensin-converting enzyme inhibitors or vasodilators to reduce blood pressure while maintaining adequate end-organ perfusion* (*Level of Evidence: C)*. With a goal of heart rate and blood pressure control, β-blockers with α-effect, such as labetalol, may be particularly advantageous. Sodium nitroprusside is a particularly useful vasodilator, given a rapid onset and easy titration as an intravenous infusion. Close monitoring for reflex tachycardia should be done with use of vasodilators—*vasodilator therapy should not be initiated prior to heart rate control because reflex tachycardia may increase aortic wall stress and risk of propagation or expansion of dissection (class III, Level of Evidence: C).*

3. **Managing complications of acute aortic dissection**

a. **Hypotension and shock.** Aortic wall rupture or hemorrhage into the pericardial space with cardiac tamponade may manifest as shock. In either event, **aggressive volume replacement should be initiated and the patient taken to the operating room promptly**. Pericardiocentesis is generally not recommended. If pericardiocentesis becomes an absolute requirement to get the patient to the operating room, enough pericardial fluid should be

removed to raise the blood pressure to an acceptable level, but no more. **If vasopressors are required for hemodynamic stabilization, norepinephrine and phenylephrine are the drugs of choice, as neither has a demonstrable effect on d*P*/d*t*. Epinephrine and dopamine should be avoided.**

b. **Acute MI.** Coronary thromboembolism and retrograde progression of the aortic dissection flap into the coronary ostia are infrequent complications of proximal aortic dissection. In this setting, **thrombolysis is contraindicated**. Coronary arteriography and percutaneous intervention are not generally recommended because these procedures will **delay surgical repair of the dissection while exposing it to mechanical complications related to angiography in an already compromised aorta**.

TABLE 26.4 Intravenous Dosing for Acute Medical Management of Acute Aortic Syndromes

Drugs	Loading Dose	Maintenance Dose
First-Line Agents		
Propranolol	1 mg IV q3–5 min (max 6.15 mg/kg)	2–6 mg IV q4–6h
Labetalol	10 mg IV over 2 min, then 20–80 mg q10–15 min (max 300 mg)	2 mg/min IV drip titrate t
Esmolol	500 μg/kg IV bolus	50–200 μg/kg/min IV co
Metoprolol	5 mg IV q5 min to effect	5–10 mg IV q4–6h to eff
Second-Line Agents in Patients with Contraindications for a-Blockers		
Enalaprilat	0.625 mg IV	0.625 mg IV q4–6h
Diltiazem	0.25 mg/kg IV over 2 min; 0.35 mg/kg IV after 15 min if no effect	5 mg/h titrate by 2.5–5 r
Verapamil	0.075–0.1 mg/kg to 2.5–5 mg/kg over 2 min	5–15 mg/h IV drip

c. IV, intravenous.

d. **Refractory hypertension.** Sufficient blood pressure reduction can be difficult to obtain, with many patients requiring several antihypertensive drugs of different classes. Adequate analgesia is essential to reduce pain-related increases in sympathetic tone and blood pressure associated with acute aortic dissection. Following initial stabilization, use of β-blockers should be continued with consideration for angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists that may slow pathologic aortic dilatation.

4. Surgical management of acute aortic dissection

a. *Patients with a proximal (type A) thoracic aortic dissection should receive emergent surgery. A partially dissected aortic root with a normal aortic valve may be repaired with supracommissural aortic valve resuspension. In the event that the aortic valve cannot be repaired or resuspended, a Bentall procedure may be performed with a prosthetic valve sewn onto a Dacron graft and used to replace the native valve with reimplantation of the coronary arteries into the graft (Level of Evidence: C).*

b. *Patients with type B dissection who have evidence of rupture or end-organ involvement should receive surgical repair with replacement of the entire segment of*

dissected aorta (Level of Evidence: C). Reattachment of the visceral arteries and T_8 to L_2intercostal/lumbar arteries are implanted into the graft conduit.

c. **Perioperative risk.** Compared with unstable patients with aortic dissection, those demonstrating preoperative stability have an improved prognosis. Nevertheless, stable patients still carry a substantial surgical mortality of 17%. When patients have features of instability—such as cardiac tamponade, shock, congestive heart failure (CHF), CVA, coma, MI, acute renal failure, or mesenteric ischemia—surgical mortality rates rise to approximately 31%. Surgical mortality increases with age. However, the relative benefits of surgery outweigh risks of nonoperated type A dissection until at least the age of 80 years. Therefore, the benefits of surgery should be measured against surgical risks of all age groups, with consideration for complexity of repair, preoperative medical comorbidities, and anticipated quality of life after surgery.

d. **Postsurgical complications of open thoracic surgical repair** include respiratory failure (5% to 15%), stroke (2% to 8%), bleeding requiring reoperation (1% to 6%), infection (1% to 5%), MI (1% to 5%), heart failure (1% to 5%), ventricular arrhythmias (1% to 5%), acute postoperative renal failure, paraplegia (2% to 10%), and mesenteric ischemia.

1. **(1)** *A brain-protective strategy to prevent stroke and preserve cognitive function should be a key element of the surgical, anesthetic, and perfusion techniques used to accomplish repairs of the ascending aorta and aortic arch (Level of Evidence: B).*

2. **(2)** Paraplegia stands among the most feared complications of descending thoracic and thoracoabdominal aortic repairs, occurring in 2% to 4% and 3% to 10% of cases, respectively. Paraplegia results from the disruption of blood flow to the anterior spinal artery via the intercostal arteries. *Cerebrospinal fluid drainage is recommended as a spinal-protective strategy in open and endovascular thoracic aortic repair for patients at high risk for spinal cord ischemic injury (Level of Evidence: B).*

5. **Percutaneous EVAR for type B aortic dissection.** EVAR represents a technically feasible and potentially effective option for nonsurgical treatment of type B aortic dissection, IMH, PAU, acute traumatic aortic transection, and pseudoaneurysm.

a. **Potential advantages of EVAR** over conventional surgery include the absence of thoracotomy, avoiding cardiopulmonary bypass and clamping of the aorta, lower hospital morbidity rates, and shorter length of hospital stays. A mortality advantage of endovascular therapy was suggested in early trial reports, although it has largely been lost with longer-term follow-up from these studies.

b. **Comparing EVAR with optimal medical management (OMM).** Although OMM remains the mainstay for acute treatment of uncomplicated type B dissection, long-term morbidity and mortality of chronic dissection remain substantial. Data on EVAR for use in descending aortic dissection are limited. The prospective INvestigation of STEnt grafts in patients with type B Aortic Dissection (INSTEAD) trial provided the first randomized evaluation of elective stent-graft placement in 140 patients with subacute or chronic uncomplicated type B aortic dissection. At 5 years, the thoracic endovascular aortic repair (TEVAR) group had lower aorta-specific mortality and less disease progression, but only using a retrospective "landmark" analysis.

In recommendations for acute or chronic type B dissections, the Food and Drug Administration (FDA) and a multidisciplinary subcommittee that included the Society for Vascular Surgery, American Association for Thoracic Surgery, Society of Thoracic Surgeons, and the Society for

Interventional Radiology, agreed to limit the definition of "complicated" dissection to rupture, impending rupture, or distal malperfusion. Using data collected from investigational device exemption clinical trials between 2000 and 2008, the investigators identified 99 patients with complicated type B dissections on the basis of these criteria. The mortality rate was 10.8% at 30 days and 29.4% at 1 year. At 30 days, rates of stroke, renal failure, and paralysis were each 9.4%. Based on these data, the FDA and SVS/AATS/STS/SIR recommend TEVAR for complicated type B dissections.

6. Postoperative surveillance after thoracic aortic repair or monitoring of chronic descending aortic dissection

a. *CT or MRI of the thoracic aorta is reasonable after type A or type B aortic dissection or after prophylactic repair of the aortic root/ascending aorta (class IIa, Level of Evidence: C).*

b. *CT or MRI of the aorta is reasonable at 1, 3, 6, and 12 months after dissection, then annually thereafter if clinically stable (class IIa, Level of Evidence: C).* In about 30% of cases, late deaths are caused by rupture of a secondary aneurysm or recurrence of the dissection. A majority of these secondary aneurysms will develop within 2 years of the initial treatment.

c. *For patients with chronic dissection, particularly if associated with a connective tissue disorder, but without significant comorbid disease, and a descending thoracic aortic diameter exceeding 5.5 cm, open repair is recommended* (*Level of Evidence: B).*

d. *Long-term, aggressive cardiovascular risk factor management is critical before and after thoracic aortic surgery and includes aggressive heart rate and blood pressure control to reduce d* P/*d*t*, lipid profile optimization, and smoking cessation (Level of Evidence: C).* In the event of medical treatment failure, including end-organ damage related to complications of aortic disease, aortic leak, or escalating visceral pain, patients with chronic descending aortic dissection should be considered for surgical treatment.

III.AORTIC ANEURYSM. An aortic aneurysm is a pathologic dilatation of the aorta to >1.5 times its normal diameter. Normal aortic diameter varies by age, sex, and modality increasing with age and body surface area. Aneurysms are classified based on involvement of the anatomic aortic segment, including abdominal aortic aneurysm (AAA) and TAA. The etiology, natural history, and treatments differ somewhat for aneurysms of each location.

A. AAA Abdominal aortic diameter >3.0 cm

1. Etiology and pathology of aortic aneurysm

a. Aneurysms of the aorta are caused by degenerative disease within the aortic wall, leading to inflammation, weakening of the aortic tissues, loss of elasticity, and dilatation of the aorta.

b. Risk factors for the development of AAA include current or past history of tobacco use, male gender, advanced age, family history of AAA, hypertension, hyperlipidemia, and atherosclerosis in other vascular beds. Less common causes include infection (*Salmonella* and *Staphylococcus aureus*), *vasculitis*, and trauma.

2. Clinical presentation

a. Signs and symptoms. AAA develops gradually over years rarely causing any symptoms. The majority of AAAs are discovered incidentally on physical examination or during radiologic evaluation of the abdomen. Most patients are asymptomatic;

therefore, the diagnosis of AAA should be considered in patients with an appropriate risk profile and family history.

1. **(1)** Rapid enlargement of the aneurysm may be associated with severe back or flank pain and herald impending rupture. Pain associated with an expanding AAA is described as sudden onset, constant, and not affected by movement or position. Occasionally, there is radiation to the legs, buttocks, or groin.
2. **(2)** Findings consistent with shock (hypotension, pallor, diaphoresis, oliguria, and obtundation) can develop rapidly with a ruptured aneurysm.

b. Physical findings

1. **(1)** Physical exam is also unreliable for accurate sizing of the aneurysm.
2. **(2)** A palpable, pulsatile mass may be felt on abdominal examination in a minority of subjects.
3. **(3)** Associated vascular disease is common among those with AAA and occasionally abdominal or femoral bruits or decreased pulses in the extremities may be felt.

3. Diagnostic testing

a. Abdominal ultrasound is the most commonly used screening tool for AAA. Aortic ultrasound has the capacity to obtain both longitudinal and transverse images of the aneurysm and has been validated to accurately measure size to within ±0.3 cm. **Major advantages of ultrasound include its wide availability, cost-effectiveness as a diagnostic and screening imaging technique, and avoidance of ionizing radiation exposure.** If imaging is adequate, ultrasound is an effective option when monitoring aneurysm growth serially. Disadvantages of abdominal ultrasound include poor definition of branch vessels; therefore, ultrasound is insufficient for preoperative evaluation.

b. CT aortography with cardiac gating allows for accurate evaluation of the aneurysm shape, and volumetric acquisition provides detailed three-dimensional analysis of spatial relations to branch vessels and diagnosis of associated acute aortopathies including PAU. CT measurements have been validated to within ±0.2 cm. CT offers an advantage of evaluating for extravasated blood in acute or subacute rupture. The major disadvantages of CT include the requirement for ionizing radiation and intravenous contrast, which limit its utility in follow-up of chronic aortic dissection.

c. MRI provides excellent definition of aneurysm size as well as suprarenal and iliofemoral extension. MRA allows for improved visualization of compromised flow to branch vessels, although it lacks sensitivity to absolutely define obstruction in the renal vessels. MRI is disadvantaged by cost and limited availability.

d. Aortography effectively defines both suprarenal and iliofemoral involvement as well as branch vessel impingement, although it tends to underestimate the size, especially when mural thrombus is present. Compared with other techniques, aortography is invasive and requires the use of intravenous contrast and ionizing radiation. Aortography is now generally reserved for planning endografting in some centers and is less useful as an initial diagnostic modality.

4. Therapy

a. Medical therapy and Surveillance

1. **(1)** Aggressive risk factor modification with control of hypertension, hypercholesterolemia, and smoking cessation is **imperative to prevent adverse events from atherosclerotic disease in other vascular beds.**

2. **(2)** β-Blockers by virtue of reducing hemodynamic stress were felt to be useful, although randomized studies failed to confirm this effect.
3. **(3)** Serial ultrasound or CT scanning is indicated in patients without symptoms that have aortic diameters of 2.5 cm or greater. Multidisciplinary guidelines recommend surveillance every 6 to 12 months using ultrasound or CT for aneurysms 4.0 to 5.4 cm in diameter, but a less frequent interval (every 2 to 3 years) for aneurysms 3.0 to 4.0 cm in diameter, and every 5 years for aortic diameter between 2.6 and 2.9 cm. Ultrasound is generally preferred for surveillance of small AAAs, owing to lack of radiation exposure.

b. Aortic repair: The risk for aortic rupture or dissection increases with size of the aneurysm. In general, aortic repair **is indicated for an aneurysm with diameter measuring 5.5 cm or if rapidly expanding (>1 cm/y)**. Controversy remains regarding medical versus surgical management of aneurysms between 5.0 and 5.5 cm and so should be managed on a case-by-case basis. For example women have a higher overall risk of rupture and tend to rupture at smaller aortic diameters compared with males and may benefit from elective repair at aortic diameters 5.0 to 5.5 cm. Symptomatic patients should also be referred for repair irrespective of the size of the aneurysm.

c. Aneurysm can be potentially repaired via open surgical or the less invasive endovascular approach.

d. **EVAR or** percutaneous aortic stent-grafting has been FDA approved for use in descending thoracic aortic or infrarenal AAA. Endovascular grafting is a less invasive option for the repair of AAA and is especially appealing for elderly patients or those with substantial cardiac, pulmonary, and renal dysfunction.

1. **(1) The EVAR procedure.** Under fluoroscopic guidance, the proximal and distal ends of the stent-graft are affixed to normal segments of the aorta above and below the aneurysmal portion, thereby sealing off the aneurysm. **Suitable anatomy is necessary for stent-grafting.** Favorable characteristics for EVAR include normal diameter of aorta distal to the renal arteries and proximal to the aneurysmal segment, minimal angulation, freedom from severe obstructive lesions, and patency of side branches and distal iliac vessels. Operative mortality for elective EVAR is low (1% to 2%). In addition, EVAR can also be considered in patients with ruptured AAA.
2. **(2) Comparing EVAR with open surgical repair.** Four randomized trials have compared endovascular repair with open surgical repair, including the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, the Endovascular Aneurysm Repair 1 (EVAR-1) trial, the Open Versus Endovascular Repair (OVER) Veterans Affairs Cooperative trial and Anevrysme de l'aorte abdominale: Chirurgie versus Endoprothese (ACE) with variable results. A meta-analysis including these trials concluded that EVAR was associated with lower short-term mortality than open repair. However, individuals undergoing EVAR had a higher reintervention rate than those undergoing open repair. As techniques improve, so too may postoperative outcomes among patients undergoing either endovascular versus open AAA repair. Further comparisons of outcome data from other ongoing trials will continue to provide appraisal of the long-term clinical benefits and cost-effectiveness of EVAR compared with conventional therapy.
3. **(3) EVAR among unsuitable surgical candidates.** Compassionate use of EVAR among patients for whom open repair is deemed too high risk because of medical comorbidities was studied in the Endovascular Aneurysm Repair 2 (EVAR-2) trial. This study failed to show any survival benefit with endovascular repair—a disappointing finding as the clearest indication for endovascular repair was traditionally thought to be for those at high risk for open repair.

4. **(4) Endoleak as a complication of EVAR.** One of the common complications of endovascular repair is endoleak (Table 26.5). Endoleak represents a failure of the stent-graft to completely exclude the aneurysm and results in persistent flow into the aneurysm, thereby increasing the risk of aneurysm expansion and rupture. Endoleaks occur in 10% to 20% of cases and are associated with more frequent reinterventions than open repair and the requirement of lifelong periodic follow-up imaging.
5. **(5) Other complications related to EVAR** include endograft migration, prosthesis infection, vascular access site-related infections, bleeding, thromboembolism, and spinal cord ischemia with paraplegia.
6. **(6)** *Periodic long-term surveillance imaging should be performed to monitor for endoleak, confirm graft position, document shrinkage or stability of the excluded aneurysm sac, and determine the need for further intervention in patients who have undergone endovascular repair of infrarenal aortic and/or iliac aneurysms (Level of Evidence: A).*

e. Surgical therapy. Surgical repair generally requires resection of the aneurysmal segment, with replacement using a Dacron tube graft inserted in place of the diseased aorta. The major branches are then reimplanted to the graft. Operative mortality for elective open repair varies from 1% to 4% depending on the degree of expertise. Given the strong association of coronary artery disease and its association with poor outcomes, preoperative cardiac risk assessment is recommended in patients referred for aortic repair. Current guidelines recommend that in absence of an active cardiac condition, additional noninvasive testing is indicated only if it will change management.

TABLE 26.5 Classification of Endoleaks

Endoleak Type	Cause of Leak about Graft
I	Inadequate seal at proximal and/or distal graft attachment
II	Retrograde arterial flow into the aneurysm sac from an aortic arterial branch within the s
III	Structural failure of the graft material (e.g., graft tear or hole, stent fracture)
IV	Stent-graft porosity
V	Aneurysmal expansion without demonstrable endoleak (“endotension”)

f. Modified from Hiratzka, LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010;55(14):e27–e129. Copyright © 2010 American College of Cardiology Foundation and the American Heart Association, Inc. With permission.

B. TAA. Thoracic aneurysms include those that involve the aorta from the level of the aortic root to the diaphragmatic crura. Extension of a descending thoracic aneurysm below the diaphragm creates a thoracoabdominal aneurysm.

1. Etiology

a. Table 26.6 gives the various classifications of TAAs as well as the segment involved and pathophysiology. The most common cause of TAA formation is medial necrosis, characterized by loss of elastic fibers and smooth muscle within the aortic media with replacement of tissue with interstitial cysts of basophilic ground substance leading to a cystic appearance.

b. Approximately 5% to 10% of patients undergoing surgery for AI are secondary to **annuloaortic ectasia**, which is a variant of cystic medial necrosis. Annuloaortic ectasia is a clinicopathologic diagnosis in which the aortic root, ascending aorta, and aortic annulus dilate, resulting in AI. This is more common in men and is typically seen in the fourth, fifth, and sixth decades of life.

2. **Clinical presentation.** Similar to AAA, most patients with thoracic aneurysm are asymptomatic at the time of diagnosis, and the condition is often discovered as an incidental finding on imaging done for other reasons.

a. **Signs and symptoms**

1. **(1) Vascular complications of the aneurysm** include AI and CHF with aortic root aneurysm, myocardial ischemia because of coronary artery compression, sinus of Valsalva rupture into the right atrium/ventricle with left-to-right shunt and CHF, or thromboembolic phenomena.
2. **(2) Compression of external structures by the aneurysm** causes superior vena cava syndrome, dysphagia from esophageal compression, or hoarseness from recurrent laryngeal nerve compression. In addition, compression of the trachea or mainstem bronchus can lead to wheezing, dyspnea, tracheal shift, cough, or hemoptysis. Chest or back pain from compression and bony involvement is described as constant, boring, and deep.
3. **(3) Rupture** presents with sudden, severe, sharp chest, or back pain. In order of decreasing frequency, TAAs rupture into the left pleural space, the pericardium (presenting as tamponade), and the esophagus (presenting as hematemesis).

TABLE 26.6 Causes of Thoracic Aortic Aneurysm

Etiology	Aortic Segment Involved	Pathophysiology
Cystic medial degeneration	Ascending aorta, aortic arch	De novo cystic medial degene
Marfan syndrome	Ascending aorta and root, aortic arch	Defective fibrillin; secondary cy
Loeys–Dietz syndrome	Aortic root aneurysms (98%) and arterial tortuosity, especially of the head and neck vessels	Autosomal dominant; defectiv receptor type I or II genes
Ehlers–Danlos syndrome, type IV	Ascending aorta, predominantly aortic arch	Defective collagen; secondary
Bicuspid aortic valve	Ascending aorta and root	Inadequate production of fibrill
Familial thoracic aortic aneurysm syndrome	Ascending aorta	Autosomal dominant, 3p24.2-2
Turner syndrome	Ascending aorta and root	Cystic medial degeneration
Advanced age		Cystic medial degeneration

TABLE 26.6 Causes of Thoracic Aortic Aneurysm

Atherosclerotic	Descending aorta	Atherosclerotic plaques, weak
Traumatic	Aortic isthmus, proximal descending aorta	Damaged vessel wall, intramu
Inflammatory	Variable	Takayasu arteritis, giant-cell antigen B27–associated spo
Infectious	Aortic root (syphilis), variable (mycotic)	Cystic medial degeneration (sy (mycotic)
Poststenotic	Ascending (aortic stenosis), descending (coarctation)	Hemodynamic insult
Postsurgical	Aortic valve replacement, status post–aortic anastomosis	Weakening of the anastomotic
Chronic aortic dissection	Variable	Weakening of false lumen ove

4. **(4) Aortic dissection.** See Section III.

b. Physical examination. Specific physical findings directly attributable to TAA **are usually absent**.

1. **(1) Cardiac.** The diastolic murmur of AI (classically right lower sternal border) and a laterally displaced point of maximum impulse are sometimes noted with chronic ascending aortic dilatation. Signs of CHF can be seen in these circumstances. Unilateral jugular venous distention can be seen in patients with venous compression.
2. **(2) Vascular.** Rarely, a pulsatile mass can be palpated in the suprasternal notch. Differential pulses in the extremities can sometimes be found. Evidence of thromboembolic events can be seen upon examination of the digits. If the aneurysm compresses the venous return, evidence of superior vena cava syndrome or lower extremity edema may be found.
3. **(3) Pulmonary.** If the aneurysm compresses part of the bronchial tree, decreased air movement or stridor is auscultated.

3. Diagnostic testing. Unique advantages and disadvantages of each radiographic technique are described in detail in preceding sections. The specific attributes of each technique when evaluating TAA are reviewed below.

a. The **chest radiograph** frequently shows widening of the mediastinum, unusual aortic contours, or displacement of the trachea or bronchi in the presence of a large TAA.

b. Both computed tomography angiography (CTA) and MRA provide excellent assessment of size and extent of aneurysmal involvement. CTA is the preferred modality for serial follow-up after surgical or endovascular repair, whereas MRA is the preferred modality when visualization of the aortic root is necessary.

c. TTE and TEE. TTE is of limited use in evaluating the thoracic aorta, except for the aortic root and proximal ascending portion. TEE can be used to visualize the entire thoracic aorta, but given the availability of noninvasive imaging to diagnose TAA, TEE is not routinely used for this purpose.

d. MRI and MRA are also useful for detecting and defining the extent of aneurysmal involvement. They allow for evaluation of the entire aorta, branch vessels, aortic valve, and pericardium.

e. Aortography allows for evaluation of the segment involved by the aneurysm as well as the branch vessels off the aorta. This procedure is currently reserved for preoperative evaluation to establish branch vessel patency.

4. Clinical course and recommendations for repair in asymptomatic TAA

a. Onset of symptoms usually heralds a more rapid course, as do larger dimensions at baseline. *Patients with symptoms suggestive of expansion of a TAA should be evaluated for prompt intervention unless life expectancy from comorbid conditions is limited or quality of life is substantially impaired (Level of Evidence: C).*

b. Rupture is the most common cause of death in these patients. Data from the Yale group found that median size at rupture for an ascending aortic aneurysm was 6.0 cm and for a descending aortic aneurysm it was 7.2 cm. ***Asymptomatic patients should be evaluated for surgical repair*** *who have degenerative TAA, IMH, PAU, mycotic aneurysm, or pseudoaneurysm, who are otherwise suitable candidates and* ***for whom the ascending aorta or diameter of the aortic sinuses is 5.5 cm or greater*** *(Level of Evidence: C).*

c. TAAs tend to grow more rapidly as they increase in size and thereby increase the risk of acute rupture or dissection. Aneurysms <5.0 cm at baseline have a mean growth rate of 0.17 cm/y, whereas those >5.0 cm grew at a mean rate of 0.79 cm/y. ***Patients with a growth rate >0.5 cm/y in an aorta that is <5.5 cm in diameter should be considered for operation*** *(Level of Evidence: C).*

d. ***For a BAV with dilated aortic root, the 2014 American College of Cardiology/American Heart Association guidelines for valvular disease recommend surgical referral when the aortic root is 5.5 cm or larger, similar to recommendations for patients without a BAV (Class I, Level of Evidence: B). For a BAV with an additional risk for dissection (family history or rapid growth), there is a Class IIa recommendation for surgery when the aortic root is 5.0 cm (Level of Evidence: C).*** This is a change from prior guidelines that recommended elective surgery at 5.0 cm for all patients with BAV.

e. *Patients undergoing aortic valve repair or replacement who also have an ascending aorta or aortic root diameter >4.5 cm should be considered for concomitant repair of the aortic root or replacement of the ascending aorta (Level of Evidence: C).*

f. ***Patients with Marfan, Loeys–Dietz, or vascular-type Ehlers–Danlos syndrome, or other genetically mediated disorders (Turner syndrome and familial TAA and dissection) should undergo elective operation at smaller diameters (4.0 to 5.0 cm depending on the condition) to avoid acute dissection or rupture (Level of Evidence: C).*** Among patients with Marfan syndrome and BAV, the ratio of maximal aortic cross-sectional area in square centimeters to the patient's height in meters with a result of >10 has also been proposed as an indication for surgical intervention, particularly because patients with this finding may be at greater risk for spontaneous dissection.

5. Therapy

a. **Medical therapy.** Long-term data on medical management for TAA are lacking. Based on one small prospective trial of patients with Marfan syndrome, patients treated with propranolol enjoyed a slower rate of aortic dilatation. Losartan when

compared with atenolol showed comparable rates of aortic root dilatation in patients with Marfan syndrome. *For patients with TAA, it is reasonable to reduce blood pressure with β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to the lowest point patients can tolerate without adverse effects (Class IIa, Level of Evidence: B). Antihypertensive therapy should be administered to hypertensive patients with TAA to achieve a goal blood pressure <140/90 mm Hg, or <130/80 mm Hg among patients with concurrent diabetes mellitus or chronic kidney disease (Level of Evidence: B).*

b. Endovascular therapy. Use of percutaneous aortic stent-grafts has been reported in aortic arch and descending thoracic aneurysms. Contemporary studies have suggested that endovascular therapy represents a safe and effective strategy and an alternative to open surgery in patients with TAA. However, several technical issues limit its generalizability. These include presence of appropriate landing zones both proximal and distal to the disease aortic segment, adequate vascular access for device delivery and device implantation, and need for concomitant subclavian and less commonly carotid artery bypass grafting, among others.

c. Surgical therapy for TAA. The technical details of repair are beyond the scope of this text. However, the basic premise is for a Dacron tube graft to be inserted in place of the diseased aorta. The main branches are reimplanted to the graft (coronary arteries, great vessels, mesenteric, and T_8 to L_2 intercostals/lumbricals). When the aortic valve is involved with aortic root dilatation, a modified **Bentall procedure** (composite prosthetic aortic valve with Dacron graft) or **aortic valve homograft** is performed. The aortic valve homograft is a cryopreserved cadaveric aortic valve with a portion of the original ascending aorta intact. Aneurysms involving both the ascending and descending aorta can be treated by a two-staged approach, with an **elephant trunk** procedure. With this, the ascending aorta and arch are replaced initially and the distal portion of the graft is suspended into the proximal portion of the descending thoracic aorta for subsequent union with a descending aorta graft placed either by open surgical procedure or by percutaneously. Overall perioperative survival is reported to be 90% to 95% for elective repair (ascending aorta) in most institutions.

1. **(1)** *Patients with Marfan, Loeys–Dietz, and Ehlers–Danlos syndromes and other patients with dilatation of the aortic root and sinuses of Valsalva should undergo excision of the sinuses in combination with a modified valve-sparing root reimplantation (David) operation if technically feasible or, if not, root replacement with valved graft conduit (Level of Evidence: B).*
2. **(2)** *For patients with degenerative or traumatic aneurysms of the descending t-thoracic aorta exceeding 5.5 cm, saccular aneurysms, or postoperative pseudoaneurysms, endovascular stent-grafting should be strongly considered if feasible (Level of Evidence: B).*
3. **(3)** *For patients with thoracoabdominal aneurysms, in whom endovascular stent-graft options are limited and surgical morbidity is elevated, elective surgery is recommended if the aortic diameter exceeds 6.0 cm, or less if a connective tissue disorder such as Marfan or Loeys–Dietz syndrome is present (Level of Evidence: C).*
4. **(4)** *For patients with thoracoabdominal aneurysms and with end-organ ischemia or significant stenosis from atherosclerotic visceral artery disease, an additional revascularization procedure is recommended (Level of Evidence: B).*

d. Complications after TAA repair. These include death (1% to 5%), MI (7.2%), CVA (4.8%), acute renal failure (2.4%), perioperative hemorrhage (7.2%), and paraplegia (6.0%) because of perioperative ischemia of the anterior spinal cord. Procedural adjuncts, including epidural cooling, distal aortic perfusion to support collateral circulation to the

spinal cord during surgery, and motor-evoked potential monitoring, have been used to reduce the rate of paraplegia.

1. **(1)** Factors associated with increased surgical risk include emergent surgery, greater age, prolonged cross-clamp time, diabetes, previous aortic surgery, and intraoperative hypotension.

IV. CONTROVERSIES AND FUTURE RESEARCH DIRECTIONS

A. Screening for AAA. The U.S. Preventive Services Task Force (USPSTF) currently recommends one-time screening for AAA by ultrasound in men aged 65 to 70 years who have ever smoked, although it makes no recommendation for screening of men that have never smoked. What's more, the USPSTF recommends against routine screening for AAA in women. These recommendations are based on a systematic review of four large randomized trials of screening for AAA, with ultrasound beneficial among ever-smoking men aged 65 to 79 years alone. Further investigation is needed to refine the concept of screening for AAA, particularly in women.

B. Risks and benefits of imaging technologies. Compared with acute coronary syndromes, acute aortic syndromes are less common, although several features of each disease overlap. When acute aortic disease is suspected, rapid and accurate assessment is required so as to avoid delays in treatment of acute coronary syndromes, as suggested by ECG. What's more, imaging techniques used for aortic disease requiring longitudinal follow-up must be cost-effective and avoid unnecessary radiation exposure. Clinical studies exploring cost-effectiveness and safety of various screening protocols are needed.

C. Clinical therapeutic trials for aortic syndromes. The National Heart, Lung, and Blood Institute has recommended an Aortic Aneurysm Clinical Trials Network be developed to test medical and surgical treatments among patients with TAA. Significant interest and efforts are underway to develop novel therapeutic targets and biomarkers for acute aortic dissection using animal models. Gene-based models that describe mechanisms of aortic disease based on specific mutations have contributed greatly to our understanding of Marfan, Loeys–Dietz, and other familial syndromes. Further collaborative efforts and expansion of existing registries are likely to improve understanding and provide more effective treatments for diseases of the aorta.

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CHAPTER 27A

Peripheral Arterial Disease

Joseph Campbell

I. INTRODUCTION

A. Peripheral arterial disease (PAD) describes a diverse set of pathophysiologic conditions that may lead to obstruction or aneurysmal degeneration in the noncoronary arterial vasculature. Although atherosclerotic disease is the most common etiology, inflammatory disorders, entrapment syndromes, trauma, cystic adventitial disease, infectious processes, and fibromuscular dysplasia may result in similar clinical presentations. PAD affects approximately 8 to 12 million Americans with healthcare expenditures in excess of 4 billion dollars. Despite its similar pathophysiologic basis to coronary disease, PAD is often underdiagnosed and undertreated, leading to excess morbidity and mortality. As such, it is incumbent on practicing clinicians to maintain a high index of suspicion for PAD in at-risk patients and to be familiar with the spectrum of clinical presentations, diagnostic modalities, and treatment strategies commonly employed. This chapter will primarily focus on atherosclerotic diseases of the arterial supply to the extremities, cerebral, and renal vasculature. Diseases of the aorta will be addressed elsewhere in this volume.

II. LOWER EXTREMITY PERIPHERAL ARTERY DISEASE

A. **Risk factors.** As a predominantly atherosclerotic process, lower extremity PAD shares several common risk factors with CAD, including age, hypertension, hyperlipidemia, diabetes mellitus, advanced CKD, and tobacco use. Similar to CAD, there also appears to be a genetic predisposition to PAD with heritability of 20% to 45% among affected families after adjustment for traditional risk factors. Recognizing the role of inflammation in atherosclerosis, there has been interest in the relevance of inflammatory biomarkers in PAD. This is largely based on observational data which have demonstrated an association between several adverse outcomes such as accelerated decline in ankle-brachial index (ABI), greater lower extremity functional impairment, and increased morbidity and mortality in PAD patients with elevated markers of inflammation such as C-reactive protein, tumor necrosis factor-α, interleukin-6, and soluble adhesion molecules.

B. **Epidemiology.** The prevalence of PAD increases significantly with age, from 2% to 3% in persons aged ≤50 years and up to 29% in persons aged >70 years. Depending on the diagnostic criteria utilized, up to 61% of patients with PAD will also have concomitant CAD and/or cerebrovascular disease. Patients with PAD have a two- to fourfold increase in risk for cardiovascular and total mortality. This increase in mortality is independent of presence of symptoms as the majority of patients with PAD do not have classic intermittent

claudication. There is a graded association between ABI and total mortality as ABI decreases <1.00 and above 1.40. Despite its association with coronary and cerebrovascular disease and the increased risk for cardiovascular and total mortality, patients with PAD often receive less aggressive treatment for comorbid cardiovascular conditions and are prescribed less antiplatelet agents when compared to their counterparts with CAD.

TABLE 27A.1 Localization of Peripheral Arterial Disease

Location of Pain	Likely Involved Segment
Buttock and thigh	Aortoiliac
Thigh	Aortoiliac, common and/or profunda femoral artery
Calf	Superficial femoral or popliteal artery[a]
Foot	Tibial or peroneal arteries

[a] Most commonly involved artery.

C.

D. Clinical presentation

1. **Symptoms and classification.** With exercise, vascular resistance in skeletal muscle falls in order to augment blood flow and delivery of oxygen and nutrients. In the face of a critical stenosis, the distal vasculature is already maximally vasodilated and cannot compensate for this increased metabolic demand. Therefore, although rest perfusion may be adequate, exercise may precipitate supply demand mismatch leading to ischemia and **claudication**. The amount of exercise required to precipitate pain is roughly related to the severity of the stenosis. Pain is usually manifested one segment below the area of severe stenosis (Table 27A.1), and the most frequently involved artery in intermittent claudication is the superficial femoral artery. The symptoms are usually promptly relieved with rest or standing. As the disease burden progresses, **limb-threatening ischemia with rest pain, tissue ulceration, or gangrene may result**. This is referred to as critical limb ischemia (CLI) and should be differentiated from acute limb ischemia (ALI), which occurs abruptly usually as a result of an embolic event or arterial thrombosis. Although management of ALI and CLI differs, prompt recognition of both entities is imperative given the risk of limb loss as well as increased morbidity and mortality associated with these conditions. Classification of CLI is presented in Table 27A.2.
2. **Physical examination.** A comprehensive lower extremity physical examination includes thorough characterization of peripheral pulses, **auscultation for bruits** in the abdomen and bilateral groins, palpation for **aneurysms** in the abdomen and popliteal arteries, assessment for skin changes including ulcers and gangrene, as well as a thorough neurologic examination. Signs of lower extremity arterial insufficiency can include coolness, dry skin, scaling, dependent rubor, pallor worse with leg elevation, and ulcerations. Rarely muscular atrophy can be seen. It is important to note that examination of the feet should be done with shoes and socks removed in order to increase the diagnostic yield.

TABLE 27A.2 Clinical Categories of Chronic Limb Ischemia

Grade	Category	Clinical Description

TABLE 27A.2 Clinical Categories of Chronic Limb Ischemia		
	0	Asymptomatic
I	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
II	4	Ischemic rest pain
	5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia
III	6	Major tissue loss—extends above transmetatarsal level, functional foot no longe

3. Adapted from Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.

E. Diagnostic evaluation

1. **ABI.** The ABI is a measurement of lower extremity perfusion, which **compares the blood pressure (BP) in a pedal artery with the higher of two brachial artery BPs**. To obtain this measurement, BP cuffs are placed on the upper arms and lower calves bilaterally and inflated above systolic pressure. As pressure is released, onset of flow is detected by placement of a Doppler probe over the brachial and both pedal arteries. The higher of the two ankle pressures on each side is compared with the highest of the two brachial pressures in order to obtain the ABI. The ABI cannot localize stenosis, but has a sensitivity of 68% to 84% and specificity of 84% to 99% for the diagnosis of PAD. Recommendations for the interpretation of the ABI are listed in Table 27A.3. Guidelines recommend obtaining a resting bilateral ABI in at-risk individuals (age > 65, nonhealing wounds, or age >50 with history of tobacco use or diabetes mellitus) and in patients with suspected claudication. Although the ABI value often correlates poorly with symptoms, this can be an effective screening tool to diagnose PAD. Following revascularization, a change in ABI of 0.15 is considered clinically significant and in an observational study of 214 CLI patients, a post-revascularization change in ABI ≥ 0.23 was associated with improved wound healing. ABI measurements are inaccurate in patients with noncompressible vessels (ABI > 1.4), in which case a toe-brachial index (TBI) can be used to document PAD. Furthermore, up to 30% of patients with CLI may have normal or near-normal ABI and thus if clinical suspicion is high, guidelines recommend utilization of alternate modalities (i.e., TBI, SPP, or TCPO2) to help establish a diagnosis.
2. **Pulse volume recordings (PVRs).** PVR refers to the graphic representation of the change in volume of the pulse contour in a specific segment of the extremity during the cardiac cycle. They are typically obtained by using BP cuffs placed at the high thigh, low thigh, calf, ankle, midfoot, and toe and may be used in conjunction with segmental pressure measurements in order to diagnose PAD and help localize the disease (Fig. 27A.1). The guidelines advocate obtaining PVR measurements as an alternate diagnostic tool to ABI, in order to localize disease to a particular segment, to follow patients post-revascularization, and in patients with noncompressible vessels. Whereas ABI measurements are rendered unusable in patients with noncompressible vessels, PVR can still yield diagnostic information through review of the pulse volume contours in addition to utilization of toe

pressures and TBI. Additionally, despite their ability to localize disease, PVR measurements do not yield any information about lesion characteristics (i.e., length, CTO) and have decreased sensitivity for distal disease when inflow lesions are present.

3. **Exercise testing.** Patients with PAD often are asymptomatic at rest and only develop leg symptoms with exertion. In such individuals, it is possible for resting ABI or PVR measurements to be normal. As a result, when suspicion for PAD is high and resting measurements are normal, this information should be supplemented with exercise testing. These protocols usually involve fixed treadmill settings of 2 miles/h at a 2% grade for a maximum of 5 minutes. Pre- and postexercise ABI or PVR measurements can be obtained with an abnormal result being defined as a decrease in the postexercise result by >20%.

4. **Duplex ultrasound.** Arterial duplex renders an anatomic assessment of the arterial system using a combination of B-mode ultrasound (US) imaging and Doppler spectral analysis. Doppler complements the standard qualitative US imaging by allowing waveform analysis and assessment of peak systolic velocities. Using the concept that velocity of blood flow increases as it flows through a stenotic lesion, peak systolic and end-diastolic velocities are measured and used to estimate the severity of a stenosis. This modality is useful for anatomic visualization of lesions and for surveillance after stenting or bypass grafting. According to the guidelines, patients who have undergone lower extremity revascularization should undergo periodic clinical and ABI assessments (class I) and a class IIa recommendation is given for routine surveillance duplex US following infrainguinal autogenous vein bypass grafts. Although there is wide practitioner variability and individual patient/procedural characteristics may warrant modification, the proposed schedule recommended is for a study at 4 to 6 weeks post-revascularization, 6 months, 12 months, then yearly with a goal of early identification of high-grade stenosis (PSV > 300 cm/s or PSVR > 3.5) and impending graft failure (PSV < 40 cm/s). Although less data exist, it may be reasonable to utilize routine duplex US screening in patients following endovascular intervention (class IIa), especially in more complex lesion subsets with higher rates of restenosis. Lastly, it is worth noting that in an observational study involving 379 infrainguinal reversed vein graft bypasses, only 29% identified as failing by duplex US assessment demonstrated a change in ABI >0.15 highlighting the importance of utilizing this modality in this patient subset as a part of a comprehensive clinical assessment.

TABLE 27A.3 Interpretation of the Ankle-Brachial Index

1.00–1.40	Normal
0.91–0.99	Borderline
≤0.90	Abnormal
>1.40	Noncompressible

5. **FIGURE 27A.1** Pulse volume recording (PVR) of the lower extremities. This PVR was obtained from a 74-year-old man with a history of diabetes mellitus who presented with persistent Rutherford class 3 claudication in left leg despite guideline-directed medical therapy and supervised exercise therapy. It demonstrates bilateral aortoiliac and superficial femoral artery disease. He was found to have flow-limiting lesions in his left common iliac artery and

external iliac artery which were stented in addition to a long superficial femoral artery chronic total occlusion which was treated with drug-coated balloon therapy.

6. **Magnetic resonance angiography (MRA).** The MRA signal is a reflection of the velocity and flow patterns of protons within the artery. The noninvasive nature of MRA and its ability to generate three-dimensional (3D) reconstructions are the main advantages of MRA over conventional angiography. Its limitations include a tendency to overestimate lesion severity secondary to flow turbulence, imaging artifact with metal clips or stents, and its association with nephrogenic systemic fibrosis (2.5% to 5.0%) in patients with a glomerular filtration rate <30 mL/min who are exposed to gadolinium contrast agents. Despite these limitations, MRA still has a class I indication to diagnose the anatomic location and severity of stenosis in patients with PAD.

7. **Computed tomographic angiography (CTA).** CTA uses an intravenous contrast agent and a multidetector scanner to obtain images that are of similar quality to those of conventional angiography. CTA has the advantage of being capable of reconstructing 3D images in virtually any oblique projection to help evaluate eccentric stenoses. Other advantages of CTA include better visualization of collaterals, anatomic assessment of inflow disease, as well as identification of aneurysms and extraluminal structures (cystic adventitial disease), which may not be detected by conventional angiography. CTA also has several disadvantages when compared with catheter-based angiography: CTA has lower spatial resolution than digital subtraction; venous opacification can interfere with visualization of arterial filling; asymmetric leg filling may miss the arterial phase in some vessels; and the enormous quantity of data obtained (up to 2,000 images) may be difficult for workstations to process and store. Several recent studies have shown the accuracy of CTA for the diagnosis of stenoses >50%, and CTA is quickly becoming an important imaging modality for the diagnosis of PAD. Currently, the American College of Cardiology/American Heart Association PAD guidelines give a class I indication for CTA in the diagnosis of the anatomic location and severity of stenosis in patients with PAD.

8. **Catheter-based angiography.** Long considered the gold standard for the diagnosis of arterial disease, this invasive procedure requires intra-arterial vascular access and contrast (often nonionic dye, although gadolinium or carbon dioxide can be used). It is recommended for the evaluation of patients for whom revascularization procedures are planned (those with lifestyle-limiting claudication, rest pain, ischemic ulceration, or gangrene) or for whom noninvasive techniques are inconclusive. Because contrast angiography demonstrates only the arterial lumen, it can underestimate lesion severity. Current guidelines give contrast angiography with digital subtraction a class I indication for patients with PAD when revascularization is considered.

F. Treatment. The three main goals of therapy for patients with PAD are **to relieve symptoms, preserve limb integrity, and improve survival from related cardiovascular diseases.** Aggressive risk factor modification is the primary therapy for the prevention of cardiovascular events. In select individuals, this is complemented by surgical or percutaneous revascularization.

1. **Antiplatelet therapy. Current guidelines advocate use of antiplatelet therapy to reduce the risk of myocardial infarction (MI), stroke, and cardiovascular mortality in patients with PAD.** Aspirin, at a dose of 75 to 325 mg daily, is recommended in the absence of a clear contraindication in patients with symptomatic PAD (class I) and

asymptomatic PAD with ABI ≤0.9 (class IIa). In a subset analysis of 6,452 patients with symptomatic PAD from the CAPRIE trial, there was a 23.8% reduction in the primary outcome of MI, CVA, and vascular death in patients treated with monotherapy using clopidogrel rather than aspirin. The EUCLID trial failed to demonstrate a benefit in terms of efficacy of ticagrelor compared to clopidogrel in patients with symptomatic PAD. In the TRA2 P-TIMI 50 trial, which randomized patients with stable atherosclerotic vascular disease to vorapaxar (PAR-1 antagonist) versus placebo, there was no change in the primary outcome of CV death, MI, or CVA, though patients treated with vorapaxar did experience less hospitalization for ALI and lower rates of revascularization. This was counterbalanced by an increased incidence of GUSTO moderate/severe bleeding, which has largely limited utilization of this agent in this patient population. Dual antiplatelet therapy (DAPT) is not routinely used prophylactically in the management of PAD. In a post hoc analysis of 3,096 patients with symptomatic and asymptomatic PAD from the CHARISMA study, treatment with DAPT did not yield a significant additive reduction in the composite endpoint of cardiovascular death, MI, or stroke. There was a reduction in the incidence of MI and hospitalization for ischemic events, although this occurred at the expense of increased risk of minor bleeding. With the above data in mind, the guidelines do not advocate for routine use of DAPT in patients with PAD, but indicate that it may be potentially appropriate in those who are perceived to be at high cardiovascular risk presuming that they do not have comorbid conditions which place them at increased bleeding risk.

2. **Anticoagulation.** The current iteration of the PAD guidelines gives a class IIb recommendation to the use of oral anticoagulation to improve patency following autogenous vein or prosthetic bypass. This is largely based on conflicting results with regard to graft patency balanced against increased rates of bleeding complications. A class III recommendation is given to the use of anticoagulation therapy as a means of reducing cardiovascular ischemic events in patients with PAD. These data and the above recommendations were largely based on patients treated with warfarin. With the advent of DOACs, several newer studies deserve consideration:

a. **ePAD trial:** In this study, 203 patients who underwent femoropopliteal endovascular revascularization were randomized to 3 months of therapy with aspirin + edoxaban or aspirin + clopidogrel. After 6 months of observation, there was a lower numerical but nonstatistically significant incidence of restenosis/reocclusion in the edoxaban group without an increase in major or life-threatening bleeding events.

b. **COMPASS trial:** This study randomized 27,395 patients with CAD or PAD in 1:1:1 ratio to aspirin 100 mg daily, rivaroxaban 5 mg BID, or aspirin 100 mg daily + rivaroxaban 2.5 mg BID. In a subgroup analysis of the study cohort, 7,470 patients with lower extremity PAD, carotid disease, or CAD with ABI <0.9 were evaluated for several PAD endpoints. In addition to a decrease in the primary endpoint of MI, CVA, and CV death, patients treated with ASA + rivaroxaban experienced a statistically significant reduction in major adverse limb events (composite of ALI, CLI, or major amputation). Although this came at the expense of an increased incidence of major bleeding in the aspirin + rivaroxaban group, there was no significant increase in fatal or critical organ bleeding.

c. The **Voyager PAD** trial is ongoing and will randomize patients with infrainguinal endovascular and surgical revascularization procedures to aspirin 100 mg daily ± rivaroxaban 2.5 mg BID. The primary efficacy outcome is a composite of MI, ischemic

CVA, CV death, ALI, and major amputation. The primary safety outcome is TIMI major bleeding. Results are expected in 2019. Given demonstrable improvement in limb-related outcomes albeit at the expense of increased bleeding seen in COMPASS, these results are eagerly anticipated and have the potential to change the current treatment paradigm in patients with PAD.

3. **Risk factor modification.** PAD is a coronary risk equivalent and as such aggressive risk factor modification is warranted.

a. **Tobacco.** Cigarette **smoking** has been associated with progression of atherosclerosis. Physician counseling is essential, as **tobacco cessation can reduce the 5-year amputation and mortality rate by 50%**. The importance of this intervention cannot be underestimated. Whenever possible, extensive counseling and referral to formal smoking cessation programs should be offered (class I). In addition, several pharmacologic therapies are available (bupropion, nicotine replacement, and varenicline) and should be prescribed when indicated.

b. **Hypertension.** Current updated guidelines recommend treatment of **hypertension** in patients with clinical cardiovascular disease or 10-year ASCVD risk >10% and BP ≥130/80 mm Hg. The use of β-blockers as antihypertensive agents in patients with PAD is ***not*contraindicated**. Given the findings of the Heart Outcomes Prevention Evaluation Study, which included patients with PAD, it is reasonable to treat patients with symptomatic PAD, irrespective of diabetes, with an angiotensin-converting enzyme (ACE) inhibitor to reduce cardiovascular events (class IIa). The SPRINT trial, which randomized 9,361 nondiabetic individuals with increased cardiovascular risk to standard (<140 mm Hg) to intensive (<120 mm Hg) BP control demonstrated a reduction in 1-year all-cause mortality and MACE (MI, other ACS, stroke, heart failure, and cardiovascular death) at the expense of elevated rates of some adverse drug effects.

c. **Hyperlipidemia.** Based on the current PAD guidelines, aggressive treatment of PAD patients with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors is indicated for all patients with PAD (class I). In the most recent iteration of the lipid guidelines, the authors advocate for high-intensity statin therapy in patients with clinical atherosclerotic disease who are <75 years old in the absence of a contraindication. In patients >75 years old and in those who are not candidates for high-intensity statin therapy, they suggest that moderate-intensity statin therapy is appropriate.

d. **Diabetes mellitus.** The management of **diabetes** in patients with PAD is important, given their increased risk of amputation (overall 20%) and increased mortality (estimated to be 50% at 5 years). Current recommendations advocate that management of diabetes mellitus in PAD patients be coordinated with members of the patient's healthcare team (class I), reflecting the importance of multidisciplinary care in this subset of patients. The PAD guidelines also acknowledge that improved glycemic control can be beneficial in CLI patients as a means of improving limb-related outcomes (class IIa), though do not advocate for a specific target. Lastly, it is worth mentioning that aggressive risk factor modification is a critical component of management for diabetic patients with PAD, and these patients should be treated with antiplatelet therapy, lipid-lowering agents, and ACE inhibitors in the absence of contraindication. Close consistent monitoring by both the patient and healthcare providers for the development of lower extremity wounds is also critical given the preponderance of neuropathy and distal infrapopliteal disease seen in these patients.

4. **Medical therapy**

a. **Exercise.** Exercise is an inexpensive, low-risk option in comparison with invasive therapies and pharmacotherapies for intermittent claudication. Potential mechanisms by which exercise improves symptoms include augmentation of collateral flow, improved rheologic characteristics of blood, decreased reliance on anaerobic metabolism, and greater oxygen extraction. **Supervised exercise programs have been shown to improve pain-free walking distance up to 180% from resting values.** In the CLEVER trial, 111 patients with aortoiliac disease were randomized to optimal medical therapy with or without stenting or supervised exercise and followed for 18 months. When compared to individuals treated with optimal medical therapy alone, those treated with either stenting or supervised exercise experienced increase in peak walking time as well as claudication onset time. For patients with claudication, current guidelines recommend a supervised exercise program with the goal of improving functional status, QOL, and leg symptoms (class I). It is also suggested that this be discussed as a treatment option for claudication prior to possible revascularization (class I). For patients who do not have access to a supervised exercise program, it is reasonable to employ a structured, home-based program (class IIa), though careful attention must be given to providing detailed instructions and ensuring compliance.

b. **Cilostazol** is a type 3 phosphodiesterase inhibitor that suppresses platelet aggregation and acts as a direct arterial vasodilator via its effect on cyclic AMP. Cilostazol also beneficially increases high-density lipoprotein, decreases triglycerides, and inhibits vascular cell adhesion molecule-1 expression, thereby decreasing vascular smooth cell proliferation. Randomized controlled trials of patients with moderate to severe claudication have demonstrated 40% to 60% increases in maximal walking distances after 12 to 24 weeks of therapy with cilostazol 100 mg twice daily. In a meta-analysis, cilostazol also demonstrated benefit in terms of restenosis, freedom from TLR, limb salvage, and amputation-free survival. **A trial of cilostazol 100 mg twice daily is recommended in all patients with PAD and intermittent claudication to relieve symptoms and improve walking distance (class I).** Cilostazol is contraindicated in patients with congestive heart failure, owing to an increased risk of sudden death associated with related phosphodiesterase inhibitors. Common side effects associated with cilostazol include diarrhea, palpitations, and headaches.

c. **Pentoxifylline.** Oral pentoxifylline is no longer recommended for the treatment of claudication (class III).

5. **Revascularization.** Historically, surgical bypass was seen as the preferred modality of revascularization, with endovascular approaches being reserved for select cases with relatively straightforward anatomy (TASC A and B). This was predominantly due to limited procedural success and worse patency rates with endovascular as compared to surgical intervention. However, with improved operator experience, various technical advances, and institution of modern pharmacologic treatment regimens, better outcomes were seen in patients treated via an endovascular approach. This, in concert with relatively high morbidity associated with surgery, led to increased adoption of an “endovascular-first” strategy.

a. **Percutaneous therapy.** Currently, endovascular revascularization is advocated for patients with lifestyle-limiting claudication despite optimal medical therapy, patients with CLI, and patients with PAD in whom revascularization is necessary to allow for another indicated percutaneous procedure (i.e., coronary stenting, hemodynamic support device insertion, TAVR). It is important to recognize that in patients who present for revascularization

in the setting of claudication the primary goal of intervention is symptom relief whereas in the setting of CLI the goal is limb salvage.

1. **(1) Aortoiliac disease:** Current guidelines support the importance of addressing inflow disease, especially in the presence of CLI. Options for percutaneous revascularization include angioplasty with or without stenting. In a meta-analysis conducted by Bosch et al. which included 14 studies comprising 2,116 patients undergoing iliac stenting or angioplasty, there was a 39% reduction in long-term failure in the stent group as compared to the angioplasty group with >90% procedural success and similar complication rates in these patients. This has caused many to adopt a primary stent strategy in patients with aortoiliac disease, especially in the setting of TASC C and D lesions.
2. **(2) Femoropopliteal disease:** This is the most common segment of the lower extremity involved in patients with PAD. Given the high degree of collateralization in the SFA, patients often present late with advanced disease, including long segments of severe stenosis and/or occlusion often with high degrees of calcification. There are fortunately several tools available to address such disease, including atherectomy devices, various specialized balloons (including cutting, Chocolate, drug-coated, and lithotripsy), and various stents (nitinol, wire-interwoven nitinol, drug-eluting, and covered). Given the high degree of mechanical stress that the superficial femoral artery is exposed to, many practicing physicians have been concerned about the potential for accelerated rates of ISR as well as stent complications such as kinking, compression, and fracture in patients who undergo stent implantation. This concern and a lack of consensus for the optimal treatment strategy have led to several clinical trials designed to address various approaches. In a randomized controlled trial including 104 patients with severe PAD, vessel patency and functional status were improved with self-expanding stent placement as compared to angioplasty alone with a stent fracture rate of 2% in the stent group. Subsequent well-conducted studies in patients treated with a wire-interwoven stent (SUPERA) as well as a drug-eluting stent (ZILVER PTX) demonstrated excellent results with regard to patency rates, need for target lesion revascularization, and rates of stent fractures. There have also been two more recent randomized trials comparing angioplasty to drug-coated balloon treatment in patients with PAD, which have similarly demonstrated excellent outcomes in terms of patency extended out to 2 years. As of now, there is not a clear consensus as to the optimal treatment strategy in patients with femoropopliteal disease, and as such clinicians must individualize treatment by carefully weighing patient, lesion, and device-specific characteristics.
3. **(3) Infrapopliteal disease:** Because of the often complex nature of infrapopliteal disease with potential for serious complications such as perforation with compartment syndrome and distal embolization, attempts at endovascular intervention should be done by physicians who specialize in invasive management of patients with PAD. Several devices including atherectomy devices, standard peripheral balloons, a variety of specialized balloons, and coronary drug-eluting stents may be used depending on the specific clinical scenario. In a recent meta-analysis which compared angioplasty to femoral tibial bypass surgery, there was no difference in rates of limb salvage between treatment groups, further supporting the feasibility of endovascular approaches in this disease subset.

b. **Surgery.** Surgical revascularization also has a class IIa indication for individuals with lifestyle-limiting claudication, acceptable perioperative risk, inadequate response to guideline-directed medical therapy, and technical aspects that favor a surgical over endovascular approach. Surgery is used to bypass long segments of diffuse disease (particularly involving the femoropopliteal segment) or when endovascular therapy fails. Various conduits, such as reversed or in situ saphenous vein grafts, Dacron grafts, and polytetrafluoroethylene (PTFE) grafts, can be used. The best outcomes are achieved with single segments of saphenous

vein grafts with less optimal results with PTFE grafts. This is reflected in the class I recommendation for use of autogenous vein bypass to the popliteal artery over prosthetic grafts. Ultimately, the decision to pursue endovascular versus surgical intervention is a complex one which must weigh several patient and procedural factors. The complexity of this decision and lack of modern comparative trials, especially in the CLI population, is a driving force behind the ongoing BEST CLI trial.

III. LOWER EXTREMITY ANEURYSMS. Aneurysms of the peripheral arteries, as in the aorta, are most commonly due to atherosclerotic disruption of the arterial media. Up to 70% of lower extremity aneurysms involve the popliteal arteries. The incidence of bilateral involvement in lower extremity aneurysm is high (45% to 68%). The majority of patients (62%) with popliteal aneurysms have been reported to have concomitant abdominal aortic aneurysms (AAAs), and this co-prevalence increases to 85% in patients with femoral artery aneurysms. Accordingly, patients diagnosed with peripheral arterial aneurysms, especially femoral or popliteal, should be screened with US for AAA and for the presence of contralateral lower extremity disease (class I). The greatest concern with lower extremity aneurysms is thrombosis and thromboembolism. Lower extremity aneurysms infrequently rupture (7% to 12%), but up to 60% will have an ischemic complication. Therefore, ALI is the most common presenting symptom. As an aneurysm increases in size, it can compress adjacent venous and lymphatic structures causing lower extremity edema. Given the risk of thrombosis, it is recommended that popliteal aneurysms >2.0 cm (class I) and femoral artery aneurysms >3.0 cm be repaired. Unless symptomatic, aneurysms of smaller caliber should be followed by annual arterial duplex US examinations (class IIa).

IV. UPPER EXTREMITY ARTERIAL DISEASE. In addition to atherosclerosis, which is the most common cause of upper extremity PAD, other pathologic states can result in stenosis of the upper extremity arteries. These disorders include vasculitis (particularly Takayasu and giant cell arteritis), FMD, thoracic outlet syndrome, ionizing radiation, and repetitive injury. Associated clinical symptoms include arm and hand claudication, digital ulceration, and neurologic symptoms caused by vertebral–subclavian steal. The diagnostic modalities are similar to those in lower extremity arterial disease. The simple clinical maneuver of checking BP measurements in both arms is an excellent screening test for significant upper extremity PAD. Risk factor modification for atherosclerotic lesions and revascularization (for symptomatic patients) are the mainstays of therapy. Finally, a high index of suspicion for concurrent cardiovascular and cerebrovascular disease should be maintained.

V. RENAL ARTERY DISEASE

A. Clinical manifestations. Renal artery stenosis (RAS) is commonly associated with two clinical syndromes: hypertension and ischemic nephropathy. Clues to the presence of RAS include the following: **abrupt onset of hypertension** (before age 30 years, often because of FMD, or after age 55 years, often because of atherosclerotic disease); **previously well-controlled chronic hypertension that becomes resistant to medical therapy** (three-drug regimen including a diuretic); **azotemia**, which is unexplained or induced by ACE inhibitor administration; and **recurrent flash pulmonary edema**, often with normal left ventricular function (because of renin-angiotensin–mediated volume overload and peripheral vasoconstriction). Physical examination in RAS may reveal hypertension,

epigastric bruits, and evidence of atherosclerosis in other vascular beds (e.g., carotid or femoral bruits and diminished pedal pulses). Renal imaging can reveal an atrophic kidney or a size discrepancy between the two kidneys.

B. Etiology and natural history. The most common causes of RAS are atherosclerosis and FMD. Atherosclerosis accounts for 90% of RAS and usually involves the ostium and proximal third of the main renal artery. The prevalence of atherosclerotic RAS increases with age, particularly in patients with diabetes, aortoiliac disease, coronary artery disease, or hypertension. Studies have suggested that the prevalence of RAS in patients with PAD may be as high as 59%. Incidence increases with age and in community-based samples has a prevalence of approximately 7% in individuals >65 years old. It is the most common cause of secondary hypertension, may account for 1% to 5% of all cases of hypertension, and may be the cause of end-stage renal failure in up to 20% of new dialysis patients. RAS is an independent risk factor of mortality in patients with other vascular diseases. Moreover, end-stage renal disease because of RAS is associated with the highest mortality (median survival of 2.7 years) among all dialysis-dependent patients. FMD accounts for <10% of cases of RAS, but should be suspected in younger patients without atherosclerotic risk factors who present with RAS. It more frequently affects the distal two-thirds of the main renal artery and its branches, and in the most common type of FMD, multifocal FMD, there is a characteristic "string of beads" appearance on angiography. The cause of FMD is unknown. Rarer causes of RAS include vasculitis, neurofibromatosis, congenital bands, extrinsic compression, and ionizing radiation.

C. Diagnostic evaluation

1. Laboratory studies. Blood urea nitrogen and serum creatinine are readily available and are often used in practice as screening tools. Although azotemia and increased serum creatinine are neither sensitive nor specific for RAS, they may be the first clue to the disease. Urinalysis in RAS usually reveals proteinuria with a bland sediment. Because of the advent of sensitive and specific noninvasive imaging modalities, plasma renin activity and selective renal vein renin measurements are not recommended as screening tests to diagnose RAS (class III).

2. Duplex ultrasonography (DUS). Arterial duplex uses a combination of B-mode US imaging and Doppler spectral analysis. Elevated peak systolic velocities, the renal-to-aortic ratio, and the presence of color and spectral turbulence are criteria used to determine the presence of significant RAS. In addition, DUS allows for the calculation of the renal resistive index (renal parenchymal peak systolic velocity minus end-diastolic velocity divided by the peak systolic velocity), which is a potential marker of renal parenchymal disease. Some data suggest that patients with an elevated resistive index may not improve after revascularization. DUS is inexpensive, widely available, and highly sensitive and specific for RAS when compared with angiography (reported sensitivities between 84% and 98% and reported specificities between 62% and 99%). It is also highly useful for surveillance of renal arteries after stenting, as flow through a stent can be easily detected, in contrast to MRA, which is limited by metal artifact. DUS for RAS must be performed in experienced centers. The test may be limited by difficulty in obtaining measurements because of excess bowel gas or obesity. It also has lower sensitivity (64%) for identifying accessory renal arteries, narrowing of which could also lead to the signs of RAS.

3. **Renal scintigraphy.** Radionuclide renal imaging is used to assess differential renal blood flow and has been used in conjunction with captopril renography to attempt to diagnose RAS. Captopril renography precipitates an ACE inhibitor–mediated fall in glomerular filtration to amplify differences in renal perfusion consistent with RAS. Because of a relative lack of sensitivity (74%) and specificity (59%) compared with catheter-based angiography, captopril renography is no longer recommended for the screening of RAS (class III).

4. **Magnetic resonance angiography.** MRA now has a class I indication as a test for the diagnosis of RAS, with reported sensitivity and specificity from 90% to 100% and 76% to 94%, respectively, when compared with angiography. MRA is noninvasive and has the ability to generate 3D reconstructions. Its limitations include expense, limited availability, lack of resolution in the setting of high-grade stenosis (often appearing as an occlusion or loss of signal), a tendency to overestimate lesion severity, and difficulty with post-stent imaging because of artifact. It is also less sensitive for the detection of FMD, given that the typical arterial beading may be subtle and resolution of MRA is still limited, particularly of the distal renal vasculature. In addition, in patients with advanced renal insufficiency or renal failure, gadolinium-containing contrast agents have been linked to nephrogenic systemic fibrosis in 2% to 3% of patients. This has complicated the use of contrast-enhanced MRI in patients with RAS and renal insufficiency.

5. **Computed tomographic angiography.** Like MRA, CTA has the capability of producing excellent 3D images of the renal arteries as well as the aorta and other visceral vessels. CTA has a sensitivity and specificity for detecting significant RAS ranging from 59% to 96% and 82% to 99%, respectively. Contrast administration (100 to 150 mL) and radiation dose remain limitations of CTA. Unlike MRA, CTA does not have significant imaging artifact with metal clips or stents and, therefore, can be used to detect in-stent restenosis.

6. **Renal arteriography.** This is the gold standard for the diagnosis of RAS. It allows for excellent visualization of the main renal and accessory renal arteries and their branches. Arteriography is often used in concert with intravascular US and fractional flow reserve in order to obtain a more complete anatomic and physiologic assessment of the renal vasculature. Disadvantages include the requirement for intra-arterial access and nephrotoxic radiocontrast.

D. **Treatment.** Despite antihypertensive therapy, RAS tends to progress and may be associated with renal ischemia and loss of renal function (i.e., renal insufficiency). Atherosclerotic nephropathy is complex and not simply related to stenosis of the renal artery. Examination of renal histology in patients with atherosclerotic nephropathy reveals other potential mechanisms for loss of function, including small-vessel occlusion from atheroemboli, intrarenal arterial stenoses, and preexisting hypertensive nephrosclerosis. Importantly, as with other peripheral vascular disease processes, a high index of suspicion for concurrent cardiovascular and cerebrovascular disease should be maintained.

1. **Medical therapy.** Aggressive antihypertensive therapy using multiple agents remains the mainstay of RAS therapy and is often the control arm of randomized trials of interventional approaches to RAS. ACE inhibitors, angiotensin receptor blockers, diuretics, β-blockers, calcium channel blockers, and various other antihypertensives have been shown to be effective in treating hypertension associated with RAS. ACE inhibitors and angiotensin

receptor blockers should not be used in patients with bilateral RAS or a solitary kidney with RAS. However, these agents can be highly effective in the management of hypertension in patients with unilateral RAS (class I). Patients with RAS should be treated to achieve BP targets consistent with the most recent iteration of the guidelines as addressed above. Aggressive atherosclerotic disease risk factor modification should be part of a comprehensive treatment plan.

2. **Percutaneous revascularization.** The principle behind revascularization is that early restoration of renal artery patency in patients with atherosclerotic RAS may improve hypertension management and minimize progressive renal dysfunction. Although there is a paucity of data from controlled clinical trials to show that revascularization for RAS improves hypertension or delays renal dysfunction, the application of current studies to real-world clinical practice has been affected by several important limitations.

a. **ASTRAL:** This study randomized 806 patients with atherosclerotic renovascular disease to medical therapy with or without revascularization. The primary outcome of progression of renal dysfunction and key secondary outcomes including major cardiovascular and renal events were similar between groups. Despite this result, it is worthwhile to note that patients with a clear indication for revascularization as well as those with a high likelihood of needing revascularization within 6 months were excluded from the trial—both important factors which limit the generalizability of the results to the patients the procedure is actually intended to benefit. Additionally, of the 403 patients randomized to revascularization, 40% had lesions <70% in severity, which brings into question whether the correct selection criteria were used.

b. **STAR:** This trial randomized 140 patients with RAS and CKD to medical therapy with or without renal stenting. The primary outcome of decrease in creatinine clearance >20% did not differ between groups at 2-year follow-up. It is noteworthy that of the 64 patients randomized to stenting, 30% did not undergo revascularization, predominately because of the fact that the lesion was not deemed to be severe at the time of angiography. Overall, only a small proportion of patients in both arms reached the primary endpoint, which resulted in the study being underpowered and thereby limiting its applicability to clinical practice.

c. **CORAL:** This is the largest and most recent trial addressing the utility of renal stenting. In this study, 947 patients with RAS were similarly randomized to medical therapy with or without stenting. At a mean follow-up time of 43 months, there was no difference in the incidence of the primary outcome of cardiovascular or renal death, MI, stroke, CHF hospitalization, progressive renal dysfunction, or need for RRT. Owing to poor enrollment, the criteria for lesion severity were lessened throughout the study, which likely resulted in inclusion of patients with less severe RAS. Since the study has been published, concern has been raised about whether the study population reflected a less high-risk population and therefore not one that would be expected to garner the greatest benefit of revascularization as compared to medical therapy.

Based on the above data, it is clear that lower risk patients with RAS can likely benefit from medical therapy without need for up-front revascularization. Therefore, the crux of the issue in defining a subset of patients who may benefit from revascularization largely rests upon accurately defining high-risk characteristics that would predict improved outcome with stenting versus medical therapy. Although currently no clear consensus exists, many practicing physicians as well as the guidelines advocate for revascularization in patients with severe RAS

(>70% stenosis or 50% to 70% stenosis with peak pressure gradient >20 mm Hg or mean gradient >10 mm Hg) in addition to progressive renal dysfunction, poorly controlled hypertension, recurrent episodes of unstable angina, or recurrent unexplained flash pulmonary edema. In terms of revascularization technique, renal artery stent placement has a class I indication for ostial atherosclerotic RAS. Stenting is also recommended as bailout therapy following failed angioplasty in renal FMD, although angioplasty alone is generally successful in this disorder. Predictors of poor outcomes with RAS interventions include significant proteinuria (>1 g/d), renal atrophy, parenchymal renal disease, and diffuse renal arterial disease. In patients undergoing renal stenting, baseline azotemia is the strongest predictor of long-term mortality (70% 5-year mortality with serum creatinine >2.5 mg/dL).

3. **Surgical revascularization.** Vascular surgery approaches to RAS include surgical bypass (aortorenal, celiac-renal, or mesenteric-renal) and endarterectomy. Perioperative mortality rates range from 1% to 5%. The comparable procedural success with percutaneous approaches and fewer major complications have led to a decline in the number of vascular surgeries for RAS. In the setting of RAS and aortic disease (either aneurysmal or occlusive), surgical revascularization with renal artery bypass grafting is the preferred approach (class I). Surgical revascularization is also recommended for patients with significant atherosclerotic RAS and clinical indications for intervention with multiple renal arteries or early branching main renal artery (class I). In patients with FMD, surgical revascularization is recommended for RAS associated with macroaneurysms or complex disease involving segmental renal arteries (class I).

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KEY REVIEWS

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CHAPTER 27B

Carotid Artery Disease

Joseph Campbell

I.EPIDEMIOLOGY AND ETIOLOGY OF STROKE

A. Annually, there are nearly 800,000 strokes in the United States and 15 million strokes worldwide. Stroke is the **third leading cause of death**in western societies and the leading cause of long-term disability in the United States.

B. Ischemic stroke accounts for approximately 85% of all strokes. Of these, 60% are embolic in nature whereas small vessel disease and large vessel atherothrombotic lesions account for 25% and 15%, respectively.

II.RISK FACTORS FOR CAROTID ATHEROSCLEROSIS

A. **Smoking and age** are the two most important risk factors for developing carotid atherosclerosis. The others, in order of importance, are **hypertension, diabetes, gender (men more than women if younger than 75 years; women more than men if older than 75 years), and hyperlipidemia**.

B. Between 30% and 60% of patients with peripheral arterial disease have carotid disease, and approximately 50% to 60% of patients with carotid disease have severe carotid artery disease (CAD). However, only 10% of patients with CAD have severe carotid disease.

III.PATHOPHYSIOLOGY

A. As with coronary disease, atherosclerotic carotid disease usually develops at branch points and bends, especially at the bifurcation of the common carotid artery and origin of the internal carotid artery (ICA).

B. The reasons that carotid stenoses become symptomatic are not completely understood, but there is a linear increase in the risk of stroke as the stenosis increases to >70%. Two hypotheses explain how carotid disease can cause stroke.

1. **Carotid plaque is highly vascularized.** Rupture of this vasculature or rupture of the plaque can result in plaque hemorrhage or ulceration, with subsequent in situ thrombus formation. This can lead to complete vessel obstruction or distal atherothromboembolism. This mechanism accounts for most cerebrovascular events caused by carotid disease.

2. Larger plaques can result in high-grade carotid stenosis or obstruction, with subsequent ischemic stroke because of a reduction in cerebral flow, in the setting of inadequate or absent collateral circulation.

IV.DIAGNOSIS

A. **History and physical examination**

1. Careful history can aid in the localization of neurologic symptoms. Hemispheric symptoms include unilateral weakness, numbness, difficulty with speech, and visual field defects, whereas vertebrobasilar symptoms can include cerebellar disturbances such as ataxia or brain stem symptoms including syncope, dysphagia, dysarthria, or diplopia. Amaurosis fugax is transient, unilateral vision loss ipsilateral to a carotid lesion.
2. **An assessment for the presence of a cervical bruit is an important part of the physical examination but should not be relied on as the sole marker for the presence of carotid disease.** In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the presence of a cervical bruit had an approximately 60% sensitivity and specificity for high-grade carotid stenosis. In the Framingham study, the presence of a carotid bruit in asymptomatic patients doubled the risk of stroke, but most of these strokes occurred in vascular beds different from those of the carotid bruit. The presence of a bruit may be a general marker for patients at higher risk for cerebrovascular and cardiovascular events.
3. **In addition to auscultation for carotid bruits, a complete evaluation in a patient with symptoms includes a focused neurologic examination to correlate symptoms with neurologic territory, a fundoscopic examination to detect retinal embolization, and a cardiac examination to rule out potential cardioembolic sources for symptoms.**
4. All patients should have an evaluation of the carotid arteries after a stroke or a transient ischemic attack (TIA). The risk of a second stroke is elevated for several years after the first stroke or TIA. Symptomatic patients with 70% or more stenosis have an 8% risk of stroke at 30 days and a 13% annual incidence of stroke. The risk of stroke in asymptomatic patients increases as the degree of carotid stenosis increases. Asymptomatic patients with 60% or more stenosis have a stroke risk of approximately 2% per year. Asymptomatic patients with 80% or more stenosis have a risk of approximately 5% per year.

B. Duplex ultrasound

1. Although carotid angiography is the gold standard, duplex ultrasound is the most widely used method for the detection and quantification of CAD. It has a sensitivity and specificity of >80% among patients with 70% to 99% stenoses and sensitivity and specificity of >95% among patients with complete carotid occlusion. Because of its high sensitivity and specificity in severe carotid disease as well as its noninvasive nature, duplex ultrasound should be the first study performed to assess for carotid disease.
2. The ultrasound diagnosis of carotid stenosis is based largely on peak systolic and end-diastolic velocities in the ICA. Duplex ultrasound criteria for carotid stenosis vary by institution, and each vascular laboratory must assess the accuracy of its criteria for stenosis in a quality assurance program. Compared with angiography, duplex ultrasound is noninvasive, is less expensive, and can be done at the bedside. Limitations include the inability to image intracranial disease, limited ability to assess collateral flow, occasional inaccuracy in distinguishing high-grade stenoses (“string sign”) from complete obstructions, and the need for an experienced sonographer. Conditions that may elevate intravascular flow velocities, such as common carotid disease, vessel tortuosity, contralateral carotid disease, or presence of a carotid stent, may result in an artificially high estimate of ICA stenosis. The ability of ultrasound to assess the posterior carotid circulation is limited.

C. Computed tomography angiography (CTA)

1. CTA offers high sensitivity and specificity for the identification of severe (>70%) CAD (sensitivity 75% to 100%, specificity 63% to 95%, negative predictive value up to 100%). CTA allows for visualization of the carotid artery lumen as well as adjacent bony and soft tissue structures. Advantages include high sensitivity (particularly for carotid artery occlusion), reproducibility, and the ability to visualize the entire carotid artery including the extracranial and intracranial portions. Disadvantages include cost and the need for contrast injection, which may be unsuitable for patients with chronic kidney disease or volume overload.

D. Magnetic resonance angiography

1. Contrast-enhanced magnetic resonance angiography (CEMRA) is rapidly gaining acceptance as a sensitive (91% to 95%) and specific (88% to 92%) test for severe carotid disease. Advantages include high sensitivity, reproducibility, and the ability to visualize the entire carotid artery, including the extracranial and intracranial portions. The use of a paramagnetic agent as a vascular contrast confers higher quality images less prone to artifact. Disadvantages include high cost and the inability to study critically ill patients, claustrophobic patients, or patients with ferromagnetic implants such as pacemakers.
2. The combination of CEMRA and Doppler ultrasound results in a lower number of misclassifications and higher sensitivity and specificity for the diagnosis of severe ICA stenosis. When there is concern regarding the accuracy of one study, it is justifiable to perform both.

E. Contrast angiography

1. Contrast angiography with digital subtraction angiography is the gold standard for assessment of carotid atherosclerosis. It allows the simultaneous assessment of the aortic arch, subclavian arteries, vertebral arteries, and intracranial circulation. Angiography enables the accurate assessment of collateral circulation. This is important because the presence of collateral circulation in medically treated patients with high-grade stenosis reduces the risk of ipsilateral stroke.
2. Two criteria are used to quantify carotid stenosis angiographically: the NASCET criteria and the European Carotid Surgery Trialists' (ECST) Collaborative Group criteria (Fig 27A.1). According to the NASCET criteria, the normal reference internal carotid diameter is the maximum diameter of the ICA distal to the lesion and distal to the carotid bulb. According to the ECST criteria, however, the normal reference diameter is determined by the estimated position of the external wall of the carotid bulb. The same lesion has a higher percentage of stenosis using the NASCET criteria compared with the ECST criteria. In addition, the NASCET criteria are difficult to apply in subtotal occlusions with collapse of the distal ICA because of underfilling. However, the NASCET criteria inherently have less variability and are now recommended as the standard for reporting of angiographic carotid stenosis in Medicare physician quality initiatives.

V.MANAGEMENT OF CAROTID DISEASE

A. Medical management

1. **Risk factor modification.** Aggressive cardiovascular risk factor modification is recommended to reduce the risk of stroke and prevent the progression of existing disease, regardless of whether or not revascularization is indicated. This includes careful attention to smoking cessation and optimal control of various cardiovascular

comorbidities including hypertension, hyperlipidemia, and diabetes mellitus according to established guidelines.

2. Antiplatelet therapy

a. **Aspirin** is the most extensively studied antiplatelet drug for the prevention of stroke and should be initiated in all patients with evidence of carotid atherosclerosis. Current guidelines advocate initiation of aspirin 75 to 325 mg daily in all patients with extracranial carotid or vertebral atherosclerosis to reduce risk of MI and other ischemic cardiovascular events.

b. Clopidogrel 75 mg daily may be used in primary prevention settings when there is a contraindication to aspirin therapy. Following a stroke, it is reasonable to use clopidogrel as an alternative to aspirin in select clinical situations depending on the risk factor profile of the patient.

FIGURE 27A.1 The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trialists' (ECST) Collaborative Group criteria for determining the degree of carotid stenosis.

c. Dual-antiplatelet therapy (DAPT) is not routinely used in patients with carotid atherosclerosis in the absence of an endovascular intervention or alternate indication (i.e., coronary stenting). This is largely driven by increased bleeding risk with DAPT.

d. Low-dose aspirin (25 mg twice daily) plus **dipyridamole** (200 mg twice daily) has been found to be more beneficial than aspirin alone or dipyridamole alone for the secondary prevention of stroke in the European Stroke Prevention Study 2. Similarly, in the European/Australian Stroke Prevention in Reversible Ischemia Trial, extended-release dipyridamole administered with aspirin was superior to aspirin alone in the prevention of MI, stroke, or vascular death.

e. The Prevention Regimen for Effectively avoiding Second Strokes trial, which enrolled over 20,000 patients with noncardioembolic ischemic stroke, showed that clopidogrel monotherapy and aspirin plus extended-release dipyridamole have similar risks and benefits for secondary stroke prevention. There was no difference between treatment with aspirin plus extended-release dipyridamole or clopidogrel for the primary outcome of recurrent stroke or the composite secondary outcome of stroke, MI, or vascular death. However, despite the nearly identical event rates, the trial failed to meet the prespecified noninferiority criteria for treatment with aspirin and extended-release dipyridamole.

f. According to the American Heart Association (AHA)/American Stroke Association (ASA) Guidelines for the Prevention of Stroke in Patients with Ischemic Stroke or TIA, the accepted treatment strategies for the secondary prevention of noncardioembolic stroke include one of the following:

1. **(1)** Aspirin (75 to 325 mg daily)
2. **(2)** Aspirin (25 mg) and extended-release dipyridamole (200 mg) twice daily
3. **(3)** Clopidogrel (75 mg daily), especially for patients with aspirin allergy or resistance

3. Antihyperlipidemic agents

a. Epidemiologic data have shown higher stroke rates among patients with high LDL and low HDL cholesterol levels. Several studies have consistently shown carotid plaque regression in patients treated with statins, and clinical trials have shown a reduction in stroke among patients treated with statins. In the Scandinavian Simvastatin Survival Study,

nonembolic strokes were significantly reduced in the statin arm. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels study demonstrated a 16% relative risk reduction in stroke with statin therapy in 4,731 patients with prior stroke or TIA randomized to atorvastatin versus placebo. In a meta-analysis of randomized trials that included a total of 165,792 patients with hyperlipidemia, each 39 mg/dL reduction in LDL cholesterol equates to a reduction in relative risk of stroke of 21.1%.

b. The beneficial effects of statins in reducing strokes are highest among patients at the highest risk for stroke. For primary prevention, all high-risk patients (e.g., diabetes, peripheral vascular disease, and CAD) should be treated with statins. For secondary prevention, all patients with a history of MI, TIA, and stroke should be on statin therapy.

4. Antihypertensive agents

a. Hypertension is the single most modifiable risk factor in the prevention of stroke, and epidemiologic data suggest that approximately 60% of all strokes are attributable to hypertension. Several randomized controlled trials (RCTs) have shown benefit of a variety of antihypertensive agents—angiotensin converting enzyme inhibitors (HOPE, PROGRESS), angiotensin receptor blockers (LIFE), and diuretics (ALLHAT) in particular.

b. Current updated guidelines recommend treatment of **hypertension** in patients with clinical cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >10% and blood pressure (BP) ≥130/80 mm Hg.

5. Anticoagulation

a. Current guidelines recommend antiplatelet agents rather than anticoagulants in patients with extracranial carotid or vertebral atherosclerosis whether or not they have ischemic symptoms, unless there is an alternate indication for anticoagulation (i.e., mechanical heart valve, atrial fibrillation).

B. Surgical management: carotid endarterectomy (CEA). CEA is the standard of care for the reduction of stroke or TIA in patients with high-grade symptomatic or asymptomatic carotid stenosis. Several trials have firmly established the utility of CEA in preventing stroke in the presence of severe carotid stenosis as compared with medical therapy. It is important to keep in mind that high-risk patients were not enrolled in these trials. Because the risk of surgery among such patients probably would be higher than reported in these trials, extrapolation of these data to high-risk patients must be done with caution.

1. Major trials

a. See Tables 27A.1 and 27A.2.

2. Complications and management of patients after CEA

a. Major complications of CEA include MI, stroke, and death. Other complications include bleeding and wound hematoma, cranial nerve injury, wound infection, bradycardia, hyper- or hypotension, and, rarely, seizures and intracerebral hemorrhage. CEA should only be performed at institutions where the perioperative stroke and death rate is at the most <3% in asymptomatic patients and <6% in symptomatic patients.

b. After CEA and in the absence of contraindications, all patients should be treated with antiplatelet therapy.

TABLE 27A.1 Trials of Carotid Endarterectomy in Symptomatic Patients

TABLE 27A.1 Trials of Carotid Endarterectomy in Symptomatic Patients

	N	Endpoint + Study Arms	Inclusion	Follow-Up (years)	Results	Notes
NASCET (1991, 1998)	659	Stroke and death CEA vs. medical therapy	• TIA/stroke < 120 d • 70%–99% stenosis by angiogram	1.5	**Any stroke or death** 15.8% vs. 32.3% **Any stroke** 12.6% vs. 27.6% **50%–69% group**5-y CVA 15.7% vs. 22.2%	• Stud • Perio • Min • Perio
ECST (1998)	3,024	Stroke and death CEA vs. medical therapy	• TIA/stroke < 6 mo • Stenosis severity by angiography	6.1	**3-y major stroke or death** 14.9% vs. 26.5%	• Stra grou • CEA olde • Long risk • Perio • Perio

CEA, carotid endarterectomy; TIA, transient ischemic attack.

TABLE 27A.2 Trials of Carotid Endarterectomy in Asymptomatic Patients

N	Endpoint + Study Arms	Inclusion	Follow-Up (years)	Results	N
VA Trial (1993) 444	Composite of TIA, TMB, stroke CEA vs. medical therapy	•≥50% stenosis by angiogram •Men only	4	**TIA/stroke/TMB:** Ipsilateral: 8.0% vs. 20.6% Total: 12.8% vs. 24.5% **Stroke:** Ipsilateral: 4.7% vs. 9.4%, *p = NS* Total: 8.1% vs. 12%, *p = NS* **Stroke/death:** 41% vs. 44%, *p = NS*	•P •P •P •S

TABLE 27A.2 Trials of Carotid Endarterectomy in Asymptomatic Patients

ACAS (1995)	1,662	Composite of ipsilateral stroke, perioperative stroke, death CEA vs. medical therapy	• < 60% stenosis by angiogram	2.7	**5-y estimate primary endpoint:** Total: 5.1% vs. 11.0% Major: 3.4% vs. 6% **Stroke/death:** Total: 25.6% vs. 31.9% Major: 20.7% vs. 25.5%	•
ACST (2004, 2010)	3,120	Perioperative MI, CVA, or death and nonperioperative stroke Compared strategy of immediate vs. deferred CEA	•≥60% stenosis by DUS	3.4	**5-y estimate primary endpoint:** Total: 6.4% vs. 11.8% Fatal/disabling: 3.5% vs. 6.1% **Follow-up stroke rates:** Total: 6.9% vs. 10.9% Fatal/disabling: 13.4% vs. 17.9%	•

d. CEA, carotid endarterectomy; CVA, cerebrovascular accident; DUS, duplex ultrasonography; MI, myocardial infarction; NS, not significant; RRR, relative risk reduction; TIA, transient ischemic attack; TMB, transient monocular blindness.

3. The ASA/American College of Cardiology Foundation (ACCF)/AHA recommendations for CEA

a. Patients at average or low surgical risk who experience nondisabling ischemic stroke or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral ICA is reduced >70% as documented by noninvasive imaging or >50% as documented by catheter angiography and the anticipated rate of perioperative stroke or mortality is <6%.

b. Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure, with an understanding of patient preferences. It is reasonable to perform CEA in asymptomatic patients who have >70% stenosis of the ICA if the risk of perioperative stroke, MI, and death is low.

c. Except in extraordinary circumstances, carotid revascularization is not recommended when atherosclerosis narrows the lumen by <50%.

C. Percutaneous carotid intervention

1. Since the first description of carotid angioplasty in 1980, a number of registry studies and trials have been published reporting high rates of procedural success. However, percutaneous carotid angioplasty is rarely performed as a stand-alone procedure because of unacceptably high rates of recoil, restenosis, and adverse procedural outcomes because of distal embolization. Carotid stenting with embolic protection device (EPD) use has become the standard of care for patients undergoing percutaneous carotid intervention.

2. Major trials

a. See Tables 27A.3 and 27A.4.

3. **Complications and postprocedure management**

a. The major periprocedural complications during carotid stenting are TIA/stroke, MI, and death. Other complications include access site issues (i.e., bleeding, pseudoaneurysm, atrioventricular fistula, dissection), renal dysfunction, bradycardia, hypotension, cerebral hyperperfusion, seizures, and intracranial hemorrhage. Advanced age and long or multiple stenoses have been found to be independent predictors of periprocedural stroke.

b. **Periprocedural cerebrovascular events** occur largely because of embolization of plaque debris and thrombus into the cerebral circulation during manipulation of the carotid plaque. Alternate mechanisms of TIA/stroke include embolization of debris from the aortic arch, iatrogenic introduction of air or thrombus, hypoperfusion in the setting of periprocedural bradycardia/hypotension, hyperperfusion syndrome, and thrombus formation on stent. In addition to employing fastidious procedural technique to minimize risk of introducing air or thrombus into system, routine use of EPDs, adequate procedural anticoagulation, and preloading with DAPT are important considerations with regard to minimizing stroke risk. All patients should undergo a thorough and well-documented neurologic examination before and after the procedure. Standardized stroke scales are often utilized (e.g., National Institutes of Health Stroke Scale, Barthel, and modified Rankin). Nursing staff should also be instructed to perform routine neurologic assessments in the first 24 hours according to established protocols and to alert the responding clinician with any changes in neurologic status.

c. **Bradycardia and hypotension** occur often during carotid stenting because of instrumentation and stretching of the carotid sinus baroreceptors. These hemodynamic effects are usually transient but can persist for up to 24 hours after intervention. When not immediately reversible with balloon deflation, management options include intravenous crystalloid infusion, atropine administration, and/or **a low-dose vasopressor infusion (i.e., dopamine or phenylephrine).** In some cases, the hemodynamic derangement can persist into the postprocedure setting, in which case continued vasopressor infusion or use of pseudoephedrine may be temporarily required. Unless the patient is hypertensive, antihypertensive and negative inotropic medications are usually withheld immediately preprocedure and postprocedure. In all cases, telemetry monitoring should be continued for 24 hours.

TABLE 27A.3 Trials of Carotid Artery Stenting in Asymptomatic Patients

	N	Endpoint Arms	+	Study	Inclusion	Follow-up (years)	Results		N
SAPPHIRE	334	Composite	of	30-d	• Candidate for CAS	1	**1-y**	**primary**	•

TABLE 27A.3 Trials of Carotid Artery Stenting in Asymptomatic Patients

(2004, 2008)		death, stroke, and MI or stroke/death after day 30 CAS with EPD vs. CEA	and CEA • Increased surgical risk • DUS criteria: Asymptomatic: ≥50% Symptomatic: ≥80%		**endpoint:** Total: 12.2% vs. 20.1% Symptomatic: 16.8% vs. 16.5% Asymptomatic: 9.9% vs. 21.5% **3-y composite endpoint:** Total: 24.6% vs. 26.9%, *p* ≥ NS Symptomatic: 21.4% vs. 29.2% Asymptomatic: 21.4% vs. 29.2%
CREST (2010, 2016)	2,502	Composite of 30-d death, stroke, and MI or ipsilateral stroke within 4 y CAS with EPD vs. CEA	• Candidate for CAS and CEA • Standard surgical risk • Symptomatic: DUS: ≥50% Angiogram: ≥70% CTA/MRA: ≥70% • Asymptomatic: DUS: ≥60% Angiogram: ≥70% CTA/MRA: ≥80%	2.5	**4-y primary endpoint:** 7.2% vs. 6.8% **10-y composite endpoint:** 11.8% vs. 9.9%, *p*≥ NS **10-y ipsilateral stroke (>36 d):** 6.9% vs. 5.6%, *p* ≥ NS **Periprocedural events:** Stroke 4.1% vs. 2.3%, *p* ≥ 0.01 MI: 1.1% vs. 2.3%, *p* ≥ 0.03
ACT I (2016)	1,453	Composite of 30-d death, stroke, and MI or ipsilateral stroke within 1 y CAS with EPD vs. CEA in 3:1 ratio	• Candidate for CAS and CEA • Standard surgical risk • Asymptomatic 180 d • 70%–99% stenosis by DUS or angiogram	1.5	**1-y primary endpoint:** 3.8% vs. 3.4 %, *p* ≥ NS **Periprocedural events:** Stroke: 2.8% vs. 1.4%, *p* ≥ NS Major: 0.5% vs.

TABLE 27A.3 Trials of Carotid Artery Stenting in Asymptomatic Patients

					0.3% MI: 0.5% vs. 0.9%, $p \geq$ NS **5-y stroke-free survival:** 93.1% vs. 94.7%, $p \geq$ NS

d. CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, computed tomography angiography; DUS, duplex ultrasonography; EPD, embolic protection device; MI, myocardial infarction; MRA, magnetic resonance angiography; NS, not significant.

TABLE 27A.4 Trials of Carotid Artery Stenting in Symptomatic Patients

	N	Endpoint + Study Arms	Inclusion	Follow-Up (years)	Results
EVA-3S (2006)	527	30-d composite of stroke or death CAS vs. CEA	• Candidate for CAS and CEA • Standard surgical risk • Retinal or hemispheric stroke/TIA within 6 mo • 60%–99% stenosis by angiogram or DUS + MRA	4	**30-d death or any stroke:** 9.6% vs. 3.9% **30-d death or disabling stroke:** 3.4% vs. 1.5% **4-y death or any stroke:** 11.7% vs. 6.1% **Periprocedural stroke:** 8.8% vs. 2.7%
SPACE (2006, 2008)	1,183	30-d death of ipsilateral stroke CAS vs. CEA	• Symptoms in past 180 d • ≥70% stenosis by DUS or angiogram • Standard surgical risk	30 d	**30-d death or ipsilateral stroke** 6.84% vs. 6.34%, non-inferiority $p \geq 0.09$ **Periprocedural stroke:** Total: 7.5% vs. 6.2%, $p \geq$ NS Ipsilateral: 6.5% vs. 5.1%, $p \geq$ NS **2-y periprocedural stroke/death or ipsilateral stroke:** 9.5% vs. 8.8%, $p \geq$ NS

TABLE 27A.4 Trials of Carotid Artery Stenting in Symptomatic Patients

ICSS (2010, 2015)	1,713	Fatal or disabling stroke in any territory CAS vs. CEA	• Candidate for CAS and CEA • Standard surgical risk • Symptoms in past 12 mo • ≥50% stenosis by DUS	4.2	**5-y fatal or disabling stroke:** 6.4% vs. 6.5%, $p \geq$ NS **5-y all stroke:** 15.2% vs. 9.4%, $p <$ 0.001 **Periprocedural events:** Stroke: 8.5% vs. 5.2% Death: 2.3% vs. 0.8%
CREST (2010, 2016)	2,502	Composite of 30-d death, stroke, and MI or ipsilateral stroke within 4 y CAS with EPD vs. CEA	• Candidate for CAS and CEA • Standard surgical risk • Symptomatic: DUS: ≥50% Angiogram: ≥70% CTA/MRA: ≥70% Asymptomatic: DUS: ≥60% Angiogram: ≥70% CTA/MRA: ≥80%	2.5	**4-y primary endpoint:** 7.2% vs. 6.8% **10-y composite endpoint:** 11.8% vs. 9.9%, $p \geq$ NS **10-y ipsilateral stroke (>36 d):** 6.9% vs. 5.6%, $p \geq$ NS **Periprocedural events:** Stroke 4.1% vs. 2.3%, $p \geq 0.01$ MI: 1.1% vs. 2.3%, $p \geq 0.03$
SAPPHIRE (2004, 2008)	334	Composite of 30-d death, stroke, and MI or stroke/death after day 30 CAS with EPD vs. CEA	• Candidate for CAS and CEA • Increased surgical risk • DUS criteria: Asymptomatic: ≥50% Symptomatic: ≥80%	1	**1-y primary endpoint:** Total: 12.2% vs. 20.1% Symptomatic: 16.8% vs. 16.5% Asymptomatic: 9.9% vs. 21.5% **3-y composite endpoint:** Total: 24.6% vs. 26.9%, $p \geq$ NS Symptomatic: 21.4% vs. 29.2% Asymptomatic: 21.4% vs. 29.2%

e. CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, computed tomography angiography; DUS, duplex ultrasonography; EPD, embolic protection device; MI, myocardial infarction; MRA, magnetic resonance angiography; NS, not significant; TIA, transient ischemic attack.

f. **Hyperperfusion syndrome** is an uncommon complication that can occur because of the rapid return of flow to a chronically underperfused cerebral vascular bed with resultant disordered autoregulation. Risk factors include **severe hypertension, critical carotid stenosis, and contralateral carotid occlusion**. The initial manifestation is often an ipsilateral headache with or without focal neurologic symptoms. This may be followed by seizures, cerebral edema, and/or intracerebral hemorrhage. This syndrome often occurs in patients with postprocedure hypertension, highlighting the importance of strict blood pressure control (systolic BP < 150 mm Hg) in patients following carotid stenting.

g. **Postprocedure antiplatelet management.** Patients undergoing carotid stenting should be preloaded with aspirin and clopidogrel at least 2 days prior to the procedure if possible. After the procedure, **lifelong aspirin therapy should be instituted**, and **clopidogrel (75 mg daily) should be continued for at least 6 weeks**. For patients with recurrent symptoms or a history of neck irradiation, clopidogrel should be continued indefinitely. The incidence of restenosis after carotid stenting is lower than after coronary stenting and ranges between 1% and 6% per year. Patients should be followed in the outpatient setting with routine clinical assessment as well as duplex US monitoring after carotid stent implantation.

4. **The ASA/ACCF/AHA recommendations for carotid stenting**

a. Carotid stenting is an indicated alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by >70% by noninvasive imaging or >50% by catheter angiography and the anticipated rate of periprocedural stroke or mortality is <6%.

b. It is reasonable to choose carotid artery stenting over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.

c. **Prophylactic carotid artery stenting might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography and 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.**

D. **Patient selection for carotid stenting versus CEA**

1. There is an abundance of RCT data demonstrating similar safety and efficacy of both carotid stenting and CEA for the treatment of severe atherosclerotic disease involving the carotid arteries. Whichever approach is chosen, it is important to recognize the importance of proper patient selection as well as adherence to guideline-recommended medical therapy. Furthermore, given the potential for devastating complications with either procedure, both should be performed only by experienced operators within the field.

2. Factors that may favor carotid stenting over CEA include difficult surgical anatomy (i.e., a high carotid bifurcation), prior neck irradiation, restenosis after CEA, as well as significant comorbidities that may increase surgical risk.

3. Given the potential for higher stroke risk and worse procedural outcomes with increasing age, CEA may be a better option in older patients. Also, anatomic

considerations such as difficult aortic or carotid anatomy (i.e., type 3 aortic arch, significant tortuosity, circumferentially calcified lesions, thrombotic lesions) may lend themselves better to CEA rather than carotid stenting. It is important to note that when the best approach is in doubt, it is best to consult with the patient, vascular medicine specialists, and vascular surgeons so that the most appropriate decision for the patient can be made.

4. Despite the well-established efficacy of both carotid stenting and CEA, the importance of aggressive medical management cannot be understated. Many of the aforementioned studies were conducted prior to the advent of the most current established medical regimens leading many to question the impact this may have on the role of carotid revascularization. Indeed, despite increasingly complex patients with carotid disease, stroke rates have continued to decline in patients with severe asymptomatic carotid disease who are being medically managed. On this basis, CREST-2 will set out to address the impact of modern aggressive medical therapy with or without carotid revascularization (carotid stenting or CEA) on the rates of stroke and survival both in the periprocedural period and in long-term follow-up in patients with asymptomatic severe (≥70%) carotid stenoses. The results of these trials are eagerly anticipated.

E. Combined CEA and coronary artery bypass grafting (CABG)

1. Patients with severe coronary disease may have severe carotid disease, and surgery in this population is a high-risk procedure. The optimal treatment strategy remains controversial. In this setting, options include simultaneous CABG and carotid intervention, staged procedures, or CABG without carotid intervention.

2. In a single center study conducted at our institution, 350 patients who underwent carotid revascularization within 90 days prior to open heart surgery (OHS) were analyzed with respect to rates of a composite of all-cause death, stroke, or MI. The population included 45 staged CEA-OHS procedures, 195 combined CEA-OHS procedures, and 110 staged CAS-OHS procedures. All patients who underwent carotid stenting were required to complete a 3- to 4-week course of DAPT prior to OHS. In this cohort, patients who underwent staged CEA-OHS experienced the highest rates of the primary outcome in the short term, primarily driven by the occurrence of MI. The early event rates were similar between the combined CEA-OHS and staged CAS-OHS groups. However, after 1 year, the patients in the CAS-OHS group experienced fewer events than both the staged and combined CEA-CABG groups. Thus, provided that concomitant carotid revascularization is required and OHS can be delayed 3 to 4 weeks to allow for a course of DAPT to be completed, CAS followed by OHS may be the most attractive strategy.

3. Although in ideal circumstances, OHS would be delayed when carotid stenting is performed, this is not always feasible. In a small, single center study comprising 20 patients who underwent CAS prior to CABG, CABG could be performed safely at a mean of 6.4 days post stent implantation. Despite the use of DAPT, there were no significant bleeding complications, and no strokes or deaths were seen at a mean follow-up of 486 days. Although perhaps not generalizable to all patients, this study does suggest that in carefully selected patients in whom carotid revascularization is needed and CEA is significantly high risk, early CABG following carotid stenting could be an option.

4. It is important to note that not all patients with severe carotid stenoses who are scheduled for OHS require carotid revascularization. Patients who are at low risk from a neurologic perspective can have their carotid disease medically managed and undergo their

OHS without concomitant carotid intervention. High-risk patients, including symptomatic individuals and those with significant contralateral disease, may benefit from either staged CAS-OHS or combined CEA-OHS, depending on the specific patient and procedural characteristics.

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CHAPTER 28

Atrial Septal Defect and Patent Foramen Ovale

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I. INTRODUCTION

A. Atrial septal defects (ASDs) constitute approximately 5% to 10% of congenital heart disease. Excluding bicuspid aortic valve and mitral valve prolapse, ASD is the most common form of congenital heart defect found among adults and is the most common acyanotic shunt lesion in adults as well.

B. Often, an atrial communication may go unrecognized into adulthood because the clinical symptoms and physical manifestations may be subtle.

C. Although survival into adulthood is the rule, overall life expectancy is decreased in patients with an unrepaired ASD. Long-term exposure to chronic right heart volume overload can have deleterious effects, such as atrial arrhythmias, pulmonary vascular disease, and right heart failure. These clinical findings are directly related to patient age, with almost all patients becoming symptomatic by the fifth or sixth decade. The presence of an atrial communication is also a potential source of paradoxical embolus.

D. A patent foramen ovale (PFO) is a specific form of interatrial communication caused by incomplete closure of the foramen ovale after birth. PFOs are present in 25% to 30% of the general population. The prevalence of PFO in patients with cryptogenic stroke is approximately 40% to 50%.

E. Atrial septal aneurysms are congenital outpouchings of the atrial septum, near the fossa ovalis. They can be detected in up to 10% of patients undergoing echocardiography and in up to 30% of patients with cryptogenic stroke, generally with a concomitant PFO.

II. ANATOMY AND EMBRYOLOGY

The primitive atrium is first partitioned into right and left atria by growth of the septum primum—a thin, crescent-shaped membrane that grows from the roof of the primitive atrium toward the endocardial cushions located between the atria and ventricles. An atrial communication initially persists as the foramen primum, composed of the free edge of the septum primum and the endocardial cushions. Before closure of the foramen primum, fenestrations develop in the septum primum that coalesce to form the ostium secundum. As the septum primum then fuses with the endocardial cushions, the ostium secundum maintains a right-to-left atrial flow that is important in the fetal circulation. **Failure of this fusion results in the development of a primum ASD.** A second septum, the septum secundum, then forms to the right of the

septum primum, growing toward the endocardial cushions and usually closing the ostium secundum. **Failure to close the ostium secundum results in the formation of a secundum ASD.**

The septum secundum forms an incomplete partition of the atria, leaving a foramen ovale (i.e., fossa ovalis). The remaining septum primum tissue on the left atrial (LA) side becomes a flap valve, or valve of the foramen ovale, and allows for the continued right-to-left shunting in the fetal circulation. At birth, when LA pressure increases, the septum primum flap closes and eventually fuses to anatomically seal the atrial septum. A "true ASD" results from a deficiency in septal development or from resorption of atrial tissue, whereas a **PFO results from failure of this septum primum flap to adequately seal the fossa ovalis**. At autopsy, a "probe-patent" PFO remains in 25% to 30% of patients.

During development, if there is overabundant or weakened septal tissue, the septum becomes very mobile. This can be visualized during echocardiography, and the degree of excursion can be measured. If the maximal excursion of the interatrial septum is **15 mm or more**, this abnormality is called an **atrial septal aneurysm**. If the amount of septal excursion is <15 mm, it is referred to as a redundant atrial septum.

ATRIAL SEPTAL DEFECTS

I. ASD TYPES (Fig. 28.1)

A. **Ostium secundum** defects or **secundum ASDs** constitute the most common type, accounting for 70% to 75% of ASDs. This defect, a true defect of the atrial septum, is located in the mid-portion of the atrial septum, within or including the fossa ovalis. Defects result from a deficient septum primum or an abnormally large ostium secundum. This type of ASD is two times more common in female patients. Isolated secundum ASD has been associated with mitral valve prolapse and other forms of congenital heart disease. It may also be associated with rheumatic mitral stenosis (i.e., Lutembacher syndrome).

B. **Ostium primum** defects or **primum ASDs** account for 15% to 20% of ASDs and are part of the spectrum of atrioventricular (AV) septal defects (also known as AV canal defects or endocardial cushion defects). These defects occur in the inferior–anterior portion of the atrial septum and are frequently associated with a cleft in the anterior leaflet of the mitral valve, leading to varying degrees of mitral regurgitation. In their complete form, they include a large ventricular septal defect and a common AV valve. Depending on the severity of dysfunction of the mitral valve, these patients may become symptomatic at a young age. This defect in the inlet septum is the most common ASD associated with Down syndrome.

C. **Sinoseptal** defects constitute the remaining 5% to 10% of septal defects. Distinct from the true ASDs described previously, these lesions involve the portion of the atrial wall derived from the sinus venosus (i.e., there is no direct communication between the right and left atria). **Sinus venosus defects** are typically at the orifice of the superior vena cava (SVC) at the junction of the right atrium or, less frequently, in the region of the inferior vena cava (IVC). These sinus venosus defects are frequently associated with partial anomalous pulmonary venous drainage of the right pulmonary veins and require a high index of suspicion for diagnosis because they are generally not visualized by standard transthoracic

echocardiography (TTE). Transesophageal echocardiography (TEE) is generally required for visualization in adults. Magnetic resonance imaging (MRI) or computed tomography may also be used for diagnosis. These defects should be considered in any patient with unexplained right atrial (RA) or right ventricular (RV) dilation. An uncommon sinoseptal defect is the partially or completely **unroofed coronary sinus**, which is located inferior and slightly anterior to the fossa ovalis. These defects are commonly associated with other forms of congenital heart disease, such as complete AV septal defect, or can be associated with an absence of coronary sinus and a left SVC that drains into the left atrium.

FIGURE 28.1 Diagrammatic representation of common atrial septal defects. ASD, atrial septal defect; 1°, primum; 2°, secundum. (Reprinted from Fyler DC, ed.*Nadas Pediatric Cardiology*. Philadelphia, PA: Hanley & Belfus; 1992. Copyright © 1992 Elsevier. With permission.)

II. PATHOPHYSIOLOGY. The magnitude and direction of the shunt through the ASD depend on the size of the defect as well as the diastolic filling properties of the ventricles. Any condition that causes reduced left ventricular (LV) compliance, such as LV hypertrophy or LV scar, or increased LA pressure, such as mitral stenosis, will increase the degree of left-to-right shunting. Conversely, conditions that cause reduced RV compliance, such as pulmonary hypertension or pulmonary stenosis, or increased RA pressure, such as tricuspid stenosis, will reduce the degree of left-to-right shunting and, in some instances, even lead to shunt reversal. In general, the ASD must be at least 10 mm in its greatest dimension to cause a significant shunt, although this can be hard to measure as most ASDs are not circular. A left-to-right shunt is considered significant when the ratio of pulmonary-to-systemic blood flow, or shunt fraction **(Q_p/Q_s), is >1.5:1.0 or when right heart chamber dilation is present.**

III. CLINICAL MANIFESTATIONS. The clinical presentation of a patient with an ASD results from the effects of long-term left-to-right shunting and subsequent volume loading of the right heart. The age at which the symptoms occur is variable and does not necessarily depend on the size of the defect.

A. **Exercise intolerance** with **fatigue** and **dyspnea** may occur, but is frequently not appreciated by the patient until after the defect has been closed. Late findings include **supraventricular arrhythmias**, such as atrial fibrillation or flutter, severe irreversible **pulmonary vascular disease**, and eventually **right heart failure**. Occasionally, a **paradoxical embolus** causing a stroke or transient ischemic attack (TIA) is the first clue to an ASD.

B. The physical findings may include a hyperdynamic cardiac impulse, the characteristic **wide or fixed split second heart sound**, and a **soft systolic murmur at the second left intercostal space** because of increased flow across the pulmonary valve. If the shunt is more than a shunt fraction (Q_p/Q_s) of 2.5:1, there may be a diastolic murmur secondary to increased flow across the tricuspid valve. A loud P_2component of the second heart sound indicates the presence of pulmonary hypertension, which can affect up to 20% of patients; if cyanosis is present, this generally suggests advanced pulmonary hypertension with reversal of shunt flow (**Eisenmenger syndrome**). An important clue to the presence of Eisenmenger syndrome is an oxygen saturation that does not significantly improve with supplemental oxygen. Another physical examination finding that may be encountered is a

holosystolic murmur characteristic of mitral regurgitation, which is often heard in a patient with a primum ASD.

IV.LABORATORY EXAMINATION

A. Electrocardiogram (ECG). The ECG can provide clues to the possibility of an ASD. The rhythm may be sinus, but may also be atrial fibrillation or atrial flutter. Inverted P-waves in the inferior leads suggest an absent or nonfunctional sinus node, as may be seen with a sinus venosus defect.

1. Secundum ASD

a. RSR′ pattern in lead V_1

b. QRS duration < 0.11 seconds (incomplete right bundle branch block)

c. Right-axis deviation

d. RV hypertrophy

e. First-degree AV block (20%)

f. RA enlargement (about 50%) with a prominent P-wave in lead II

2. Primum ASD

a. RSR′ pattern in lead V_1

b. Left-axis deviation

c. First-degree AV block, classically seen with right bundle branch block and left anterior fascicular block

B. Chest roentgenogram may reveal cardiomegaly because of right heart enlargement. With large left-to-right shunts, the central pulmonary arteries and vascular markings may appear prominent. In the setting of advanced pulmonary vascular disease, however, the pulmonary arteries may appear large but have oligemic peripheral lung fields, the so-called vascular pruning.

V.DIAGNOSTIC STUDIES

A. Echocardiography is the primary means by which an ASD is diagnosed. TTE can document the size of the defect as well as the direction of the shunt flow and occasionally the location of the pulmonary veins in the younger patient. In the adult, transesophageal studies are generally required for a full anatomic assessment. An ASD should be suspected when right-sided chamber enlargement is noted on echocardiography and no other cause is identified.

1. Typical transthoracic views for imaging an ASD include the parasternal short-axis view, the apical four-chamber view, and the subcostal coronal and sagittal views. Findings include RA and RV enlargement, which indicate a functionally important defect. An estimate of RV pressure should be made via the jet of tricuspid insufficiency, and evidence for RV pressure and volume overload should be noted via observation of septal motion in systole and diastole, respectively. Evidence of left-to-right (or right-to-left) shunting across the defect should be demonstrated using color Doppler techniques. Evidence of RA and RV enlargement in the absence of an obvious cause on echocardiography, such as tricuspid regurgitation or an ASD, should prompt a search for a sinus venosus defect and/or partial anomalous pulmonary venous drainage. Intravenous contrast (i.e., agitated saline) and TTE can identify a shunt, but TEE is usually required to demonstrate a sinus venosus defect. Of note, in isolated partial anomalous pulmonary venous return, the intravenous contrast study will be negative.

2. TEE is usually required in the adult patient for further anatomic definition and to determine whether the defect is amenable to percutaneous closure. Contrast studies with agitated saline are helpful in confirming the presence and location of atrial shunting. The mid-esophageal four-chamber and bicaval views are preferred, with injection of agitated saline through an upper extremity vein. **Injection into the left arm** may be particularly helpful to establish the presence of a persistent left SVC that drains into the coronary sinus or directly into the left atrium. In the diagnosis of a sinus venosus defect, care must be taken to evaluate the location of the pulmonary veins for evidence of anomalous drainage.

B. Cardiac catheterization is typically not required for diagnostic purposes except to assess pulmonary pressures and resistance, to assess for coronary artery disease before planned surgical closure in the adult patient, or as part of a planned transcatheter device closure. Right heart catheterization can be performed in most cases using a standard end-hole catheter. The lateral camera is helpful in directing the catheter posterior before advancing across the ASD. Our standard is to perform a complete right heart catheterization, including oximetry measurements and hemodynamic assessment.

1. Oximetry samples obtained during catheterization demonstrate a step-up within the right atrium because of shunting across the defect. Careful interrogation of innominate vein saturation and SVC saturation is important to exclude a step-up at the SVC level that would support the existence of associated partial anomalous pulmonary venous drainage. Desaturation in the left atrium systemically confirms right-to-left shunting and should prompt further investigation of RV and pulmonary artery pressures. Other diagnoses producing a similar picture include large ventricular septal defects with tricuspid regurgitation, partial or complete AV canal defects, or systemic arteriovenous fistulas.

The significance of the defect can be assessed by calculating the **shunt fraction (Q_p/Q_s)**, which is the ratio of pulmonary blood flow (Q_p) to systemic blood flow (Q_s). Oximetry values, obtained during right heart catheterization and used previously to determine if a step-up is present, can be helpful for shunt calculation as follows:

The mixed venous saturation is obtained in the setting of an ASD by multiplying the SVC saturation by 3, adding the IVC saturation, and then dividing the sum by 4. If the pulmonary vein saturation is not directly measured, it can be assumed in the absence of considerable lung disease to be 95%.

2. Hemodynamic assessment may reveal modest elevations in RV and pulmonary artery pressures. An important assessment is comparison of pulmonary artery pressure with systemic pressure and measurement of pulmonary vascular resistance. If pulmonary pressures are elevated, the response to oxygen or other vasodilators should be assessed. Alternatively, the ASD can be balloon occluded with assessment of hemodynamics to ensure that closure is safe. Examples of the usual catheterization findings with and without pulmonary vascular disease are illustrated in Figure 28.2.

Using a derivative of Ohm's law, $P = Q \times R$, an ASD will increase the flow (Q) to the lungs, and, therefore, increase the pulmonary pressure (P) without a significant change in resistance (R). Findings that may preclude eventual ASD closure include one or more of the following:

pulmonary vascular resistance more than one-half of the systemic vascular resistance or an indexed pulmonary vascular resistance >7 Wood units/m^2.

3. Angiography is typically not necessary for diagnostic purposes. Some transcatheter closure device protocols include angiography, typically performed in the right pulmonary vein or levophase from a main pulmonary artery injection in the left anterior oblique and cranial projections. This may be an important way to confirm the absence of additional defects, such as partial anomalous pulmonary venous drainage, before proceeding with transcatheter device closure.

C. **Cardiac MRI** can be helpful, as it can provide additional information beyond echocardiography. MRI provides an excellent assessment of RV size and function, especially if views obtained with echocardiography are not diagnostic. MRI is also excellent at determining the location of the pulmonary veins as well as calculating ventricular volumes and shunt fraction.

VI. TREATMENT.

Medical intervention is typically not required preoperatively because many patients are asymptomatic. Congestive symptoms may be improved with standard diuretic therapy. Rhythm disturbances such as atrial fibrillation require attention with respect to rate control and anticoagulation. Endocarditis antibiotic prophylaxis during dental procedures is not required in the setting of an isolated ASD before surgery, but it is warranted for 6 months after surgical or device closure (American Heart Association/American College of Cardiology class IIa).

FIGURE 28.2 Catheterization data derived from two studies of the same female patient. The data obtained at age 13 (**A**) were interpreted as compatible with a small atrial septal defect of insufficient size to require closure. Some years later, she had developed pulmonary vascular obstructive disease (**B**) and was no longer shunting enough to recommend surgery. Death occurred 5 years later. AO, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; numeric values within the schematic, oxygen saturation (%); numeric values outside the schematic, pressure (mm Hg). (Adapted from Fyler DC, ed. *Nadas Pediatric Cardiology*. Philadelphia, PA: Hanley & Belfus; 1992. Copyright © 1992 Elsevier. With permission.)

A. **Surgical or transcatheter therapy.** The mainstay of therapy is closure of the defect by surgical or transcatheter techniques. Because of the reduced life expectancy associated with an unrepaired ASD, closure is recommended at diagnosis if there is evidence of a hemodynamically significant shunt ($Q_p/Q_s \geq 1.5:1$), evidence of right heart dilation, and evidence of probable paradoxical embolism or associated symptoms. In the setting of pulmonary hypertension, pulmonary reactivity to vasodilators should be documented and a net left-to-right shunt demonstrated during catheterization before consideration for closure. Alternatively, the defect can be temporarily balloon occluded at the time of catheterization, and the hemodynamic effects are directly measured. Situations in which ASD closure should not be pursued are listed in Table 28.1 and include advanced pulmonary hypertension (Eisenmenger syndrome) and severe LV dysfunction with elevated LA pressure.

B. **Primary surgical closure** has been the standard approach for many years. Generally, surgical closure is the treatment of choice for ostium primum, sinus venosus, and coronary sinus defects. Patients with secundum ASDs and anatomy that is not amenable to

percutaneous closure (ASD diameter > 35 mm; inadequate septal rims to permit device deployment; or close proximity to AV valves, coronary sinus, or venae cavae) are also candidates for open surgical closure. Depending on the defect size and location, the secundum ASD can be closed by primary suture or, if needed, by the use of an autologous pericardial or synthetic patch. Ostium primum defects require patch closure as well as repair of the likely cleft mitral valve. Repair of sinus venosus defects is technically more challenging, as the pulmonary veins often have anomalous drainage and require rerouting.

1. Important preoperative risk factors include older age at operation, presence of atrial fibrillation, and elevated pulmonary pressure and resistance.
2. Postoperatively, patients are at risk for heart block, which is a significant complication in these cases. They are also at risk for postpericardiotomy syndrome, more so than after other surgery for congenital defects. Atrial arrhythmias may persist in short- and long-term follow-ups because the RA and RV sizes may take time to return to normal, so anticoagulation is often recommended for several months after surgery. In some centers, prophylactic β-adrenergic blockade is advocated empirically for 3 to 6 months after surgery.

C. **Transcatheter closure** of a secundum ASD has become an attractive alternative to surgical closure and is now considered the treatment of choice. Any patient with an isolated secundum ASD may be suitable for transcatheter closure, which is generally assisted with TEE or intracardiac echocardiography in addition to fluoroscopy. Catheter closure decreases hospital length of stay, avoids surgical wounds and their possible complications, and significantly speeds up postprocedure recovery. With the devices available today, defects with a resting diameter of <35 mm may be considered. In general, the gently stretched diameter of the defect is approximately 6 to 8 mm greater than the resting diameter. The defect must be located centrally with adequate room for the device to be positioned, without interference of other intracardiac structures such as the AV valves, coronary sinus, or pulmonary veins. The U.S. Food & Drug Administration (FDA) has approved three devices for the closure of secundum ASDs: the Amplatzer Septal Occluder (AGA Medical Corporation, Golden Valley, MN) approved in December 2001; the Helex Septal Occluder (WL Gore & Associates, Flagstaff, AZ) approved in August 2006; and the CardioSEAL Septal Occlusion System (NMT Medical, Boston, MA). Studies have proved the safety and efficacy of catheter-based closure of a secundum ASD compared with surgical closure. The Amplatzer device consists of two disks made of Nitinol wire mesh filled with polyester fabric and separated by a narrower waist, which is appropriately fitted by balloon sizing. It is inserted percutaneously through a 6F to 12F sheath, depending on the device size required. The Helex device is also disk-like and consists of expanded polytetrafluoroethylene patch material supported by a single Nitinol wire frame. Major complications, such as cardiac perforation or device embolization, occur very rarely (generally fewer than 1% of cases), and successful closure of the defect is achieved in up to 95% of all patients. After closure, antiplatelet therapy, frequently aspirin and clopidogrel, is prescribed for a minimum of 6 months, after which time the device is generally believed to be endothelialized.

TABLE 28.1 Conditions Where ASD Closure Is Not Favored

Defect is too small to be hemodynamically significant

TABLE 28.1 Conditions Where ASD Closure Is Not Favored

Pulmonary hypertension is too advanced
Severe LV dysfunction, where ASD is acting as a "pop-off" valve for the left ventricle
In most cases where ASD is diagnosed in pregnancy, closure can be postponed until 6 mo after de

ASD, atrial septal defect; LV, left ventricular.

VII. PROGNOSIS. Hemodynamically significant ASDs are associated with increased morbidity and mortality. Long-term outcomes can be improved by closing these defects, especially if performed early in life. Atrial arrhythmias are common, especially in older patients, and are the result of long-standing atrial stretch. Arrhythmias, particularly atrial flutter and fibrillation, contribute to a significant portion of the morbidity and mortality of older patients, particularly the risk of systemic embolization and the resultant stroke. It has been demonstrated that age at the time of surgical repair is inversely related to the risk of subsequent atrial fibrillation or flutter after repair and argues for earlier closure. Some have advocated for consideration of a concomitant ablation procedure in high-risk patients, but the available data do not generally support this.

The functional capacity of patients frequently improves after closure of the ASD, and often they do not realize how severely their functional capacity had been affected until after the defect is closed. In addition, improvements in LV filling and systemic cardiac output are seen rapidly after defect closure. Reduced RA and RV volumes can be seen within 24 hours and continue to improve over the course of the first year following closure.

PFO AND ATRIAL SEPTAL ANEURYSM

I. PATHOPHYSIOLOGY. PFO can result in transient right-to-left shunting of blood flow, usually when RA pressure exceeds LA pressure such as during coughing or straining. These defects generally do not cause significant hemodynamic derangements. The clinical importance of an atrial septal aneurysm or a PFO is its impact on the risk of stroke. PFO features that increase the risk of a paradoxical embolus include large tunnel lengths (≥4 mm), high mobility of the valve of the foramen ovale, a well-formed eustachian valve, and a resting right-to-left shunt.

II. CLINICAL MANIFESTATIONS. Generally these defects are asymptomatic, most often coming to attention in patients with cryptogenic (unexplained) stroke. PFO is more common in patients with cryptogenic stroke than in the general population, but PFO alone has not been shown to be an independent risk factor for cryptogenic stroke. There are now accumulating data to suggest that an isolated PFO is not associated with an increased risk of recurrent ischemic stroke. The data in patients with both a PFO and an ASD are conflicting but suggest increased risk of recurrent stroke when both lesions are present. PFO should be suspected in young patients who sustain a stroke, as more than one-half of stroke patients younger than 45 years have a PFO. Other less common clinical associations with PFO include migraine headaches, platypnea–orthodeoxia syndrome, and decompression illness in divers and those who work in high altitudes.

III. DIAGNOSTIC STUDIES. **Echocardiography** can easily differentiate between an ASD and a PFO if the interatrial septum is well visualized. If this is not possible via a transthoracic approach, a TEE may be necessary. A simple way to determine if a shunt is present is the "**bubble study**," which is the injection of agitated saline via an upper extremity vein. If shunting is not present at rest, the patient can perform a Valsalva maneuver, which augments right-to-left shunt. If bubbles can be seen in the left atrium or the left ventricle within **three** cardiac cycles on TTE, the diagnosis of an interatrial right-to-left shunt is established. Generally, administration of agitated saline in patients with suspected right-to-left shunts is considered safe, but there have been rare case reports of cerebral ischemic events from passage of bubbles into the systemic circulation.

TEE will likely be required in most adults for better visualization of the interatrial septum. TEE helps to differentiate between a PFO and a secundum ASD, both of which can have positive bubble studies. TEE also allows assessment of other potential sources of emboli such as atheroma in the aortic arch, thrombus in the LA appendage, or cardiac tumors.

IV. TREATMENT. Unfortunately, there is no clear consensus on primary or secondary prevention measures for patients found to have a PFO or atrial septal aneurysm. In general, atrial septal abnormalities are not treated for primary prevention of stroke. Regarding secondary prevention, most patients with neurologic events are treated with antiplatelet agents (either aspirin or a thienopyridine, or both), anticoagulants (warfarin), and percutaneous or surgical closure, although no clear consensus exists. Several randomized controlled studies have failed to demonstrate a benefit of closure over medical therapy by intention-to-treat analysis. The CLOSURE I trial examined the role of PFO closure for first time stroke/TIA and found no difference in the composite primary end point of stroke or TIA at 2 years, all-cause 30-day mortality, and neurologic mortality between 31 days and 2 years, with closure compared with aspirin, warfarin, or both. The PC-Trial examined the role of PFO closure for secondary prevention of cryptogenic embolism and found no difference in the composite primary end point of death, nonfatal stroke, TIA, or peripheral embolism with closure compared with standard medical therapy. A third randomized trial, RESPECT, was included in a meta-analysis with CLOSURE I and PC-Trial and found that closure did not offer a significant benefit by intention-to-treat analysis over medical therapy in preventing recurrent strokes. There were several significant limitations to these trials (short duration of follow-up, low event rates, attrition bias) that preclude definitive conclusions regarding the merits of closure. Recently, the CLOSE trial has reported that recurrent stroke was less common in patients with cryptogenic and PFO with large interatrial shunt who were randomized to PFO closure compared with those receiving antiplatelet therapy. Follow-up period was greater than 5 years and atrial fibrillation occurred more frequently in the PFO closure group. Additionally, the RESPECT study reported a significant reduction in recurrent stroke in the PFO closure group when the follow-up period was extended past 5 years. Finally, the Gore REDUCE trial has also reported that PFO closure with the addition of antithrombotic therapy was superior in preventing recurrent stroke in the cryptogenic stroke population compared with antithrombotic therapy alone but as in the CLOSE trial, atrial fibrillation was commoner in follow-up with PFO closure. Patient selection for device closure is critical as is excluding other potential sources of stroke. It is still unclear

whether PFO closure is superior to anticoagulation with warfarin or newer anticoagulant agents. Device closure is mainly performed in patients with recurrent cryptogenic stroke despite aggressive medical therapy. The same devices utilized for ASD closure are generally used to percutaneously close PFO. Contraindications to percutaneous closure are noted in Table 28.2.

Primary surgical closure of PFO is generally not pursued, unless the patient needs concomitant surgery for other conditions. Indiscriminant repair of PFO incidentally found at surgery may actually increase short-term stroke risk and should therefore be avoided.

There is a dearth of data to support PFO closure in patients with migraine headaches. The Migraine Intervention with STARFlex Technology trial randomized 147 participants with severe migraine headaches and right-to-left shunt consistent with PFO to either percutaneous closure or sham procedure. After 6 months, there was no statistically significant difference in the primary end point of complete cessation of migraine headache or in a host of secondary end points including change in severity, quality, and frequency of headache as well as quality of life. As such, device closure should only be performed in migraine patients who are part of a randomized clinical study.

TABLE 28.2 Contraindications to Percutaneous PFO Closure

Presence of an alternative source of emboli
Severe pulmonary hypertension
Recent gastrointestinal bleeding
Presence of congenital heart defect that needs surgical repair
Documented hypercoagulable state
Hypersensitivity or contraindication to antiplatelet or anticoagulant therapy
Unexplained fever or infection

Patients with platypnea–orthodeoxia syndrome (acute arterial desaturation with change in position from supine to upright) should be considered for closure, because oxygen saturation generally improves with successful elimination of the right-to-left shunt.

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CHAPTER 29

Ventricular Septal Defect

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David Majdalany

I.INTRODUCTION

A. Ventricular septal defect (VSD) is one of the most common congenital heart defects in both children and adults. The prevalence in neonates has been reported to be as high as 5% when screened with color Doppler echocardiography, although most of these are miniscule defects that close spontaneously within the first year. Thus the true prevalence is difficult to ascertain, given that many defects close spontaneously and patients are frequently asymptomatic with smaller lesions. VSDs are frequently associated with other congenital defects, particularly infundibular stenosis or valvar pulmonary stenosis. Isolated VSDs account for about 20% to 25% of all congenital heart defects in childhood. Unlike many other congenital abnormalities, males and females appear to be affected equally.

B. Isolated VSDs are found in approximately 10% of adult patients with congenital heart disease. This reflects the natural tendency for spontaneous closure during infancy and an improved ability to confirm the diagnosis in childhood, which leads to surgical closure.

C. Natural history

1. Spontaneous closure occurs most commonly with smaller, restrictive VSDs, usually before the age of 2 years. In general, nearly 35% of perimembranous defects close spontaneously and 75% to 80% of all small VSDs close spontaneously by 10 years of age. These higher rates of spontaneous closure in more recent series are a reflection of the ability to diagnose much smaller defects with contemporary echocardiographic modalities. Large and nonrestrictive defects have significantly lower spontaneous closure rates (approximately 10% to 15%); malalignment defects rarely close spontaneously. Defects close by two mechanisms: (1) by muscular septum growth and (2) by "aneurysmal tissue" from a septal leaflet of the tricuspid valve as in the case of perimembranous defects. For VSDs that persist, a restrictive nature can protect the patient from pulmonary vascular injury given the flow-limiting nature of these defects.

2. Endocarditis is a risk because of the presence of a high-velocity, turbulent jet into the right ventricle. Endocarditis most frequently involves the septal leaflet of the tricuspid valve apparatus at the point of jet impact. The incidence of endocarditis varies widely in the literature, but ranges from 1% to 15%.

3. Muscular VSDs have a lower incidence of endocarditis, as the jet is attenuated prior to reaching the tricuspid valve. Risk factors include age >20, male sex, and those with unrepaired VSDs (when there is an indication for repair). Although there is an

increased risk of endocarditis in the presence of a VSD, the American College of Cardiology and the American Heart Association (AHA) do not recommend antibiotic prophylaxis in the acyanotic patient with an uncomplicated VSD and no prior history of endocarditis.

4. A large VSD during childhood is typically associated with significant **left-to-right shunt** and eventual development of congestive heart failure. Children with very large defects usually present during infancy or early childhood with signs and symptoms of heart failure and pulmonary hypertension. Patients with moderate-sized VSDs can survive to adulthood before detection. Given the gradual development of symptoms in these patients, they may not present until late in the disease course. In these patients, the excess right-sided flow may lead to pulmonary vascular disease and Eisenmenger physiology if left untreated. As pulmonary vascular resistance increases, the left-to-right shunt changes to a right-to-left flow. The VSD murmur disappears during this transition and is often replaced by the murmur of tricuspid and pulmonic regurgitation. After Eisenmenger physiology has developed, patient survival beyond the fourth decade becomes highly variable, but with close medical follow-up and attention to special risks (i.e., general anesthesia, pregnancy), patients may live much longer and into their seventh decade. Complications in patients with Eisenmenger syndrome include pulmonary hemorrhage, endocarditis, cerebral abscess, arrhythmias, thromboembolism, renal insufficiency, and the complications associated with erythrocytosis. Poor prognostic factors in this population include syncope, congestive failure, and hemoptysis.

5. Risk factors for decreased survival include cardiomegaly seen on the chest radiograph; elevated pulmonary artery systolic pressure (>50 mm Hg and/or more than one-half of the systemic pressure); cardiovascular symptoms such as shortness of breath, fatigue, or dyspnea on exertion; and progressive aortic insufficiency. Good prognostic factors include normal left ventricular (LV) size and function, small left-to-right shunt, normal pulmonary pressures or resistance, an intact vasodilator response in the pulmonary vasculature, and lack of symptoms.

6. Genetic factors play a significant role in this disease, as in other forms of congenital heart disease. Having an affected father increases the risk of VSD in the offspring to 2%; moreover, an affected mother appears to confer an even higher risk of recurrence in offspring—as high as 6% to 10%. In general, VSDs arise because of a combination of polygenic, multifactorial abnormalities. However, several monogenetic abnormalities leading to VSDs such as mutations in the transcription factors TBX5 and GATA4 have been described, and approximately 5% of patients have chromosomal abnormalities including trisomy 21, 18, and 13.

II.ANATOMY

A. Embryology. Partitioning of the ventricular mass begins as a muscular ridge in the floor of the ventricle near the apex. This ridge later undergoes active growth, which forms the muscular ventricular septum. Concomitantly, the endocardial cushions fuse and the two regions meet, completing closure of the interventricular foramen. Figure 29.1 shows anatomic localization of VSDs.

B. Defect size. The consequences of a VSD depend on the size of the defect and the pulmonary and systemic vascular resistances. Smaller defects provide higher resistance to flow and will have little impact on right-sided flow. **The VSD is** described as **small** when the defect size is **less than one-third of the size of the aortic root, moderate** when the defect size is **less than one-half of the size of the aortic root,** and **large** when the defect

size is equal to or **larger than the size of the aortic root.** However, other indirect measures, including clinical signs and symptoms and echocardiographic features, must be taken into consideration when determining the size and clinical significance of a VSD. VSD size is often classified on the basis of its hemodynamic consequences:

FIGURE 29.1 Anatomic localization of ventricular septal defects.

1. **Restrictive** VSDs result in a significant pressure gradient between the left and right ventricles (e.g., pulmonary/aortic systolic pressure ratio <0.3) and are associated with a small shunt ($Q_p/Q_s \leq 1.4:1$).
2. **Moderately restrictive** VSDs produce an intermediate interventricular gradient and result in a moderate shunt ($Q_p/Q_s = 1.4$ to 2.2:1).
3. **Nonrestrictive** VSDs are usually larger than 1 cm^2 and are associated with a large shunt ($Q_p/Q_s > 2.2:1$). The pressures in the left ventricle and right ventricle will eventually approach equalization, and the amount of flow across the defect will be determined by the ratio of pulmonary-to-systemic vascular resistance.

C. VSD types

1. **Membranous** defects are the most common type, accounting for approximately **70% to 80% of VSDs**. The membranous septum is the area under the aortic valve on the left side and next to the septal leaflet of the tricuspid valve on the right side. Most of these defects extend into the infundibular region and are then referred to as perimembranous. **Membranous defects** are less likely to be associated with additional intracardiac defects and **have a high rate of spontaneous closure**. However, when there is malalignment of the defect, spontaneous closure is unlikely.
2. **Muscular** defects account for approximately 5% to 20% of VSDs and can be single or multiple (i.e., Swiss cheese septum). These defects, when single, also have a high spontaneous closure rate.
3. **Inlet or atrioventricular (AV) canal–type** defects account for approximately 5% to 8% of cases. These defects rarely close spontaneously, are usually large, and are associated with abnormalities of the AV valves. These abnormalities range from cleft mitral and tricuspid valves to the common AV valve, as seen in complete AV canal defect. This type of defect in the inlet ventricular septum is commonly seen in patients with Down syndrome (trisomy 21).
4. **Supracristal or subaortic** defects account for approximately 5% to 7% of cases and are located immediately beneath the pulmonary and aortic valves. These defects vary in size but are often small. Because of their **proximity to the aortic valve, aortic leaflet tissue can prolapse through the defect resulting in aortic regurgitation**.

D. Associated lesions. Approximately 20% of VSDs are associated with many other forms of congenital heart disease, including aortic coarctation, bicuspid aortic valve, and patent ductus arteriosus. Of patients who present with a VSD, 5% to 10% will develop aortic regurgitation because of poor support of the right coronary cusp and the Venturi effect caused by the VSD jet, resulting in prolapse of one of the aortic valve leaflets. Discrete, fibrous subaortic stenosis and right ventricular (RV) outflow tract obstruction are less common associations. Less than 10% develop subvalvular pulmonary stenosis or an obstructive muscle bundle referred to as a double-chamber right ventricle. VSD, in addition

to the genetic abnormalities mentioned, is also associated with transposition of the great arteries and tetralogy of Fallot.

III. CLINICAL PRESENTATION. Adult presentation occurs most frequently in small, restrictive VSDs and occasionally occurs in patients with moderate lesions and associated pulmonary hypertension or with Eisenmenger syndrome in large, unoperated lesions.

A. Symptoms. The most common symptoms in adult patients with hemodynamically significant VSD are dyspnea on exertion and exercise intolerance. The symptoms are related to the degree and chronicity of left-to-right shunt and the resultant increase in pulmonary pressure and resistance.

B. Physical findings. The auscultatory findings classically include a holosystolic murmur of varying intensity. Smaller muscular defects may produce a high-frequency early systolic murmur that ends before the second heart sound (S_2) because of closure from muscular contraction of the septum. The pitch of the murmur can be a clue to the size and nature of the defect. Smaller and more restrictive defects produce higher pitched and louder murmurs that may be associated with a palpable thrill. Another important feature is the intensity of the pulmonary component of S_2, which if increased suggests increased pulmonary pressure. An RV heave may be appreciated in patients with RV volume overload. A diastolic flow rumble at the apex may be heard in large left-to-right shunts because of increased flow across an otherwise normal mitral valve. Depending on associated lesions, other findings may be present such as a diastolic murmur of aortic insufficiency that may occur with subaortic defects. A prominent systolic ejection murmur at the left upper sternal border suggests subvalvular pulmonic stenosis or double-chamber right ventricle. As pulmonary hypertension and right-to-left shunting develop, other signs including cyanosis, elevated jugular venous pressure, enlarged and pulsatile liver, clubbing, and a decrease in murmur intensity may occur. A systolic murmur in this setting often reflects concomitant tricuspid insufficiency. Notably, the murmur of a large VSD is often less harsh and more blowing in nature than that of a small VSD because of the absence of a significant pressure gradient across the larger defect which results in less turbulent flow.

C. The **differential diagnosis** on examination includes tricuspid or mitral regurgitation, acyanotic tetralogy of Fallot with a pulmonary outflow murmur, isolated subvalvular pulmonic stenosis, and hypertrophic cardiomyopathy.

IV. LABORATORY TESTS

A. The **electrocardiogram (ECG)** may be unremarkable with small defects or reveal left atrial and LV enlargement in patients with larger defects. An inlet or AV canal defect can be diagnosed from the ECG based on the presence of marked left-axis deviation. Right-axis deviation suggests elevated RV and pulmonary artery pressure. After surgical repair, right bundle branch block may occur.

B. A **chest radiograph** is often helpful in determining the degree of left-to-right shunt. A small-sized or normal-sized heart with normal pulmonary vascular markings on the chest radiograph suggests a hemodynamically insignificant lesion, whereas cardiomegaly and left atrial and LV enlargement are seen with large left-to-right shunts. A large defect associated with a small heart and oligemic lung fields should raise the suspicion of pulmonary vascular disease.

V. DIAGNOSTIC TESTING

A. **Echocardiography** is the diagnostic modality of choice for VSDs and associated lesions. Transthoracic echocardiographic imaging is almost always sufficient in the child and young adult, but transesophageal echocardiographic imaging may be required in some older adult patients. Defect size and location should be defined using two-dimensional and color Doppler techniques. Complete scans of the ventricular septum from multiple acoustic windows should be made to rule out additional defects. Optimal images are usually obtained from the parasternal long-and short-axis views and the apical four-chamber view; other views may fail to visualize the VSD jet, owing to perpendicular alignment of the echocardiographic probe and the jet. In the younger patient, subcostal coronal and sagittal views may also be helpful. Measurements of left atrial and LV size are key to determining the amount of volume load and magnitude of the left-to-right shunt. Echocardiographic features of pulmonary hypertension are helpful in confirming the impending reversal of shunt. Quantification of shunt velocity provides an estimate of the restrictive nature of the defect. Higher velocities indicate a more restrictive defect, reducing the likelihood that the patient has experienced pulmonary vascular insult. Systemic blood pressure should be noted when the velocity across the VSD is measured. Assuming no LV outflow obstruction, RV pressure can then be estimated based on the gradient across the VSD. This pressure can also be estimated if tricuspid insufficiency exists. A **perimembranous VSD** can be associated with a **ventricular septal aneurysm formed by the septal leaflet of the tricuspid valve bowing into the defect**. Similarly, supracristal VSDs are associated with aortic insufficiency caused by prolapse of the right or left coronary cusps into the VSD. A complete evaluation is always indicated to exclude other associated findings such as aortic coarctation, atrial septal defect, patent ductus arteriosus, and RV or LV outflow tract obstruction.

B. **Catheterization** is seldom needed in the management of isolated VSD in the infant or child. Surgical correction, when indicated, proceeds in most cases based on echocardiographic evaluation. In the adult, catheterization should be considered if anatomic questions remain despite transthoracic and transesophageal echocardiography or if pulmonary hypertension is suspected based on these studies. Hemodynamic assessment should include quantification of cardiac index and careful oximetric definition of the shunt level and quantity. A step-up in saturation measured at the pulmonary artery level confirms persistent left-to-right shunt across the defect and should correlate with acceptable pulmonary artery pressures and resistance. Evidence of low pulmonary artery saturations is expected with elevations in pulmonary resistance. Simultaneous comparison of RV pressure with systemic pressure is mandatory in these cases, along with the documentation of changes in response to oxygen or nitric oxide administration. Left ventriculography performed with **left anterior–oblique and cranial angulation** demonstrates the defect in most cases. If an inlet-type defect is present, the hepatoclavicular view (about 40° left anterior–oblique and 40° cranial) is usually adequate. Right ventriculography does not adequately opacify the left ventricle unless there is suprasystemic RV pressure. Coronary angiography should be performed when patients are felt to be at risk for coronary artery disease and likely to require operative intervention. Aortography can be helpful in eliminating the possibility of an associated ductus arteriosus or coarctation of the aorta.

C. Cardiac **computed tomography** (CT) can be used to assess VSD anatomy in patients with suboptimal echocardiographic images, but unlike magnetic resonance imaging

(MRI), CT does not provide added information about shunt fraction and carries additional risk associated with radiation and intravenous contrast administration.

D. **MRI**, using spin–echo and velocity-encoded cine sequences, can also be used to delineate VSD location and shunt fraction. MRI is particularly helpful in patients with associated complex lesions and those with inadequate echocardiographic images.

VI. THERAPY.

Factors supporting intervention include cardiomegaly on the chest radiograph, significant left-to-right shunt (pulmonary-to-systemic flow ratios >1.5:1), elevated but responsive pulmonary vascular resistance, symptoms of congestive failure or associated lesions such as aortic insufficiency, RV or LV outflow tract obstruction, and recurrent endocarditis. Management of VSD after myocardial infarction is discussed separately in Chapter 3.

A. **Medical management** in symptomatic cases without Eisenmenger physiology involves anticongestive measures such as the use of diuretics and digoxin. Efforts should then be focused on addressing suitability for surgical closure. Endocarditis is a recognized complication of VSD. In the patient with culture-proven endocarditis, 4 to 6 weeks of antibiotics should be administered parenterally before consideration of intervention. This must be tailored to the individual patient's clinical status and the infective organism's identification and sensitivity as well as the presence of concomitant valvular lesions and prosthetic material. For patients who have developed elevated pulmonary vascular resistance, selective pulmonary vasodilators, including phosphodiesterase-5 inhibitors, prostacyclin analogs, and endothelin receptor antagonists, may improve hemodynamics and exercise tolerance.

B. **Transcatheter device closure** of VSDs is being performed on an investigational or compassionate-use basis in selected medical centers. The Amplatzer Muscular VSD Occluder is U.S. Food & Drug Administration approved and can technically close many muscular defects. Perimembranous defects, however, pose particular problems for transcatheter closure, given their close proximity to the conduction system and the AV and semilunar valves, although recent data from the investigational Amplatzer Membranous VSD Occluder are promising. Although long-term data from these devices are lacking, recent studies show that the rate of complete closure for the Amplatzer membranous device at 6 months is 96% and is 100% for the muscular occluder at 3 to 96 months follow-up. Complications with these devices include early or late-onset complete heart block, arrhythmia, tricuspid valve damage resulting in stenosis or regurgitation, and mechanical device failure during deployment. Transcatheter closure of VSDs after ventricular septal rupture in the setting of myocardial infarction has also been performed in selected individuals who are considered high-risk surgical candidates. Surgery, however, is still the preferred treatment modality in this setting.

C. **Surgical closure** continues to be the primary means of defect repair. Outcomes after VSD closure are good in children, with low mortality rates of 2% to 3%. Repair of VSDs in patients with evidence of increased pulmonary artery pressure is generally performed before the age of 2 years and, in many centers, in the first year of life. Surgical closure in the symptomatic adult appears to be well tolerated, with acceptable mortality and improved functional status. Irreversible pulmonary vascular disease with Eisenmenger physiology, however, is a general contraindication for surgical closure because right heart failure will often develop thereafter. Pulmonary artery banding (performed to limit

pulmonary blood flow) was more frequently done in the past and is now reserved for the few patients who are very small, who have lung disease, or who have complex, multiple VSDs. Postoperative sequelae include residual patch leaks, as well as supraventricular and ventricular arrhythmias. More recent studies have shown the presence of a residual shunt following surgical closure in 5% to 31% of patients depending on the type of VSD that was repaired. Recent data suggest that postsurgical residual VSDs <2 mm close spontaneously within 1 year in the majority (83%) of patients.

D. In children for whom transcatheter and surgical approaches are technically difficult or particularly high risk, a **hybrid approach** has been explored. In these patients, a sternotomy is performed, and the device is placed through the anterior wall of the right ventricle under fluoroscopic and echocardiographic guidance.

E. According to the AHA guidelines, **antibiotic prophylaxis** is recommended in three situations in relation to congenital heart disease: (1) unrepaired cyanotic defect (i.e., VSD with right-to-left shunt), (2) repaired defect (i.e., VSD) with prosthetic material/device for the first 6 months, and (3) repaired defect (i.e., VSD) with residual defect at the site of a prosthetic patch/device. In addition, excellent oral hygiene and regular dental examinations are an important component in reducing the risk of developing infective endocarditis.

F. **Eisenmenger syndrome** is usually referred to in the context of ***irreversible pulmonary hypertension from long-standing exposure of the pulmonary vasculature to left-to-right shunting*** across a VSD. However, this physiology can occur as a result of any left-to-right shunt, including patent ductus arteriosus and, less commonly, isolated atrial septal defect. As a result of the elevated pulmonary pressures, the direction of shunting is reversed across the defect, producing systemic cyanosis and its associated complications. As described above, newer agents aimed at decreasing resistance in the pulmonary vasculature may be beneficial in these patients. **Pregnancy is poorly tolerated and is contraindicated in the presence of Eisenmenger syndrome.**

G. Long-term follow-up is required in patients whose VSDs were repaired later in life, because the majority of patients already have some degree of pulmonary hypertension, LV dysfunction, or both. Patients with residual shunt after repair, arrhythmias, or conduction blocks also require continued follow-up.

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CHAPTER 30

Patent Ductus Arteriosus and Coarctation of the Aorta

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I. PATENT DUCTUS ARTERIOSUS—INTRODUCTION

A. The ductus arteriosus is fully developed by 6 weeks of gestation and connects the main pulmonary trunk with the descending aorta at approximately 5 to 10 mm distal to the origin of the left subclavian artery. The purpose of the patent ductus arteriosus (PDA) is to efficiently carry partially oxygenated blood from the right ventricle to the descending aorta and back to the placenta for oxygenation. This process diverts blood flow away from the lungs which would constitute wasted circulation and thus reduces the total workload of the fetal ventricles. A PDA occurs when the ductus arteriosus fails to close and regress after birth to form the ligamentum arteriosum. It occurs in 1:2,000 live births, but it is relatively uncommon among the adult population. In infants, it accounts for 10% to 12% of all congenital heart disease.

B. **Natural history.** The natural history depends on the size of the PDA, the direction of the shunt, and the development of any associated complications. At birth, 95% of patients with isolated PDA have left-to-right shunts and normal, or near-normal, pulmonary pressures. Patients with normal pulmonary artery pressures and no evidence of chronic left ventricular volume overload have a better prognosis. With a PDA, **congestive heart failure (CHF) can occur** because of chronic left heart volume overload because of excess dumping of arterial circulation back into the pulmonary circuit and subsequently the left chambers of the heart. In patients with death related to PDA, CHF is the most common cause. Development of right-to-left shunting is also an ominous sign because it reflects the development of advanced pulmonary vascular disease and associated elevation in right-sided cardiac pressures.

C. **Risk factors.** Factors that **increase risk for PDA** include **maternal rubella infection, birth at high altitude, premature birth, female sex, and genetic factors**. In infants born at <28 weeks of gestation, there is a 60% incidence of PDA, and PDAs are twice as common in females as they are in males. Most cases of PDA are seemingly sporadic, but it is likely a multifactorial inheritance with the requirement of genetic predisposition and an environmental trigger that is induced during a vulnerable period. In a family in which one child has a PDA, there is approximately a 3% risk of having a PDA in subsequent offspring.

II. ANATOMY AND PATHOPHYSIOLOGY

A. Embryology. The ductus arteriosus is a **normal and essential component** of cardiovascular development that originates from the distal sixth left aortic arch. A PDA is most commonly funnel shaped with the larger aortic end (ampulla) distal to the left subclavian artery, then narrowing toward the pulmonary end, with insertion at the junction of the main and left pulmonary arteries (Fig. 30.1). Closure usually begins at the pulmonary artery end which explains why the duct is most commonly conical toward the pulmonary artery entrance. With a right aortic arch, the ductus arteriosus more commonly connects the left innominate or subclavian artery with the left pulmonary artery or, alternatively, joins the right pulmonary artery and the aortic arch just distal to the right subclavian artery. Rarely, bilateral PDAs can also occur. On occasion, the insertion of the ductus is juxtaductal to the left subclavian artery. It varies in length and in the term fetus has a diameter of approximately 10 mm, similar to that of the descending aorta.

FIGURE 30.1 Patent ductus arteriosus. (From CCF Medical Arts—Courtesy of Joe Pangrace. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007–2018. All Rights Reserved.)

B. Fetal circulation. The presence of the ductus arteriosus in the fetal circulation is essential to allow **right-to-left shunting of nutrient-rich, oxygenated blood from the placenta to the fetal systemic circulation, thereby bypassing the fetal pulmonary circuit**. In the normal fetal circulation, oxygenated blood travels from the mother through the placenta to the fetus. The oxygen-rich blood traverses the fetal inferior vena cava, right atrium, right ventricle, and main pulmonary artery. The fetal pulmonary arteries are constricted and have high pulmonary vascular resistance. Oxygenated blood bypasses the fetal pulmonary circulation and enters through the ductus arteriosus to the lower resistance systemic circulation. Oxygenated blood then enters the fetal aorta distal to the left subclavian artery, perfuses the fetal systemic circulation, becomes deoxygenated, and returns to the maternal circulation. **The ductus arteriosus is kept open by low arterial oxygen content and prostaglandin E2 (PGE2). The fetus has high circulating concentrations of prostaglandins, particularly PGE2, owing to low fetal pulmonary blood flow and decreased prostaglandin catabolism in the lungs, as well as to the fact that the placenta produces prostaglandins.**

C. Birth. Several **changes occur at birth** to initiate normal functional **closure of the ductus arteriosus within the first 15 to 18 hours of life**. Spontaneous respirations result in increased blood oxygen content and decreased pulmonary vascular resistance, resulting in increased blood flow to the lungs. Prostaglandin levels decrease because of placental ligation and increased metabolism of prostaglandins within the pulmonary circulation by prostaglandin dehydrogenase. **The combination of increased oxygen content and lowered circulating prostaglandin levels usually results in closure of the ductus arteriosus.** Generally, the ductus arteriosus is hemodynamically insignificant within 15 hours and completely closed by 2 to 3 weeks. The **fibrotic remnant** of this structure persists in the adult as the **ligamentum arteriosum**. **Spontaneous closure of a PDA is unlikely in term infants after 3 months and in preterm infants after 12 months.**

III. CLINICAL PRESENTATION

A. Symptoms. Severity of symptoms depends on the degree of left-to-right shunting, which in turn is determined by three interrelated factors: the size of the PDA, the pressure difference between the aorta and pulmonary artery, and the systemic and pulmonary vascular resistances. PDA size is categorized by the degree of left-to-right shunting determined by the pulmonary-to-systemic flow ratio: Q_p:Q_s (Table 30.1). Between 25% and 40% of patients with PDA are asymptomatic, especially those with a small PDA. They are often diagnosed by auscultation of a continuous murmur on examination or incidentally during diagnostic testing. With larger PDAs, symptoms may develop. The **most common symptom is exercise intolerance** followed by dyspnea, peripheral edema, and palpitations. Increased volume shunted left to right through the PDA increases left ventricular output. By Frank–Starling law, the resultant increase in preload will lead to a greater stroke volume. The left ventricle must compensate by hypertrophy and eventual dilation leading to overt left heart failure. Given the excess volume load in the LA and LV, functional mitral regurgitation and/or pulmonary edema may occur. **PDA is more commonly associated with premature birth infants and/or respiratory distress** because of two reasons: (1) decreased metabolic function of the immature lungs resulting in increased circulating concentrations of PGE2 and (2) increased sensitivity of the ductus arteriosus smooth muscle to PGE2. It can be difficult to clinically separate which signs and symptoms are due to lung disease from those that are due to a "silent" ductus arteriosus. Deterioration in ventilatory status of an infant recovering from neonatal respiratory distress syndrome or failure to show improved respiratory status at an age when they should start to recover from the primary pulmonary disease can be a hint of clinically significant PDA.

B. Physical examination. Patients with PDAs may present with a wide range of physical findings. Pulse pressure may be wide because of diastolic runoff into the PDA, and peripheral pulses may be bounding. The jugular venous pressure is often normal with a small PDA, whereas with a large PDA, prominent *a*- and *v*-waves may be present. Precordial palpation often reveals a normal precordial impulse with a small PDA and a prominent left ventricular impulse with a large PDA. A **harsh, continuous murmur may be heard at the left first or second intercostal space**. The murmur envelops the second heart sound (S_2) and decreases in intensity during diastole. A small PDA has a soft, high-frequency, continuous murmur, whereas a large PDA classically has a machinery-like, loud murmur. With a large PDA, a mid-diastolic apical murmur may occur because of increased diastolic flow across the mitral valve. If **pulmonary hypertension** is present, a right ventricular lift may be present and the pulmonic component of S_2 will have increased intensity. The duration of the diastolic murmur reflects pulmonary artery pressures; elevated pulmonary artery pressures lead to a decreased gradient for left-to-right flow through the PDA during diastole, which results in a shorter diastolic murmur. As pulmonary pressure increases, the systolic component of the murmur shortens. Right-to-left flow may not generate a systolic murmur. For patients with a right-to-left shunt, a pathognomonic physical finding is **differential cyanosis of the lower extremities and left hand**.

TABLE 30.1 PDA Size by Q_p:Q_s

Q_p:Q_s	Size
<1.5	Small

TABLE 30.1 PDA Size by Q_p:Q_s	
1.5–2.2	Moderate
>2.2	Large

C. PDA, patent ductus arteriosus.

D. Complications. The most common complications of PDA include **CHF, infective endarteritis**, **PDA aneurysm,** and **pulmonary hypertension**. CHF occurs through volume overload of the left side of the heart and may be accompanied by **atrial fibrillation**. Vegetations generally develop on the pulmonary side of the PDA, and septic lung emboli may occur. Typical organisms include *Streptococcus viridans*and *Staphylococcus aureus*. Untreated PDAs with audible murmurs have a risk of infective endocarditis of 0.45% per year after the second decade. Spontaneously occurring **aneurysms of the ductus arteriosus** have been reported, although they are typically seen in association with endarteritis or among very young or very old patients. Pulmonary hypertension develops as a result of increased pulmonary vascular flow from a large PDA with significant left-to-right flow. Elevation in right-sided pressures may eventually result in Eisenmenger physiology, right-to-left flow, and isolated cyanosis and clubbing of lower extremities (occurring in 5% of unrepaired PDA patients) with signs of pulmonary hypertension.

E. Differential diagnosis. The differential diagnosis of PDA includes ventricular septal defect associated with aortic insufficiency, aortopulmonary window, pulmonary atresia with systemic collateral vessels, innocent venous hum, and arteriovenous communications such as pulmonary arteriovenous fistula, coronary artery fistula, systemic arteriovenous fistula, and ruptured sinus of Valsalva aneurysm.

IV. LABORATORY TESTING

A. Hematology. Blood laboratory results are generally unremarkable, although compensatory erythrocytosis may be present in the setting of long-standing cyanosis resulting from a right-to-left shunt.

B. Electrocardiogram (ECG). ECG is neither sensitive nor specific for PDA. The ECG for a patient with a small PDA is often normal. Depending on the duration and hemodynamic significance of the PDA, electrocardiographic criteria for left atrial enlargement or left ventricular hypertrophy may be present. If pulmonary hypertension exists, the ECG may demonstrate right ventricular hypertrophy or right atrial enlargement.

C. Chest radiography (CXR). CXR is neither sensitive nor specific for PDA. A normal chest radiograph implies a small, hemodynamically insignificant PDA. With a large PDA, left atrial and left ventricular enlargement may be present, as well as increased pulmonary vascularity. With right-to-left shunting from pulmonary hypertension, the main pulmonary artery is frequently enlarged. The PDA occasionally appears as a separate convexity between the aortic knob and the pulmonary trunk. Calcification of the PDA may be visualized in older individuals.

V. DIAGNOSTIC TESTING.

Standard two-dimensional transthoracic echocardiography (TTE) combined with Doppler is the preferred initial diagnostic modality because of its low cost and noninvasive nature. Transesophageal echocardiography (TEE) may be

required in subjects with suboptimal echocardiographic windows. Cardiac catheterization is typically reserved for therapeutic intervention.

A. **TTE** has a 42% sensitivity and 100% specificity for the diagnosis of PDA. The suprasternal notch view is usually best for demonstrating the PDA, particularly its aortic origin. The complete course of a PDA may be difficult to follow in some patients because of its tortuosity. Color Doppler imaging can often reveal flow between the descending aorta distal to the left subclavian artery and the pulmonary trunk. It is imperative to demonstrate color Doppler flow within the pulmonary artery, typically on a high parasternal short-axis view. Color Doppler and continuous wave Doppler help determine the direction of flow in the PDA. The timing of flow (systolic or diastolic) depends on pressure gradients between the systemic and pulmonary circulation. Quantitative assessment of shunt velocity is valuable to estimate the degree of restriction across the PDA. This measurement becomes important when planning transcatheter intervention. **Diastolic aortic flow reversal is seen in the descending aorta if the shunt is significant.** Associated left atrial and left ventricular enlargement also suggests a hemodynamically significant lesion.

B. **TEE** may be required if TTE windows are suboptimal or nondiagnostic. TTE and TEE have nearly 100% specificity for the diagnosis of PDA, but TEE has a much higher sensitivity (97%) than TTE (42%).

C. **Cardiac catheterization** is generally discouraged for diagnostic purposes. In the most recent American College of Cardiology/American Heart Association (ACC/AHA) 2008 guidelines, there is a class III recommendation against using cardiac catheterization to diagnose uncomplicated PDA with adequate noninvasive imaging. Rarely, PDAs that remain undiagnosed by physical examination or noninvasive testing may be diagnosed during left heart or right heart cardiac catheterization by recognizing the unexpected course of the catheter as it crosses the PDA by measuring a step-up in the oxygen saturation at the level of the left pulmonary artery or by documenting pulmonary opacification by descending aortography.

1. A PDA is best demonstrated by a **descending aortogram** performed in the **lateral projection** with a standard angiographic catheter positioned just below the ductal ampulla. If biplanar imaging is used, the right anterior–oblique cranial projection is sometimes helpful.

2. A PDA can be crossed from the main pulmonary artery or from the descending aorta, with the latter being easier and best guided by the lateral projection. Oximetric sampling typically demonstrates an increase in saturation in the main pulmonary artery compared with the right ventricle. Pulmonary artery and right ventricular pressures may be slightly elevated but typically remain below systemic levels. The presence of systemic pulmonary pressures generally indicates severe and advanced pulmonary vascular disease.

D. **Magnetic resonance imaging (MRI) and computed tomography** may be useful in defining the anatomy in patients with unusual PDA geometry and in patients with associated abnormalities of the aortic arch.

VI. THERAPY. Treatment differs depending on whether the individual is a preterm infant or not. Given the sensitivity of the PDA to prostaglandins in the premature infant, indomethacin (a prostaglandin synthesis inhibitor) can be administered to close the PDA. The use of oral, or preferably, intravenous indomethacin to constrict the PDA has led to successful nonsurgical closure in a large proportion of treated infants, with the best

results administered before 10 days of age in preterm infants. This medication is not effective in term infants or older individuals.

In the event that medical treatment is unsuccessful or not possible, surgical or catheter closure can be performed. ACC/AHA 2008 guidelines for adults with congenital heart disease recommend closure of PDA (catheter or surgical) if there is **left atrial or left ventricular enlargement or if pulmonary arterial hypertension (PAH) is present** with net left-to-right shunt (class I) or of an **asymptomatic small PDA by catheter device** (class IIa). PDA closure is **contraindicated** in patients with **PAH and right-to-left shunt**. Successful closure of PDA generally results in a good prognosis and may prevent adverse left ventricular remodeling resulting from volume overload.

The shape and size of a PDA determine the mode of therapy. Small- or moderate-caliber PDAs are generally closed percutaneously with coils. Large PDAs may require the Amplatzer Duct Occluder (ADO) or surgery. Heavily calcified PDAs represent a relative contraindication to surgical closure because of an increased risk of bleeding and incomplete closure with surgery. Cardiopulmonary bypass may be required for heavily calcified PDAs. PDAs with significant right-to-left shunts and Eisenmenger physiology should generally not be closed. In patients with pulmonary vascular resistance >8 U/m^2, lung biopsy has been recommended to determine candidacy for closure. However, even histologically severe pulmonary vascular disease may resolve after closure of the PDA. Reactivity of the pulmonary vascular bed to pulmonary vasodilating agents or significant reduction in pulmonary artery pressure during test occlusion may signal reversibility of pulmonary hypertension, but the absence of these findings does not rule out the possibility of reversibility in the long term, and natural history may be significantly altered by treating with pulmonary vasoactive medications.

A. Since the early 1990s, **transcatheter techniques** have become the **first-line therapy for most PDAs**. Many centers use single or multiple stainless steel coils to achieve complete closure. Numerous devices have been adapted or are under clinical investigation to allow transcatheter closure of larger defects. These procedures can often be performed on an outpatient basis, and complete closure rates at follow-up generally exceed 90% to 95% in most studies. The mortality rate is typically <1% at experienced centers. Success has been reported even when ductal calcification has been apparent, but large clinical series are lacking.

1. **Percutaneous coil occlusion.** Percutaneous coils were developed in 1992 and are the **preferred treatment for older children and adults with PDAs <3.5 mm in diameter**. Embolization coils have thrombogenic strands spanning the coils and are placed across the PDA to occlude flow. Advantages include low cost, small-caliber venous access, and easy implantation. Advances include detachable coils and development of a snare-assisted technique, both of which allow assessment and fine-tuning to ensure correct coil position before actual release of the coil. The coils are loaded at the tip of a catheter, the catheter is placed in the PDA under fluoroscopic guidance, and the coils are then deployed. Selected coil sizes are 2 to 2.5 times the narrowest diameter of the PDA. With moderate-sized or large-sized PDAs, multiple coils may be used. However, as PDA size becomes larger (>3.5 to 4.0 mm), percutaneous, 0.038-in. coils become a less desired closure option, and alternative therapies become preferred. Although complete closure is usually accomplished with a single coil in

children, multiple coils are frequently needed for complete closure in the adult. Although coil embolization may occur, the snare-assisted technique is almost always successful at percutaneous removal of the coil.

2. The **ADO**, a cone-shaped plug occluder made of thrombogenic wire mesh delivered with a 5F to 7F venous system, is the **preferred device for percutaneous closure of moderate to large PDAs**. The ADO stents the PDA, and blood is forced to flow through the center of the device, which is lined with thrombogenic wire mesh. The PDA then essentially clots off. Advantages include simple implantation, ability to retract the ADO into the sheath and redeploy if needed, and high success rates. There is an 89% occlusion rate on postprocedure day 1 and 97% to 100% complete occlusion after 1 month.

3. **Complications** of transcatheter closure are rare. The most common complication is embolization of the coil or device. Embolized coils can usually be retrieved; but even when this is impossible, adverse consequences are rare. Other potential complications include flow disturbance in the pulmonary artery or aorta from device protrusion, hemolysis from high-velocity residual shunting, vascular access complications, and infection.

B. Surgical closure. In 1938, the first successful closure of a PDA was performed, which, coincidentally, was the first repair of a congenital heart defect. Surgical closure is the most effective method for complete closure and is usually performed without cardiopulmonary bypass by double ligation and division of the PDA. In addition, it has been shown to be the most cost effective over time with fewer complications compared with transcatheter occlusion methods. Ligation may be performed without division, but there is a risk of recanalization of the PDA in up to 20% of cases. In neonates and premature infants, ligation without division is performed because of the small size of the structures. With continued advances in percutaneous closure devices, **surgery has become second-line therapy for most adults with PDAs**. If surgery is necessary, the procedure is >95% successful and has a low complication rate. The operative mortality rate is <1%. However, the thoracotomy approach can be painful for adults and necessitates inpatient recovery. Newer surgical techniques such as transaxillary thoracotomy and video-assisted thoracoscopic ligation have improved surgical morbidity.

C. Antibiotic prophylaxis. The most recent guidelines from the AHA recommend antibiotic prophylaxis for endarteritis only in the setting of transcutaneous closure of the PDA for 6 months after the procedure; and prophylaxis is not recommended for those with repaired PDA without residual shunt.

D. Follow-up. If immediate duct closure is demonstrated after the procedure, a 6-month follow-up with TTE should suffice to assess for residual flow through the PDA. If residual shunt exists after the procedure, TTE should be performed every 2 to 3 months and early repeat attempt of complete closure considered, depending on the size of the residual shunt or the presence of hemolysis. For long-term follow-up, annual transthoracic echocardiograms are adequate.

VII. COARCTATION OF THE AORTA.

Coarctation of the aorta (CoA) has been found at autopsy in approximately 1 in every 1,550 individuals. It accounts for 5% to 10% of congenital heart disease and occurs more frequently in whites (7:1) and males (2:1). The disorder is typically diagnosed in childhood but may go undetected well into adulthood. Most patients develop persistent systemic hypertension, often as children, and are at risk for premature coronary artery disease. Cases usually occur sporadically, but an

autosomal-dominant inheritance pattern has been observed. It is frequently associated with bicuspid aortic valve, and coarctation should be excluded in patients with bicuspid aortic valve and hypertension. Coarctation also occurs in 15% to 35% of patients with Turner syndrome. Potential catastrophic complications include aortic rupture or dissection and cerebral berry aneurysm rupture.

A. Anatomy. CoA usually consists of a **narrowing in the region of the ligamentum arteriosum**, the remnant of the ductus arteriosus, just distal to the origin of the left subclavian artery. Most coarctations, therefore, are juxtaductal. The exact anatomy, however, varies, and the coarctation may include a long segment, the transverse arch, or the abdominal aorta. Rarely, tortuosity of the arch is identified. The main anatomic substrate is a prominent posterior shelf of the aorta, composed predominantly of thickened media.

B. **Embryology.** The exact embryonic origin remains uncertain, but two main theories exist. The first suggests that the narrowing is caused by aberrant ductal tissue that constricts the aorta at the time of ductal closure. The second proposes that aortic hypoplasia develops as a consequence of reduced blood flow in utero.

C. **Associated cardiac defects** include **bicuspid aortic valve** in 50% to 85% of cases, valvular and subvalvular aortic stenoses, ventricular septal defects, PDA, and congenital malformations of the mitral valve (i.e., smaller orifice, supravalvular ring, and parachute mitral valve resulting from a single papillary muscle). Multiple left-sided heart lesions may be associated with CoA and are often referred to as the **Shone complex**.

D. **Associated extracardiac defects include intracranial aneurysms,** especially within the circle of Willis (3% to 5% of cases), hemangiomas, hypospadias, and ocular defects.

VIII.CLINICAL PRESENTATION

A. **Symptoms.** For patients with CoA who survive to adulthood, symptoms are usually negligible and nonspecific. Patients may complain of headaches, nosebleeds, cool extremities, leg weakness, or claudication with exertion. More serious manifestations include angina and heart failure.

B. **Physical examination**

1. A thorough cardiovascular examination may identify a systolic ejection murmur at the left upper sternal border that radiates to the intrascapular area located immediately anterior or posterior to the CoA. The murmur may be longer in systole and even continue into diastole, depending on the degree of obstruction. Increased flow through the collateral intercostal arteries can produce a continuous murmur appreciated diffusely over the precordium.

2. Upper extremity hypertension is often present, usually in conjunction with **diminished and delayed femoral pulsations**. CoA should always be considered in the differential diagnosis of refractory hypertension, especially in younger patients.

3. Funduscopic examination may demonstrate a “corkscrew” tortuosity of the retinal arterioles.

IX.DIAGNOSTIC TESTING

A. The **ECG** is frequently normal but may demonstrate manifestations of long-standing hypertension, such as left ventricular hypertrophy and left atrial enlargement.

B. **Chest radiography.** Cardiomegaly, dilated ascending aorta, and prominent pulmonary vasculature are common. **Rib notching** usually develops by 4 to 12 years of age

and is caused by enlarged intercostal collaterals. The **classic "3" or inverted-E sign is pathognomonic** for CoA and is created by a dilated left subclavian artery above the CoA and poststenotic dilation of the aorta below the CoA.

C. **Echocardiography** is most useful in infants and children. In adults, the suprasternal notch view is most helpful; color Doppler can be used to localize the site of turbulence. Continuous wave Doppler can assess the pressure gradient. If severe narrowing is present, persistence of flow in diastole (widening of the flow profile from systole into diastole) is seen by continuous wave Doppler in the aorta below the coarctation, such as in the abdominal aorta. This is a useful method to ascertain the presence of significant coarctation, even if imaging the direct site of the obstruction is impossible. A complete study should measure left ventricular size and ascending aortic size, determine aortic valve anatomy and function, and identify any potential associated congenital anomalies. TEE can also better define the anatomy if TTE proves inadequate.

D. **MRI** provides excellent anatomic and hemodynamic information (Fig. 30.2). MRI is increasingly utilized as a first-line investigation before catheterization, particularly in adults. This enables the precise anatomy to be delineated and helps in the decision making regarding surgery or catheterization as treatment options. Serial MRI scans may be used to follow results of therapeutic procedures. It is also useful in evaluating the intracranial vessels for associated berry aneurysms.

E. **Cardiac catheterization** provides excellent image data and pressure information and is often more reliable than echocardiography in adults. An **aortic angiogram** in left anterior–oblique or caudal and direct lateral projections usually best defines the lesion. Pressures should be obtained in the left ventricle and the ascending aorta, and the gradient across the lesion should be measured. A **pullback pressure of >20 mm Hg** signifies hemodynamic significance and usually warrants intervention if concomitant clinical factors allow. A **gradient of >50 mm Hg** generally mandates intervention. The presence of collateral vessels may falsely diminish the gradient.

X.THERAPY. Several factors need to be taken into account when deciding on optimal therapy for CoA, including the age of the patient, the anatomy of the coarctation, any prior CoA operations, and the local surgical expertise. Whatever mode of treatment is chosen, the presence of postprocedural upper extremity hypertension influences survival.

FIGURE 30.2 Magnetic resonance imaging of aorta showing coarctation in typical position in descending thoracic aorta.

A. In general, **medical therapy** for CoA has very limited utility, but it may be useful in a supportive role along with mechanical treatment. Hypertension should be medically treated, with the goal of controlling blood pressure and preventing end-organ damage.

B. **Percutaneous management**

1. **Percutaneous balloon angioplasty** is generally less effective than surgery for treatment of primary coarctation. Neonates and infants treated with angioplasty experience high rates of recurrent CoA (about 50% to 60%) and aneurysm formations (5% to 20%); therefore, surgical repair is preferred in this patient population. Likewise, balloon angioplasty of the unoperated coarctation in adults is controversial, with data suggesting higher rates of restenosis and aneurysm formation compared with surgical repair. Procedural complications can include acute aortic rupture (rare), aortic dissection, femoral artery trauma, recurrent

coarctation (8%), and aneurysm formation (8% to 35%). The suspected mechanism for late aneurysm formation is intimal tear at the site of cystic medial necrosis within the coarctation site. It should be noted that the clinical impact of aneurysm formation is unclear, as most defects are small and have a low risk of rupture. Percutaneous angioplasty, however, is the preferred therapy for recurrent postsurgical coarctation. The procedure is successful in reducing the gradient to <20 mm Hg in approximately 80% of interventions, with only a 1.5% incidence of late aneurysm formation.

2. **Stent implantation.** Theoretically, stent implantation may mitigate the development of aneurysm or dissection for a few reasons. By apposing the torn intima to the media and through dispersion of force, stenting may limit vascular trauma. It can also oppose the vascular recoil of the coarcted segment and avoid overdilation. By allowing the use of smaller balloons and graded inflations in staged procedures, stents may also reduce rates of aneurysm formation. Early and intermediate outcomes are promising, with a good safety and efficacy profile as well as lower rates of restenosis and aneurysm formation compared with balloon angioplasty. Despite the lack of long-term outcome data, stenting has become the preferred treatment modality in adults and adult-sized adolescents with native CoA. For recoarctation, balloon angioplasty with or without stenting is preferred in adults as well, as long as the anatomy is suitable.

C. **Surgery** remains the therapy of choice in neonates and infants. Three types of surgical repair have been used for correction of CoA: resection of the stenosed segment with end-to-end anastomosis, use of a subclavian flap, and patch aortoplasty. The approach with the best long-term outcome and sustained resolution of obstruction has been resection of the stenosed segment with end-to-end anastomosis. This approach carries with it the lowest risk of recurrent CoA (3%) and late aneurysm formation (rare). Paradoxical hypertension and bowel ischemia may occur in the postoperative period. Major surgical complications include paraplegia caused by perioperative spinal cord ischemia (0.4% to 1%), residual coarctation, aneurysm formation at the site of repair, and, rarely, death. Survival rates of >90% at 10 years and 84% at 20 years have been reported. Late deaths after surgical repair are related primarily to coronary artery disease, CHF, and aneurysm rupture. Young age favorably influences outcomes after surgery.

XI. FOLLOW-UP.

Lifelong follow-up is indicated after the diagnosis of CoA is established, especially after any type of mechanical repair. Key issues to be cognizant of include the progression of hypertension either at rest or with exercise, development of CoA recurrence, aneurysm formation, left ventricular dysfunction, and associated aortic valve dysfunction and aortopathy when bicuspid valve is present. In patients repaired at older ages, hypertension commonly persists despite treatment by percutaneous intervention or surgery. Serial echocardiography is an important component of follow-up. Advanced imaging modalities such as computed tomography or MRI are used increasingly post repair to screen for aortic wall complications, with a preference for MRI given the radiation and contrast issues. Therefore, these patients should be considered “treated” and not “cured” despite repair.

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CHAPTER 31

Complex Congenital Heart Disease

Baran Aksut
David Majdalany

I. TETRALOGY OF FALLOT (TOF). TOF is the most common form of cyanotic heart disease. It occurs in approximately 1 in 3,000 live births and accounts for 10% of congenital heart disease in infants. It is also the most common congenital heart disease condition requiring surgical correction in the first year of life. The earliest description of TOF dates back to the 17th century; however, Fallot is credited with describing the classic features of the disease in 1888. Surgical treatment for TOF did not become available until well into the 20th century, and it dramatically improved life expectancy. The **current reparative approach has shifted from palliative shunt procedures to primary surgical repair**, most recently with valve-sparing techniques and usually performed in infancy. Without surgical intervention, only about 10% of patients survive beyond the age of 20 years. Adults with TOF usually have undergone surgical repair or palliation. A wide and complex spectrum of TOF exists, including association with pulmonary atresia, absent pulmonary valve, and atrioventricular (AV) canal defects. Classic "simple" TOF is discussed here.

A. Anatomy

1. Anterocephalad deviation of the outlet septum results in four defining features:

a. *Right ventricular (RV) outflow tract obstruction*

b. *Nonrestrictive ventricular septal defect (VSD)*

c. *Aortic override of the ventricular septum* (>50% over the right ventricle)

d. *Right ventricular hypertrophy (RVH)*

2. Associated defects. Anomalous origin of the left anterior descending coronary artery from the right coronary artery (5%) or a prominent conal branch from the right coronary artery can occur. These vessels cross the RV outflow tract. This anatomic feature is important to surgeons because infundibular resection or future conduit placement may be needed in this location and can lead to inadvertent arterial damage. Right aortic arch occurs in 25% of cases. A secundum atrial septal defect (ASD) occurs in 15% of cases, completing the pentalogy of Fallot. Persistent left superior vena cava is found in 5% of patients. Among adult patients, aortic insufficiency can occur naturally from long-term dilation of the aortic root, after endocarditis or as a postoperative sequela. Rare complications include pulmonary hypertension, supravalvular mitral stenosis, and subaortic stenosis. There is an association

with deletion in the chromosome 22q11 region, which is also present in DiGeorge syndrome and/or velocardiofacial syndrome.

B. Clinical presentation

1. Patients who have not undergone surgical repair have variable clinical features, depending on the amount of RV outflow tract obstruction, degree of aortic override, and, to a lesser extent, systemic vascular resistance, all of which dictate the amount and direction of shunting across the VSD.

a. With severe RV outflow tract obstruction, patients have **central cyanosis** and **clubbing** by 6 months of age. Hypoxic "spells" may be seen and are characterized by tachypnea, dyspnea, cyanosis, or even loss of consciousness or death. If the obstruction is mild, however, the shunt through the VSD may be left-to-right, resulting in "pink tet" with minimal symptoms.

b. On physical examination, the patient is usually cyanotic and clubbed. A prominent RV impulse may be appreciated because of equalization of right and left ventricular pressures. A lift may be palpated under the right sternoclavicular junction in patients with a right-sided arch. The first heart sound (S_1) is usually normal, but the second heart sound (S_2) is often single because of an inaudible P_2. Auscultation is notable for a **prominent systolic ejection murmur at the left upper sternal border,** possibly with an associated thrill. The shorter the murmur, the more severe the infundibular pulmonary stenosis. The murmur of aortic insufficiency may be audible along with an aortic click resulting from a dilated overriding aorta. Continuous murmurs may be heard because of aortopulmonary collateral vessels. The presence of these vessels is more likely in the setting of pulmonary atresia, but they can also be acquired if RV outflow tract stenosis develops gradually.

2. Most adult congenital patients will have undergone surgical repair with or without a prior palliative procedure. The term "**palliation**" (as opposed to "repair") in these patients refers to a surgical procedure that consists of a **systemic-to-pulmonary artery shunt** (modified Blalock–Taussig shunt, classic Blalock–Taussig shunt, Potts shunt, or Waterston shunt; Table 31.1). These procedures are initially performed to supplement the deficiency of antegrade pulmonary blood flow and are taken down at the time of complete repair. The latter two procedures have been abandoned because of associated uncontrolled pulmonary blood flow and the subsequent development of pulmonary hypertension.

a. Patients who have undergone palliative repair alone have variable clinical findings, depending on the type of palliation performed. In those who have undergone a classic Blalock–Taussig shunt, the brachial pulse on that side may be diminished or absent. If patent, shunts can produce a continuous murmur. Continuous murmurs can also result from aortopulmonary collaterals. Branch pulmonary artery stenosis at prior shunt insertion sites can produce unilateral systolic or continuous murmurs. Systolic ejection murmurs may be audible depending on the degree of antegrade flow across the outflow tract.

3. Complete (or total) repair consists of patch closure of the VSD and variable degrees of RV outflow tract resection and reconstruction. It may involve pulmonary valvotomy, RV outflow tract patch augmentation, transannular patch enlargement, or placement of a right ventricle–to–pulmonary artery conduit (i.e., bioprosthetic or homograft). Distal branch pulmonary artery stenosis may have been repaired, or residual lesions may be present. These patients typically have first undergone a palliative shunt procedure, but the current surgical approach has shifted to primary complete repair in infancy.

a. Patients are often asymptomatic. They may present with late symptoms such as dyspnea, exercise intolerance, palpitations, signs of right heart failure, or syncope.

b. The jugular venous pressure is usually normal unless there is RV dysfunction, in which case elevated jugular venous pressure with a prominent *a* wave is seen. The brisk pulse of aortic insufficiency may also be appreciated. On palpation, there may be an RV lift or a lift under the right sternoclavicular junction when the arch is right sided. Some degree of turbulence almost always remains across the RV outflow tract and produces a variable systolic ejection murmur at the left upper sternal border, with radiation to the back and peripheral lung fields. Of importance is the presence of associated pulmonary insufficiency. This, even if severe, may occasionally be inaudible due to low-pressure hemodynamics. It is generally appreciated at the left upper sternal border, sometimes producing a to-and-fro murmur together with the outflow tract murmur. A high-frequency systolic murmur at the left lower sternal border suggests the presence of a residual VSD (often due to a small leak in the VSD patch). Continuous murmurs from collateral formation or prior shunts may be appreciated. The diastolic murmur of aortic insufficiency may also be heard.

C. Laboratory examination

1. Chest radiographic findings depend on the surgical history. The presence of a right aortic arch may be confirmed. A concave deficiency of the left heart border reflects various degrees of pulmonary arterial hypoplasia. Upturning of the apex from RVH causes the classic finding of a "boot-shaped" heart. Pulmonary vascular markings may vary throughout the lung fields, depending on associated branch pulmonary artery stenosis and relative blood flow. Calcification or aneurysmal dilation of surgical conduits or RV outflow tract repair may be visible on plain radiographs.

TABLE 31.1 Index of Postoperative Anatomy among A Congenital Heart Disease

Underlying Pathology	Procedure	Notes
Single ventricle Hypoplastic left heart Tricuspid atresia	**1. Norwood**	Incorporation of native aorta and pu be hypoplastic or atretic) to proc ventricle
Pulmonary atresia with intact ventricular septum Unbalanced complete AV canal defect		Main pulmonary artery is transected Pulmonary flow is maintained with **shunt** **Atrial septectomy** is often performe atrial level
	2. Bidirectional Glenn	Usually performed at 4–6 mo if pulm and resistances are adequate Anastomosis of the **superior vena** usually with takedown of a previo artery shunt and repair of pulm necessary Term *bidirectional* is used in descri

TABLE 31.1 Index of Postoperative Anatomy among A Congenital Heart Disease		
		both right and left pulmonary arter
	3. Fontan	Usually performed at 1–5 y depend cyanosis Anastomosis of **inferior vena cava** atrial lateral tunnel or extracardiac Pulmonary blood flow is achieved p a ventricular pumping chamber
dTGA (ventriculoarterial discordance)	**Rashkind**	**Atrial balloon septostomy** to c pulmonary circulation
	Blalock–Hanlon	Surgical atrial septectomy
	Mustard or Senning (atrial switch)	Baffle material (Mustard) or native a pulmonary venous blood → right v blood → left ventricle → pulmonar
	Jatene (arterial switch)	Great arteries are transected and r ventricle Coronary arteries are removed with reimplanted to the appropriate sin
	Rastelli	For dTGA with VSD and pulmonary VSD patch closure that directs left v the aorta Pulmonary valve is oversewn Valved conduit from the right ven create RV outflow
Deficient pulmonary artery or RV outflow tract Pulmonary atresia, tetralogy of Fallot with hypoplastic pulmonary arteries	**Classic Blalock–Taussig**	Native subclavian artery anastomo artery
	Modified Blalock–Taussig	Expanded polytetrafluoroethylene (subclavian or innominate artery to
	Waterston shunt	Anastomosis between the ascending
	Potts shunt	Anastomosis between the descendi

2. AV, atrioventricular; RV, right ventricular; TGA, transposition of the great arteries; VSD, ventricular septal defect.

3. An **electrocardiogram** usually demonstrates sinus rhythm with RVH. Both atrial and ventricular rhythm disturbances can be present. The QRS axis is usually normal or rightward. If left axis deviation is present, an associated AV canal defect should be suspected. A patient who has undergone surgical repair typically has right bundle branch block. **A QRS duration of >180 ms is a predictor of sustained ventricular tachycardia and sudden cardiac death.**

D. Diagnostic testing

1. Echocardiography

a. For a child or young adult, transthoracic echocardiography may be the only modality necessary for diagnosis. For adults or patients who have undergone surgical intervention, catheterization or magnetic resonance imaging (MRI) may be necessary in order to identify the presence and location of residual lesions.

1. (1) It is clinically useful to identify a residual VSD or the presence of aortic insufficiency. Palliative shunts are often best visualized in the suprasternal notch view, where the subclavian arteries course distally.
2. (2) Continuous flow is typically demonstrated with color Doppler techniques. Less common shunts may be difficult to image in adult patients. Aortopulmonary collateral vessels are extremely difficult to visualize but may be seen in suprasternal notch views of the descending aorta.

b. **Transesophageal echocardiography** may allow improved imaging of the intracardiac anatomic structures in adults, but limitations often remain with regard to the distal pulmonary arteries, and additional testing is frequently necessary.

2. **Cardiac magnetic resonance (CMR) imaging** is considered the gold standard for evaluating the right ventricle and quantitating pulmonary insufficiency in these patients. It can demonstrate the presence of scar, distal pulmonary arterial anatomy, and RV aneurysms, as well as other associated defects. It can also provide hemodynamic information about residual lesions. Previously placed shunts and possibly aortopulmonary collateral vessels can be identified as well. The anatomic information may be sufficient to proceed with surgical treatment or to guide the interventional cardiologist in planning a transcatheter procedure.

3. **Cardiopulmonary testing** should be performed as a baseline study and with progression of symptoms. It is useful in determining the timing for reintervention in the setting of RV volume overload secondary to free pulmonary insufficiency.

4. **Quantitative pulmonary flow scans** are useful to determine discrepancies in pulmonary flow that may be caused by branch pulmonary artery stenosis. These scans also provide objective baseline clinical information when obtained after surgical or transcatheter intervention.

5. The role of **cardiac catheterization** is decreasing with the advent of other imaging modalities but can be helpful in assessing residual shunts, branch pulmonary stenosis, and pulmonary hypertension.

a. **Right heart catheterization.** Residual shunts are actively sought at the atrial and ventricular levels. The pulmonary arteries and branches are evaluated extensively in search of peripheral pulmonary stenosis. Findings at right heart catheterization and their clinical significance are as follows:

1. (1) RV pressure is generally systemic in a patient who has not undergone surgical repair.
2. (2) After surgical repair, elevated RV pressure suggests the presence of residual obstructive lesions, the levels of which are to be documented.
3. (3) Careful pullback recordings are performed from the branch pulmonary arteries to the right ventricle because stenosis at each level is possible.
4. (4) The presence of stenosis at a prior shunt site is expected.
5. (5) RV end-diastolic pressures may be elevated in the setting of pulmonary insufficiency.

b. **Left heart catheterization** is performed if noninvasive studies suggest residual VSD.

1. **(1) Angiography** includes a cranialized right ventriculography and possibly selective pulmonary arterial injections if hemodynamic findings suggest stenosis.
2. **(2) Left ventriculography** better demonstrates residual VSD in the presence of subsystemic RV pressures.
3. **(3) Aortic root injection** demonstrates the presence of aortic insufficiency, confirms the presence of grossly abnormal coronary artery origins or branching patterns, and reveals prior surgical shunts or aortopulmonary collateral vessels. If present, shunts and collateral vessels are best visualized in the posteroanterior and lateral projections after selective injection by hand.
4. **(4) Selective coronary angiography** is recommended in the care of adult patients to exclude acquired coronary artery disease and to identify the path of any anomalous coronaries before surgical intervention. **The anomaly that is not to be missed is the left anterior descending artery originating from the right coronary artery**—it crosses the RV outflow tract anteriorly and can be damaged during surgery.

E. Therapy and follow-up care

1. Medical treatment

a. If an adult has **not been surgically treated or has undergone palliative treatment**, a relatively well-balanced situation must exist. However, the following problems are to be expected.

1. **(1)** Long-term effects of RV outflow obstruction
2. **(2)** Progressive infundibular pulmonary stenosis
3. **(3)** Exposure of the pulmonary circulation to systemic shunt flow
4. **(4)** Development of distal pulmonary arterial stenosis, typically at shunt sites
5. **(5)** Erythrocytosis
6. **(6)** Chronic hypoxemia
7. **(7)** Pulmonary hypertension
8. **(8)** Paradoxical emboli
9. **(9)** Atrial and ventricular arrhythmias
10. **(10)** Increased risk of aortic insufficiency over time
11. **(11)** Endocarditis

b. Follow-up care increasingly involves **patients who have undergone surgical repair** and management of residual postoperative lesions.

1. **(1)** These patients are at increased risk for **sudden cardiac death**. Atrial and ventricular rhythm disturbances are common in the postoperative patient. Frequent Holter monitoring is warranted for this reason. Atrial tachyarrhythmias are found in up to one-third of patients and are predictive of morbidity and mortality. If patients are found to have nonsustained ventricular tachycardia, an electrophysiologic study and possibly an implantable cardioverter–defibrillator implantation can be considered. Atrial and ventricular arrhythmias may be the presenting problem for postrepair patients when a component of the repair is failing. There are no data to support prophylactic antiarrhythmic therapy to lower risk of sudden death in this patient population. An increased incidence of ventricular rhythm abnormalities has been associated with RV volume overload from pulmonary insufficiency and with QRS prolongation >180 ms (QRS duration correlates with degree of RV dilation).
2. **(2) Pulmonary insufficiency** can be tolerated for years, even decades, but chronic volume loading of the right ventricle can lead to diminished exercise tolerance, dysrhythmias, and **right heart**

failure. Pulmonary insufficiency is the most common indication for redo surgery after an initial repair.

3. **(3)** Residual VSD
4. **(4)** Progressive dilation of the ascending aorta
5. **(5)** Residual RV outflow tract gradient
6. **(6)** RV outflow tract aneurysm at previous patch site

c. Recent **infective endocarditis guidelines** have departed considerably from prior iterations in that antibiotic prophylaxis is recommended only for those who are at highest risk for adverse outcomes from endocarditis. Specifically, prophylaxis is still appropriate for patients with TOF who are unrepaired, including those who have undergone a palliative procedure. For patients with TOF who have undergone total repair, antibiotic prophylaxis is now recommended only for 6 months following the placement of prosthetic material or device or if there is a residual defect at, or adjacent to, the site of prosthetic material (VSD patch leak, for example). If the pulmonary valve has been replaced or repaired with prosthetic material, antibiotic prophylaxis is appropriate as well.

2. The primary therapeutic consideration for patients with TOF is **surgical intervention**—either repair or reintervention.

a. The goal of **total repair** is to relieve the outflow tract obstruction while maintaining the competency of a preferably native pulmonary valve with closure of the VSD. Some younger patients need extensive reconstruction of the RV outflow tract with early placement of a bioprosthetic valved conduit or homograft. In time, these usually become restrictive to flow and/or are insufficient. The result is progressive right heart hypertrophy, fibrosis, and failure if revision is not performed.

b. A common indication for **reintervention** is pulmonary valve replacement (PVR) for severe pulmonary valve insufficiency. The ideal timing for PVR, however, remains controversial. Cardiac MRI may be helpful in determining optimal timing, and there is evidence to support pursuing pulmonic valve replacement before the RV end-diastolic volume index reaches 160 mL/m^2.

c. Other indications for **reintervention** include the replacement or revision of conduits/homografts in the presence of symptoms, residual VSD with reasonable shunt (approximately 1.5:1), RV pressures greater than two-thirds of systemic pressures because of residual obstructive lesions, progressive aneurysmal dilation of RV outflow tract patch, residual systemic–pulmonary shunts with left ventricular volume overload, clinically significant arrhythmias, symptomatic or progressive aortic insufficiency, and significant progressive aortopathy (>5.0 cm).

3. Although the mainstay of therapy has been surgical, **transcatheter techniques** are increasingly used to treat patients in certain situations. For the most part, transcatheter therapies for adults with TOF are limited to patients who have undergone prior surgical treatment, with attention to residual obstructive lesions in the main pulmonary artery, right ventricle–to–pulmonary artery conduit, or distal pulmonary arteries. Prior shunt sites may become stenotic with time and necessitate balloon angioplasty and possibly stent placement. Residual VSD and ASD may be closed percutaneously in select situations. Percutaneous pulmonic valve replacement has been approved for use both in Europe and the United States. The Melody valve (Medtronic; Minneapolis, MN) is a therapeutic option available for selected patients with stenotic or regurgitant conduits.

II. COMPLETE TRANSPOSITION OF THE GREAT ARTERIES (DTGA). This is a relatively common congenital anomaly that occurs with a prevalence of 20 to 30 in 100,000 live births and is found more often in males (2:1). It is not associated with other syndromes and does not tend to cluster in families. Although it represents **5% to 8% of all congenital heart disease**, it accounts for **25% of deaths in the first year of life**. Adult patients almost invariably have undergone prior surgery and carry with them important morbidities that require ongoing surveillance and care.

A. Anatomy

1. The defining feature of this anomaly is **ventriculoarterial discordance**, in which there is an abnormal alignment between the ventricles and the great arteries. Hence, the aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle, creating two parallel circuits instead of one in series. Deoxygenated blood flows from the right atrium across a tricuspid valve → right ventricle → aorta, whereas oxygenated blood flows from the left atrium across the mitral valve → left ventricle → pulmonary artery. Unless there is bidirectional shunting at the atrial (ASD), ventricular (VSD), or great artery level (patent ductus arteriosus) to allow mixing of blood, this anatomy is incompatible with life (Fig. 31.1).
2. There is an abnormal spatial relationship between the great arteries such that instead of the normal spiral configuration, they run parallel to one another. The **aorta is rightward and anteriorly displaced**, whereas **the pulmonary artery occupies a position more leftward and posterior**. This is the most common pattern, but other configurations can also be seen, such as side-by-side great arteries with the aorta to the right or an aorta directly anterior to the pulmonary artery.
3. Associated cardiac anomalies include **VSD in 40%** to 45% of cases (usually perimembranous but can involve any portion of the interventricular septum), **left ventricular (or subpulmonary) outflow tract obstruction in 25%**, aortic coarctation in 5%, patent foramen ovale (PFO), and patent ductus arteriosus. Patients with these associated cardiac anomalies are considered to have **complex** transposition, whereas patients without these associated anomalies are considered to have simple transposition.
4. This lesion is also referred to as "dTGA," in which the "d" refers to the dextroposition of the bulboventricular loop, which is characterized by a right-sided right ventricle.
5. The coronary anatomy in dTGA is variable. The aortic sinuses are described according to their relationship to the pulmonary artery, such that the "facing sinuses" are closest to the pulmonary artery. The most frequent coronary arrangement is when the "left-facing" sinus gives rise to the left main coronary artery, whereas the "right-facing" sinus gives rise to the right coronary artery.

B. Natural history and surgical repair

1. Without surgical intervention, survival beyond infancy is dismal, with 89% mortality by the first year of life and worse outcomes for those without an associated lesion to allow for adequate mixing of blood. At birth, infants are treated with intravenous prostaglandin E to keep the ductus arteriosus open, and some may undergo a **Rashkind procedure** (Table 31.1) to improve oxygenation until definitive surgery can be performed.
2. Adults invariably have undergone some type of cardiac surgery, although in rare cases they may present with Eisenmenger physiology (see subsequent text) if a "balanced" situation exists with a concomitant large VSD and pulmonary vascular disease.

Surgical repairs include the atrial switch procedure **(Senning or Mustard operation)**, the **arterial switch** procedure (Fig. 31.2), or the **Rastelli operation** (Table 31.1).

C. Clinical presentation

1. The clinical presentation of the surgically repaired patient with dTGA depends on the type of previous surgery. Although no longer cyanotic, these patients have a host of mid- to late-term morbidities that require lifelong surveillance. Patients who have undergone an arterial switch procedure are approaching adulthood only now and presenting in adult congenital cardiology clinics.

2. Atrial switch (Mustard or Senning)

a. Patients who have undergone an atrial switch operation often report New York Heart Association (NYHA) functional class I–II symptoms but on exercise testing may have significant exercise intolerance. They have a systemic right ventricle, which, over time, can develop systolic dysfunction and progressive tricuspid regurgitation. These patients may present with signs and symptoms of congestive heart failure—the most common cause of death. Arrhythmias are common, and patients may present with palpitations, presyncope, or syncope. Venous baffle obstruction can lead to peripheral edema, hepatomegaly, ascites, and fatigue because of low cardiac output. The obstruction of the superior limb can produce a superior vena cava syndrome. Pulmonary venous baffle obstruction can lead to fatigue, exertional dyspnea, and chronic cough. Baffle leaks are often asymptomatic, but large leaks can lead to intracardiac shunting and cyanosis.

FIGURE 31.1 Complete (d) transposition of the great arteries.

b. On physical examination, focus should be on signs of AV regurgitation and heart failure. There may be an RV heave at the left sternal border on palpation. S_2 is loud at the second left intercostal space from an anterior aorta. Audible splitting of the S_2 may indicate the development of pulmonary hypertension.

3. Arterial switch

a. This has become the standard corrective surgery for those born without significant left ventricular outflow obstruction. The majority of these patients are asymptomatic with NYHA functional class I symptoms. Arrhythmias are not a significant problem with this subset. Few will present with chest pain, and in these patients ischemia must be ruled out.

b. The physical examination is sometimes notable for turbulence across the RV outflow tract, which may be palpated as a thrill. The diastolic murmur of aortic insufficiency should also be sought.

4. Rastelli operation

a. Both atrial and ventricular arrhythmias are mid- to late-term complications, and patients with these conditions may present with palpitations or syncope. Conduit obstruction may manifest as insidious exercise intolerance, dyspnea, or new-onset arrhythmias. On physical examination, the character of the pulmonic ejection murmur should be carefully noted to evaluate for conduit obstruction.

D. Laboratory examination

1. The **chest radiograph** of patients with dTGA displays a narrow mediastinum because of the parallel orientation of the great arteries. The cardiothoracic silhouette is normal. The pulmonary vasculature is normal in patients without pulmonary

hypertension. The right ventricle–to–pulmonary artery conduit in patients who have undergone a Rastelli procedure may be visualized on plain radiograph because of calcification.

FIGURE 31.2 Arterial switch operation.

2. In patients who have undergone an atrial switch operation, the **electrocardiogram** may display an ectopic atrial or junctional rhythm because of loss of sinus node function. There is usually right-axis deviation and RVH as a result of the systemic position of the right ventricle. In patients who have undergone arterial switch, RVH is distinctly abnormal and suggests pulmonary outflow tract obstruction. After a Rastelli operation, the electrocardiogram is notable for a right bundle branch block, and patients may develop complete heart block.

E. Diagnostic testing

1. **Transthoracic echocardiography** in atrial switch patients can assess the degree of tricuspid regurgitation and estimate RV function. Color Doppler is helpful in detecting baffle leaks or obstruction, although more detailed analysis may require transesophageal echocardiography. For those who have undergone arterial switch, transthoracic echocardiography can assess left ventricular function and help exclude supravalvular and pulmonary artery stenosis. Two-dimensional Doppler can be used to look for conduit stenosis after the Rastelli operation and estimate RV systolic pressures. It can also exclude any residual VSDs in these patients.
2. As in the TOF population, **CMR** imaging has emerged as an invaluable imaging modality for patients with repaired dTGA. For post–atrial switch patients, CMR imaging is used to quantify the size and function of the right ventricle, assess tricuspid regurgitation, and evaluate the systemic and pulmonary venous limbs of the atrial baffle for potential obstruction or leaks. In patients who have undergone arterial repair, right and left ventricular function can be quantitated and both the right and left outflow tracts examined. Focus is placed on the great arteries to look for the presence of supravalvular and branch pulmonary artery stenosis as well as dilation of the neo-aorta. Conduit stenosis and gradients as well as RV size and function can be determined in those who have had a Rastelli operation.
3. **Cardiopulmonary testing** is very useful in detecting subtle clinical changes and decrease in functional capacity. As mentioned previously, there is often a discrepancy between self-reported symptoms and performance on metabolic exercise testing. Patients who have undergone atrial switch often have chronotropic incompetence and may benefit from pacemaker implantation. Stress testing may be useful in patients after arterial switch to detect coronary artery stenosis and resultant ischemia.
4. **Quantitative pulmonary flow scans** are an important part of the diagnostic workup for suspected pulmonary artery or branch pulmonary artery stenosis in those who have undergone arterial switch repair. It is useful to obtain these scans before and after potential intervention to assess for functional improvement.
5. **Cardiac catheterization** does not have a role in the routine management of these adult patients. It does have a role, however, in the diagnosis and treatment of baffle obstruction and leaks, pulmonary hypertension, pulmonary artery stenosis, coronary artery stenosis, conduit obstruction, and residual VSD.

F. Therapy and follow-up

1. Follow-up should focus on potential late complications after repair and depends on the type of surgery the patient has undergone.

a. Atrial switch

1. (1) Arrhythmias including sinus node dysfunction and intra-atrial reentry tachycardia (frequent Holter monitoring is recommended)
2. (2) RV dysfunction
3. (3) Tricuspid regurgitation
4. (4) Sudden cardiac death
5. (5) Baffle obstruction or leak
6. (6) Pulmonary hypertension
7. (7) Endocarditis

b. Arterial switch

1. (1) Supravalvular or peripheral pulmonary artery stenosis
2. (2) Pulmonary outflow tract obstruction
3. (3) Neo-aortic regurgitation and aortic root dilation
4. (4) Coronary artery stenosis leading to ischemia and sudden death
5. (5) Left ventricular dysfunction
6. (6) Endocarditis

c. **Rastelli operation**

1. (1) Atrial and ventricular arrhythmias
2. (2) Complete heart block
3. (3) Sudden cardiac death
4. 4 Left ventricular dysfunction
5. 5 Conduit stenosis
6. 6 Endocarditis

2. **Medical management**

a. In the treatment of systemic RV dysfunction, there are limited data to suggest any long-term benefits from applying the evidence-based drugs utilized for left ventricular dysfunction. Despite this, angiotensin-converting enzyme (ACE) inhibitors are often utilized for afterload reduction. β-Blockers should be used with caution in patients after atrial switch repairs, because this could precipitate heart block (due to sinus node and AV conduction abnormalities).

b. As mentioned previously, the latest **infective endocarditis** guidelines have changed such that in the absence of valve replacement or prosthetic material used to repair a valve, implantation of prosthetic material within the last 6 months, or prosthetic material accompanied by residual leaks, it is no longer officially recommended that dTGA patients postrepair receive antibiotic prophylaxis.

3. Late intervention options include both surgical and transcatheter procedures and, again, depend on the type of repair. Systemic ventricular failure may ultimately require workup for orthotopic heart transplantation.

a. **Atrial switch**

1. 1 The procedure of choice in patients with baffle obstruction is transcatheter stent implantation, with best results in the systemic venous baffle. Although technically more challenging, transcatheter dilation of the pulmonary venous baffle can be performed but may require surgical

revision. Clinically significant baffle leaks can be treated with catheter-based techniques as well as with septal occluder devices.

2. 2 In view of the high prevalence of atrial arrhythmias and sinus node dysfunction, these patients are referred for radiofrequency ablation procedures and pacemaker implantation.

3. 3 Conversion to an arterial switch for systemic RV dysfunction or left ventricular "training" by pulmonary artery banding has not been reliably successful in the adult population and has been largely supplanted by cardiac transplantation in many centers.

b. Arterial switch

1. 1 Percutaneous balloon angioplasty with or without stent placement is an excellent option for those with pulmonary artery and supravalvular or branch pulmonary artery stenosis with suitable anatomy. Balloon angioplasty being a safe procedure, there is an approximately 15% restenosis rate, with lower risk after stent implantation. The greatest success lies with branch pulmonary artery stenosis.

2. 2 Coronary artery stenosis can be treated with both stenting and coronary bypass surgery.

3. 3 Severe neo-aortic regurgitation is treated surgically with either valve repair or replacement.

c. Rastelli operation

1. 1 All right ventricle–to–pulmonary artery conduits inevitably fail and require replacement. There is a role for percutaneous stenting of conduit obstruction in some patients, because this can delay the need for surgery. These transcatheter procedures have a risk of stent fracture as well as potential for coronary artery compression, which can lead to catastrophic outcomes in the catheterization laboratory.

2. 2 Residual VSD leaks may be amenable to closure by percutaneous means but often require surgical revision. Clinically significant residual left ventricular outflow tract obstruction is also managed surgically.

III. CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES (CCTGA).

Ventricular inversion or ccTGA is a rare congenital anomaly that occurs in <1% of children with congenital cardiovascular defects. Among these patients, it is equally rare to have no other associated structural abnormalities. The natural history of ccTGA is gradual congestive heart failure caused by systemic AV valve insufficiency and systemic ventricular dysfunction, even in the absence of other associated malformations. The presence of associated defects and conduction abnormalities contributes to a further decrease in life expectancy without intervention. Life expectancy is generally good but does not reach normal.

A. Anatomy

1. The defining feature of this congenital abnormality of cardiac looping is **AV and ventriculoarterial discordance**. Blood flows from the right atrium across a mitral valve → right-sided, morphologic left ventricle → pulmonary artery → lungs → left atrium across a tricuspid valve → left-sided, morphologic right ventricle → aorta (Fig. 31.3).

2. The great arteries are not in their normal configuration and often run parallel to one another instead of crossing. The pulmonary artery is more posterior and rightward than usual, and the aorta is more anterior and leftward.

3. The anatomic coronary arteries, like the AV valves, follow their respective ventricles. The left-sided coronary artery resembles the anatomic right coronary artery as it courses in the AV groove and gives rise to infundibular and marginal branches. The right-

sided coronary artery resembles the morphologic left coronary artery, which branches into the anterior descending and circumflex arteries (Fig. 31.4).

4. The conduction system likewise follows the respective ventricle, as the right-sided, morphologic left ventricle depolarizes first. Accessory AV nodal tissue is located anteriorly with respect to normal, and the His bundle must traverse anterior to the pulmonary artery and along the superior margin of a VSD if present. There is increased risk of acquired **complete heart block** in this lesion because of the abnormally placed AV node and its extended course. Approximately 30% of adolescents and adults develop complete heart block, the incidence of which is 2% per year without surgical intervention, with the site of block being within or above the His bundle. Accessory pathways have been described and are typically left sided in the presence of an Ebstein anomaly–like malformation of the left-sided (tricuspid) AV valve.

FIGURE 31.3 Congenitally corrected (l) transposition of the great arteries. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle. **FIGURE 31.4** Schematic representation of coronary artery origins and branching in the normal heart (**A**) and in a congenitally corrected transposition (**B**).

5. Isolated ccTGA is the exception. **Associated lesions** are common and are considered in the diagnostic evaluation. They include VSD (70%), pulmonary outflow obstruction (~40% and usually subvalvular), or abnormalities of the left-sided, systemic tricuspid valve. Up to 90% of patients have an abnormality of the tricuspid valve in some form (i.e., dysplastic or Ebstein-like tricuspid valves).

B. Clinical presentation

1. Because physiologic blood flow is preserved, patients may have no symptoms through adulthood in the absence of other structural lesions or associated complications. This scenario is rare, however, because associated lesions commonly dictate the clinical features.

2. Without associated structural abnormalities, **failure of the systemic morphologic right ventricle** with various degrees of systemic AV valve (tricuspid) insufficiency is the norm. In this setting, the patient has nonspecific descriptions of fatigue, shortness of breath, and exercise intolerance or congestive failure. Patients may have **syncope or presyncope** caused by conduction abnormalities or complete heart block.

3. On physical examination, there is a loud A_2 caused by an anterior and leftward aorta. The murmurs of a VSD or pulmonary stenosis may also be appreciated. Tricuspid insufficiency can be heard with systemic ventricular failure.

C. Laboratory examination

1. In the usual anatomic configuration of ccTGA, the aorta is anterior and to the left, which produces a **chest radiograph** with a straight left heart border. The left pulmonary artery is not well defined, and the ascending aorta is not visible on the right. The chest radiograph may appear normal or reflect the presence of associated lesions, such as increased pulmonary flow from a VSD or decreased pulmonary flow in the setting of pulmonary stenosis. Dextrocardia occurs in approximately 20% of these patients, and the diagnosis should be suspected if seen with abdominal situs solitus.

2. The typical **electrocardiogram** shows a left axis deviation. Among pediatric patients, there is loss of the usual Q waves in the precordial leads, with deep Q waves in leads II and aVF reflecting reverse septal activation. A variety of AV node conduction abnormalities may manifest with time and progress to complete heart block.

D. Diagnostic evaluation

1. In most instances, the diagnosis can be made with **echocardiography**. The essential findings of AV and ventriculoarterial discordance must be demonstrated. Imaging may be difficult in the presence of dextrocardia or mesocardia. Close attention must be paid to the morphologic details of each chamber.

a. The morphologic **right ventricle** is identified on the basis of its **triangular** shape, the presence of **trabeculations and moderator band**, an inferiorly positioned AV valve, and the presence of AV valve attachments to the interventricular septum.

b. The morphologic **left ventricle** is identified on the basis of its bullet shape, smooth wall, and more superiorly positioned AV valve and absence of AV valve attachments to the interventricular septum. In the case of ccTGA, these relationships are preserved but reversed.

c. Apical four-chamber and subcostal images are particularly helpful. The suprasternal notch view is essential in evaluating the great vessels that lie parallel to each other.

d. The **aortic arch** typically lies to the left of midline in the sagittal plane and can often be visualized from the high left parasternal position. Because variations in great vessel position occur, the spatial orientation must be clarified.

e. **Associated defects** (e.g., systemic AV valve insufficiency, VSD, and outflow tract obstruction) with ccTGA must be excluded or defined.

2. **Catheterization is unnecessary** for the diagnosis of ccTGA but may be helpful in preoperative planning with regard to the hemodynamic significance of associated lesions. In rare instances, ccTGA is diagnosed by catheterization and was not recognized during routine echocardiography. An unusual arterial catheter course is caused by the anterior and leftward position of the aorta in most instances. The left-sided coronary artery typically arises from the posterior sinus and assumes a right coronary branching distribution, whereas the right-sided coronary artery arises from the anterior and rightward sinus and assumes a typical left coronary branching distribution (Fig. 31.4). Because the ventricular septum often lies in the sagittal plane, ventriculography is usually best performed in the straight posteroanterior and lateral projections.

E. Therapy

1. **Medical management** is dictated primarily by the associated malformations.

a. In the rare case of isolated ccTGA, the risk of development of conduction abnormalities is cumulative over time; therefore, periodic Holter monitoring is warranted. Permanent pacemaker placement is often needed.

b. The systemic AV valve and ventricle may show signs of failure that necessitate initiation of heart failure measures in the form of diuretics and afterload reduction, although data are lacking on the use of agents such as ACE inhibitors or β-blockers in systemic right ventricles.

c. Associated lesions such as pulmonary stenosis or atresia, severe systemic AV valve regurgitation, or VSD may likewise contribute to the medical treatment of these patients, but often also necessitate surgical intervention.

d. The American Heart Association (AHA) guidelines do not recommend routine antibiotic prophylaxis for these patients unless they have had recent placement of prosthetic material within the preceding 6 months or have a leak at, or adjacent to, the site of a previous prosthesis.

2. **Surgery**

a. Infants and children who are brought to medical attention early often need surgical intervention in the form of relief of pulmonary outflow tract obstruction or placement of palliative shunts, depending on the associated lesions.

b. For selected children, a **double switch** procedure may be performed. An **atrial switch** corrects the AV discordance by baffling atrial blood to the appropriate ventricle (i.e., oxygenated blood diverted from the left atrium rightward to the right-sided left ventricle and vice versa by the Mustard or Senning procedure). **Arterial switch** is performed in the same operation to restore anatomic ventriculoarterial concordance. The double switch operation may necessitate a period of "training" of the left ventricle by means of pulmonary artery banding. The results of this operation are generally less favorable in older patients in whom the right ventricle has been the systemic ventricle for a more prolonged period. The intermediate-term results of this procedure are encouraging, but data for long-term results are limited. Those with a large VSD may undergo atrial baffling with a **Rastelli operation** (see Table 31.1).

c. Adult patients with symptoms of progressive systemic AV valvular insufficiency may need valve repair or replacement. Most centers that have reported results with this procedure have found improved functional status after surgical treatment and acceptable risks. The timing of surgical intervention among patients with less severe symptoms is a topic of debate, but it is agreed that referral should be considered early before irreversible changes in ventricular function occur.

IV. EBSTEIN ANOMALY.

This anomaly of the tricuspid valve represents 0.5% of congenital heart defects. The natural history of this lesion varies from early death to nearly normal expected survival, depending on the degree of tricuspid valve involvement and the presence and type of arrhythmias. An increased risk of **sudden death** irrespective of functional class, presumably caused by arrhythmia, has been observed. **Predictors of poor outcome** include earlier **age** at presentation, **cardiomegaly**, severe **RV outflow abnormalities**, and **disproportionate dilation of the right atrium** relative to the other chambers. There is an association with maternal lithium administration, but most cases are sporadic.

A. Anatomy

1. The **tricuspid valve** is morphologically and functionally abnormal. The basic features include adherence of the septal and posterior leaflet to the myocardium, which lowers the functional annulus toward the RV apex. This results in the classic **atrialization** of the right ventricle (Fig. 31.5) and dilation of the true tricuspid annulus. The anterior leaflet is usually not displaced but is redundant and may be fenestrated and tethered.

2. **Associated structural anomalies** include a **PFO or ASD** (found in ≥80%), **VSD, mitral valve prolapse, and pulmonary stenosis**. ccTGA is associated with Ebstein-like anomaly of the tricuspid (systemic) valve.

B. Clinical presentation

1. **Signs and symptoms** are variable.

a. The presence of a severely insufficient valve can be apparent at birth because of right-to-left shunting across a stretched PFO or ASD, resulting in cyanosis. Pulmonary vascular resistance is high in the neonate and worsens cyanosis, but as pulmonary vascular resistance falls, cyanosis may resolve. In adulthood, as tricuspid regurgitation becomes long-standing with associated decreased RV compliance, cyanosis can reappear. In subtle cases, the anomaly may not be evident until adulthood and then results in nonspecific fatigue, shortness of breath, palpitations, near-syncope, or syncope. In the presence of an interatrial communication, patients may present with paradoxical embolization or brain abscess. Because the spectrum of involvement varies greatly, a high index of suspicion must be maintained.

FIGURE 31.5 Section through the right atrioventricular junction. **A:** Normal heart, showing the right atrium (A) and right ventricle (V). **B:** Mild degree of Ebstein anomaly. **C:** Severe Ebstein anomaly. In (**B**) and (**C**), there is apparent displacement of the tricuspid valve. (From Adams FH, Emmanouilides GC, Riemenschneider TA, eds. *Moss' Heart Disease in Infants, Children, and Adolescents*. 4th ed. Baltimore, MD: Williams & Wilkins; 1989, with permission.)

b. The downward displaced septal leaflet creates a substrate for **accessory pathways**, and clinical Wolff–Parkinson–White syndrome is found in 10% to 25% of patients. Arrhythmias include supraventricular tachycardia mediated by an accessory pathway or caused by atrial arrhythmias from progressive atrial dilation. The combination of atrial fibrillation or flutter conducted rapidly across an accessory pathway is often poorly tolerated.

2. **Physical examination**

a. General inspection usually reveals normal jugular venous pulsations despite severe tricuspid regurgitation, which is masked by a large compliant atrium. Cyanosis may be present as a result of right-to-left shunting at the atrial level. Digital clubbing will vary depending on the amount of cyanosis.

b. The most common auscultatory findings are the regurgitant murmur of tricuspid insufficiency, gallop rhythms, multiple systolic ejection sounds, and a widely split S_2.

C. Laboratory examination

1. **Chest radiography** may reveal cardiomegaly, caused by right atrial enlargement from tricuspid insufficiency. Typically, it is described as a globe-shaped heart with a narrow waist.

2. The **electrocardiogram** can demonstrate PR prolongation, right atrial enlargement ("Himalayan" P waves), and superior axis with or without right bundle branch block (Fig. 31.6). The QRS amplitude is characteristically low over the right precordial leads because of a diminutive right ventricle. The preexcitation pattern, if present, is almost always type B (i.e., left bundle branch pattern). Deep Q waves may be seen in leads II, III, and aVF from fibrotic thinning of the RV free wall and/or septal fibrosis.

D. Diagnostic evaluation

1. The diagnosis can be confirmed with transthoracic or transesophageal **echocardiography**, with the tricuspid valve readily visualized in the parasternal short-axis, apical four-chamber, and subcostal views.

a. **Apical displacement of the septal leaflet** from the insertion of the anterior mitral valve leaflet by at least 8 mm/m^2 body surface area is considered diagnostic. In less obvious cases, only tethering of the septal leaflet may be found, defined as at least three accessory attachments of the leaflet to the ventricular wall causing restricted motion. An imperforate valve may rarely occur.

b. The **anterior leaflet** may produce functional obstruction of the pulmonary outflow tract. The leaflet in this circumstance is often called "sail-like." The pulmonary outflow is carefully studied to discern functional obstruction from such a leaflet rather than true anatomic atresia of pulmonary outflow.

c. Views of the **atrial septum** are included in all studies to assess the size of the ASD and degree of shunting, if present.

d. The size of the **right ventricle** and true tricuspid annulus is assessed because size guides the feasibility of surgical intervention.

FIGURE 31.6 Lead V_1 of an electrocardiogram from a newborn infant with Ebstein anomaly demonstrates marked right atrial enlargement and an rSR′pattern.

e. The size and function of the **left ventricle** are assessed. The shape of the left ventricle may be unusual because of extreme leftward bowing of the ventricular septum. Left ventricular function can be affected, and abnormalities may affect long-term outcome.

f. **Associated lesions** must be excluded, such as ASD, RV outflow tract obstruction, patent ductus arteriosus, and, in rare instances, mitral valve abnormalities with associated insufficiency.

2. **Cardiac catheterization is unnecessary** for the diagnostic evaluation of Ebstein anomaly, except to exclude coronary artery disease in adult patients with risk factors for whom surgical intervention is planned. Increased risk of cardiac arrest during catheterization has been reported. A diagnostic right heart study may be indicated in the presence of associated hemodynamic abnormalities as part of preoperative planning.

3. Formal **electrophysiologic study** may be considered for patients with arrhythmias or for those being considered for surgical treatment. Radiofrequency ablation of accessory pathways is performed.

E. Therapy

1. A large number of adult patients may undergo **medical treatment**, which includes standard heart failure medications such as diuretics and digoxin. There are no good data to support ACE inhibitors in right heart failure due to Ebstein anomaly. Particular attention must be focused on the management of atrial dysrhythmias, which become more common with age. Permanent pacemaker therapy is required in 3.7% of patients, mostly for AV block and rarely for sinus node dysfunction. Endocarditis prophylaxis is no longer recommended for these patients unless they are cyanotic and unrepaired, have undergone placement of prosthetic material within the preceding 6 months (i.e., ASD occluder device),

have a leak adjacent to or at the site of prosthetic material, or have had tricuspid valve replacement.

2. **Surgical correction** is usually recommended for patients with NYHA functional class III–IV symptoms despite medical therapy. The tricuspid valve may be repaired primarily or complete replacement may be necessary, and an interatrial communication, if present, is closed. Patients with significant cardiomegaly, cyanosis, or arrhythmias are considered for surgical intervention. Favorable results have been achieved at centers experienced in the care of adult patients, and functional class has improved after therapy.

3. **Transcatheter closure** of an interatrial shunt can be considered in select patients with cyanosis at rest (oxygen saturation < 90%). Patient selection must be carefully evaluated, as closure of an ASD or PFO may lead to worsening RV dysfunction because of increased right-sided heart pressures. In the case of paradoxical embolic events (i.e., stroke), ASD/PFO closure is considered.

V. EISENMENGER SYNDROME.

Eisenmenger syndrome is the clinical phenotype of an **extreme form of pulmonary arterial hypertension associated with congenital heart disease**. Over the last few decades, rapid advances in the modalities of diagnosis and treatment of congenital heart disease have resulted in the ability to repair defects at a much younger age. Pulmonary vascular injury is prevented in many of these children. However, Eisenmenger syndrome is still seen in older patients and occasionally in younger patients, particularly in those from developing countries where access to care may be limited. The natural history of Eisenmenger syndrome is variable; and although a cause of significant morbidity, many Eisenmenger patients survive 30 years or more after the onset of the syndrome.

A. Physiology.

Patients with a systemic-to-pulmonary circulation connection will initially have left-to-right shunting of blood because of the lower pulmonary vascular resistance compared with systemic vascular resistance. Over time, because of excessive flow to the pulmonary vasculature, resulting in increased shear and circumferential stress, pulmonary vascular resistance increases. Eventually, the shunt reverses, creating right-to-left flow. Although the classic form of the disease was initially used to describe the long-term consequences of a VSD, it can occur with any congenital defect with an initial left-to-right shunt, including ASD, AV canal defect, patent ductus arteriosus, aortopulmonary window, and surgically created systemic-to-pulmonary artery shunts. It is important to note, however, that the **physiology and clinical presentation differ depending on the *level* of shunt**. In contrast to patients with nonrestrictive shunts at the ventricular or arterial level, most patients with ASDs do not develop Eisenmenger syndrome, and if they do, they present much later in life. In this case, atrial-level shunting is determined by the compliance of the ventricles and is not due to systemic or suprasystemic pulmonary artery pressures.

B. Clinical presentation of Eisenmenger syndrome has multiorgan involvement

1. **Symptoms.** Pulmonary congestion (from the left-to-right shunt) in early childhood may be evident from the history, but improves as the shunt reverses with ensuing cyanosis. Exercise intolerance is very common. Hypoxemia can lead to erythrocytosis and symptoms of hyperviscosity (e.g., headache, dizziness, fatigue, and cerebrovascular accidents). These patients can have a bleeding diathesis due to thrombocytopenia and inadequate clotting factors. This can complicate the management of intrapulmonary

thrombosis, which occurs in up to one-third of patients. Hemoptysis is a common symptom—alone or caused by pulmonary infarction. Infectious complications include bacterial endocarditis and septic cerebral emboli. Atrial arrhythmias and symptoms of congestive heart failure are usually a late sign and are associated with an increased risk of sudden cardiac death.

2. **Physical examination.** The initial murmur of the associated lesion goes away with reversal of the shunt. Cyanosis and digital clubbing are present, and arterial pulses may be diminished. The cardiac examination reveals signs of elevated right heart pressure, such as jugular venous distention with a prominent *v* wave, a right parasternal heave, a loud pulmonary component of S_2 (sometimes palpable), a right-sided S_4, a holosystolic murmur of tricuspid regurgitation, and a diastolic decrescendo murmur of pulmonary regurgitation. Signs of congestive heart failure such as peripheral edema, ascites, and hepatosplenomegaly are seen later in the disease course.

C. Laboratory examination

1. **Chest radiography** is variable. It may show dilated, even calcified, central pulmonary arteries. Reduced peripheral lung markings are not commonly seen. Patients with ASDs tend to have cardiomegaly due to RV enlargement.

2. The **electrocardiogram** shows evidence of right atrial enlargement and RV hypertrophy. The presence of atrial arrhythmias should be investigated, particularly in the presence of palpitations.

D. Diagnostic evaluation

1. **Echocardiography.** Two-dimensional echocardiography helps in the detailed assessment of the level of the defect, associated lesions, and ventricular function. Doppler measurements can demonstrate and assess the size of the shunt as well as RV pressure and volume overload.

2. **Cardiac catheterization.** Cardiac catheterization is often necessary in these patients to assess the pulmonary vascular resistance. Demonstration of pulmonary vasoreactivity to oxygen, nitric oxide, or other pulmonary vasodilators is prognostic for these patients and can help identify which patients will most benefit from advanced therapies for pulmonary arterial hypertension.

E. Therapy

1. **Medical management**

a. Chronic nocturnal oxygen therapy has not been shown to be beneficial, although it may improve symptoms in some patients. Anticoagulation is controversial because it can also predispose to hemorrhage or hemoptysis, but it is helpful in preventing thromboembolic events. Hyperviscosity can be managed in ***symptomatic*** patients by performing phlebotomy with isovolumic replenishment, but **routine phlebotomy is contraindicated** because of its effect on iron stores, oxygen-carrying capacity, and increased risk of stroke. Monitoring of iron levels and iron replacement, therefore, is paramount. The management of right-sided heart failure is problematic, and the use of digoxin in these patients is controversial. Diuretics should be used cautiously because aggressive diuresis predisposes to hyperviscosity and decreases preload. Endocarditis prophylaxis is warranted.

b. Over the last few years, the treatment of pulmonary hypertension in Eisenmenger syndrome has undergone a paradigm shift. While traditional therapy focused on preventive and palliative measures, there is accruing evidence to suggest that the **disease is in**

fact modifiable and that selective pulmonary vasodilators are not only safe but likely beneficial in this population. These agents include endothelin antagonists, prostacyclin analogs, and phosphodiesterase-5 inhibitors. The only randomized, placebo-controlled trial performed to date in Eisenmenger patients, BREATHE-5, showed reduction in pulmonary vascular resistance and improvement in exercise capacity (with no detriment to oxygen saturation) using bosentan (an endothelin antagonist). In general, intravenous treatments are avoided in this population in view of the risk of paradoxical embolism and increased infectious risk with indwelling lines.

2. **Surgical management.** Selected patients may be candidates for combined heart–lung transplantation or lung transplantation with concomitant repair of the intracardiac defect, if feasible. Timing of these interventions may be difficult because of the relatively long-term survival of these patients after the onset of the disease process and the recent availability of selective pulmonary vasoactive therapy.

F. Eisenmenger syndrome in special situations

1. **Travel** to areas of high altitude should be avoided because it may result in acute right heart failure. Air travel, however, is not contraindicated, as cabin pressures during commercial flights are generally well tolerated.
2. **Pregnancy** in these patients is high risk to the fetus and the mother (>50% maternal mortality) and is generally contraindicated. Given the high risk of maternal and fetal mortality, contraceptive methods (preferably without the use of estrogen) are critical. Elective termination should be discussed with pregnant Eisenmenger patients.
3. **Noncardiac surgery** is also associated with high risk and should be performed under the supervision of anesthesiologists familiar with Eisenmenger syndrome.

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CHAPTER 32

Syncope

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I. INTRODUCTION. Syncope is a common medical problem with an occurrence of 3.0% in men and 3.5% in women in the general population. It accounts for approximately 1% of emergency room visits and 6% of medical admissions. It is defined as a **sudden and transient loss of consciousness accompanied by loss of postural tone with ultimate complete recovery.** It has a bimodal presentation with peak incidence at 20 and 80 years of age. The recurrence rate and prognosis of syncope is mainly dictated by the underlying causative mechanism.

II. ETIOLOGY AND PATHOPHYSIOLOGY. Syncope is ultimately caused by **a transient interruption or reduction of cerebral blood flow.** Cessation of brain blood flow for at least 6 to 8 seconds is enough to cause syncope, and reduction in systolic blood pressure (SBP) to less than 60 mm Hg is also associated with syncope. **Prompt identification of the specific cause behind the episode can help minimize expensive evaluations and guide therapy to prevent recurrences and decrease morbidity.** Based on the underlying pathophysiology, syncope is classified into **reflex-mediated syncope, orthostatic hypotension (OH), and cardiac syncope** (Table 32.1).

A. **Reflex-mediated syncope** is **responsible for two-thirds of all syncopal events.** It results from an exaggerated or inappropriate reflex, which causes unopposed parasympathetic tone leading to inappropriate vasodilation (vasodepressive effect) and/or bradycardia (cardioinhibitory effect). This group can be subclassified into the following:

B. **Vasovagal syncope ("common faint")** is the **most common cause of syncope irrespective of age, gender, or comorbidities.** It is usually triggered by prolonged sitting or standing, emotional stress, or hot environments. Orthostatic stress is thought to be central in the development of vasovagal syncope causing a decrease in preload. A ventricular contraction on a less than full left ventricle leads to the activation of ventricular mechanoreceptors, which results in an increased parasympathetic tone ultimately causing syncope via sudden bradycardia and/or hypotension. Other potential mechanisms include release of endogenous opioids or nitric oxide and primary central nervous system activation.

C. **Situational syncope** is usually associated with distension of hollow viscera (micturition, defecation, cough, postexercise, and trumpet playing) which triggers a vagally mediated reflex that causes syncope via vasodilation and bradycardia.

D. **Carotid sinus syncope** causes less than **1% of syncope**; yet it accounts for **25% to 50% of unexplained syncope events in patients over 50 years**. Hypersensitivity of

carotid baroreceptors is important in this situation because their activation, with or without obvious triggers (shaving, swimming, turning head, or wearing a tight collar), leads to syncope via bradycardia (70% of cases), hypotension (10%), or a mixed response in the rest of cases.

E. **OH** accounts for **10% of all syncope episodes**, but is the **most common cause of syncope in the elderly**. It is characterized by an impaired sympathetic tone leading to **insufficient peripheral vasoconstriction during gravitational stress**, especially during position changes. Inappropriate drop in blood pressure with orthostatic stress defines OH. The following are the most common forms of OH:

TABLE 32.1 Cardiovascular Causes of Syncope

Neurally mediated (vasovagal)
Situational
Micturition
Defecation
Postprandial
Swallowing
Coughing
Sneezing
Glossopharyngeal neuralgia
Orthostatic syncope
Carotid sinus syncope
Cardioinhibitory
Vasodepressor
Mixed
Mechanical
Aortic stenosis
Hypertrophic cardiomyopathy
Atrial myxoma
Mitral stenosis
Pulmonic stenosis
Pulmonary hypertension or embolism
Myocardial infarction
Cardiac tamponade
Electrical
Second- and third-degree AV block
SSS
SVT
VT
Torsade de pointes
Pacemaker malfunction

F. AV, atrioventricular block; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

1. **Classic OH** is defined by a decrease in SBP exceeding 20 mm Hg; and diastolic pressure (DBP) drops of at least 10 mm Hg within 3 minutes of standing.
2. **Initial OH** is characterized by a brief (<30 seconds) but exaggerated drop in blood pressure of more than 40 mm Hg with rapid normalization afterwards.
3. **Delayed OH,** common in the elderly, presents as a slow progressive decline in blood pressure with prolonged standing. The lack of bradycardia sets orthostatic episodes apart from reflex-mediated hypotension.

Common causes of OH include **dysautonomic syndromes**, **volume depletion, medications, diabetes mellitus, alcohol abuse, infection, and varicose veins**.

4. **Dysautonomic syndromes** are divided into two categories. **Primary autonomic failure** includes pure autonomic failure (i.e., Bradbury–Eggleston syndrome) and multisystem atrophy (i.e., Shy–Drager syndrome). **Secondary causes** include amyloidosis, Parkinson disease, Lewy body dementia, tabes dorsalis, and multiple sclerosis.

G. **Cardiac syncope** is the **second most common cause of syncope** responsible for 10% to 20% of all syncope episodes. It carries a **high rate of recurrence and a poor prognosis**.

1. **Arrhythmia induced** is the most common form of cardiac syncope and the main **cause of syncope in patients with known cardiac disease**. The arrhythmic heart rate is the main factor leading to syncope in close interplay with the type of arrhythmia, cardiac preload, left ventricular function, and vascular adaptation. Commonly identified rhythms include **sick sinus syndrome, atrioventricular block (AV block), and ventricular tachycardia (VT), and less common** but important potential causes include supraventricular tachycardia (SVT) and torsade de pointes. Specific syndromes with known electrophysiologic abnormalities may be involved and should be sought in the appropriate circumstances such as Wolff–Parkinson–White syndrome, arrhythmogenic right ventricular dysplasia, long QT syndrome, and Brugada syndrome.
2. **Mechanical cardiac syncope** frequently occurs with exertion and arises from left ventricular outflow obstruction, as seen in aortic stenosis or hypertrophic obstructive cardiomyopathy (HOCM). **Right ventricular outflow obstruction such as pulmonic stenosis** may also result in syncope. Typically, exertion leads to a drop in peripheral vascular resistance, and hypotension develops given the inability to increase flow because of fixed cardiac output in the setting of mechanical obstruction. Arrhythmias and altered baroreceptors response also play a role in syncope in patients with an obvious mechanical cause. **Myocardial ischemia, pulmonary embolism, and cardiac tamponade** should be kept in mind as potential causes of syncope. Up to 7% of patients older than 65 years with myocardial ischemia may present with syncope.

H. **Unexplained etiology.** Up to half of patients with syncope have no identifiable cause after initial presentation. **Asystole** has been identified as an underlying mechanism in **50% of patients over 40 years of age with no structural heart disease and normal electrocardiogram (ECG) presenting with recurrent syncope**. A new classification has been proposed for unexplained and/or recurrent syncope using precipitating mechanism (bradycardia or asystole, tachycardia or none to minimal rhythm variation) rather than the underlying etiology. Recent evidence revealed higher diagnostic yields when identifying mechanism of syncope via ECG monitoring compared with conventional assessment. This classification aims to promote an early use of ECG monitoring during workup of

unexplained syncope to allow prompt use of ECG-tailored therapy in selected cases to ultimately improve treatment efficacy.

III.CLINICAL PRESENTATION. A thorough history and physical examination can provide a clue to the diagnosis in up to 50% of cases. **The most important** aspects of history taking during syncope evaluation are as follows (Table 32.2):

A. Pertinent medical history. The initial approach should focus on

1. **Patient age** as **young patients** are more likely to have **reflex-mediated syncope, whereas the elderly** commonly present with **carotid hypersensitivity** or **OH**

2. **Comorbidities with special attention to history of heart disease,** such as valvular stenosis, cardiomyopathy, or myocardial infarction. The presence of any of these may suggest more malignant causes such as VT.

3. **Family history** looking for syncope and/or sudden cardiac death in family members

4. **Medications review** for their potential causative role or interaction with other medications

5. **Circumstances before syncope**; whether there is association with any particular activity, exertion, or change in position; and the frequency of occurrence

a. Syncope **during exercise suggests cardiac etiology**. Similarly, **noise and strong emotion** are known triggers of long **QT-related syncope**.

b. An event **after exertion** in young athletes or syncope triggered by **pain, prolonged standing, and hot or crowded environments** is indicative of **vasovagal syncope.**

TABLE 32.2 Clinical Features Suggesting Specific Causes

Symptoms or Finding	Diagnostic Consideration
After sudden unexpected pain, unpleasant sight, sound, or smell	Vasovagal syncope
During or immediately after micturition, cough, swallow, or defecation	Situational syncope
With neuralgia (glossopharyngeal or trigeminal)	Bradycardia or vasodepresso
Upon standing	OH
Taking hypotensive medication	Drug-induced syncope
Symptoms within 1 h after meals	Postprandial hypotension
Prolonged standing at attention	Vasovagal
Well-trained athlete after exertion	Vasovagal
Changing position (from sitting to lying, bending, turning over in bed)	Atrial myxoma, thrombus
Syncope with exertion	Aortic stenosis, pulmonary HOCM, coronary artery dis
With head rotation, pressure on carotid sinus associated with vertigo, dysarthria, diplopia with arm exercise	Carotid sinus syncope TIA, st

c. HOCM, hypertrophic obstructive cardiomyopathy; OH, orthostatic hypotension; TIA, transient ischemic attack.

d. Adapted from Kapoor WN, Smith M, Miller NL. Upright tilt testing in evaluating syncope: a comprehensive literature review. *Am J Med*. 1994;97(1):78–88. Copyright © 1994 Elsevier. With permission.

e. **Situational syncope** presents during **urination, defecation, cough, postexercise, and trumpet playing**.

f. **Carotid syncope** is triggered by **shaving, swimming, head turning, or neck extension.**

6. **Prodrome** with diaphoresis, warmth, nausea, abdominal discomfort, or ear ringing is common in vasovagal syncope (except in in elderly patients), whereas none or short prodrome with palpitations suggests cardiac syncope. Seizures are typically preceded by an aura.

7. **The syncopal event** provides useful information to differentiate syncope from other causes of loss of consciousness, so an effort must be made to contact witnesses.

a. Syncope is a transient loss of consciousness (<30 seconds). Vasovagal syncope might present with generalized pallor, whereas cardiac syncope could reveal cyanosis.

b. Occasionally, syncope is accompanied by **mild muscular jerking** (convulsive syncope) as a result of cerebral anoxia. The evaluating physician must make every effort to distinguish this from seizure and pseudoseizure.

8. **Recovery postsyncope** with persistent somnolence, fatigue, and nausea from minutes to hours is suggestive of vasovagal syncope, whereas fast recovery is seen after tachycardia or bradycardia. Seizures commonly present with prolonged (hours) confusion and transient focal neurologic deficits.

B. **Physical findings.** The **physical examination is important, especially when the patient is unable to describe the event** and no witnesses are available, because certain findings on examination can direct the physician in the diagnostic evaluation. A **comprehensive examination**includes

1. Blood pressure measurement in both arms

2. **Orthostatic vital signs** should be serially checked immediately upon standing and after 3 and 5 minutes of orthostatic stress. **SBP drop of over 20 mm Hg or to less than 90 mm Hg and DBP decreases over 10 mm Hg** are **diagnostic for OH.**

3. Evaluation for the presence of carotid bruit and assessment of the carotid upstroke

4. **Carotid sinus massage testing** should be considered in **patients over 40 years of age with syncope of unknown etiology** after initial assessment. Massage is performed on one side followed by contralateral side for 5 to 10 seconds under continuous ECG and beat-to-beat blood pressure monitoring. A **diagnosis of carotid sinus hypersensitivity** is made when massage elicits an asystolic **sinus pause >3 seconds or drop in SBP over 50 mm Hg. Carotid sinus syndrome** is made only when **symptoms accompanies carotid hypersensitivity**. Contraindications include carotid bruits, significant carotid stenosis, or myocardial infarction or stroke within 3 months.

5. Cardiac examination **evaluating heart rhythm, heart rate, extra heart sounds** (such as S_3, S_4, or tumor plop), and murmurs
6. **Peripheral pulses** for evidence of peripheral vascular disease and entities such as subclavian steal; and dermatologic clues that may suggest collagen vascular disease or vasculitis
7. Neurologic examination for focal neurologic deficits

IV. MANAGEMENT. The initial management of syncope includes a thorough history, physical examination, and an ECG. The following systematic stepwise assessment is recommended (Fig. 32.1):

A. Determine likelihood of syncope versus nonsyncopal event (stroke, transient ischemic attacks, normal pressure hydrocephalus, seizures, metabolic causes, and psychogenic). Syncope is highly likely when there is **complete loss of consciousness** of **rapid onset** and **short duration** accompanied by **loss of postural tone** followed by **complete recovery**. If one or more of these criteria are absent, nonsyncopal causes must be ruled out before proceeding with syncopal assessment.

B. Identify specific cause of syncope (Table 32.3). The most important goal during this step is to rule out structural heart disease. A **single ECG** offers the possible **diagnosis in approximately 5%** of cases. The following **ECG findings are suggestive of heart-related** syncope:

1. Persistent sinus bradycardia <40 beats/min or sinus pauses >3 seconds
2. Mobitz II second or complete heart block
3. Bifascicular block or alternating left and right bundle branch block (RBBB)
4. Preexcited or wide QRS complexes
5. Rapid paroxysmal SVT
6. VT or nonsustained polymorphic VT with abnormal QT interval
7. RBBB with ST elevation in leads V1 to V3 (Brugada syndrome)
8. Inverted T-waves in precordial leads with epsilon waves and ventricular late potentials (arrhythmogenic right ventricular dysplasia)
9. Ischemia signs with or without myocardial infarction

C. Risk-stratify syncope events of unknown etiology. The main goal is to identify those with unexplained syncope at higher risk of cardiovascular event or cardiac sudden death. A number of validated risk scoring systems exist including San Francisco Syncope Rule, Evaluation of Guidelines in Syncope Study (EGSYS) score, and Osservatorio Epidemiologico sulla Sincope nel Lazio score. The following are the main high-risk features:

1. **Severe structural or coronary artery disease** (e.g., heart failure, low ejection fraction, or previous myocardial infarction) is the major predictor of VT and death.
2. **ECG findings suggestive of cardiac syncope** as described before
3. **Severe anemia** (hematocrit < 30%) **and electrolyte abnormality**

D. Assess need for hospital admission. It is recommended to admit only cases of syncope with **suspicion for cardiac etiology** or syncope of **uncertain etiology** at an increased risk of major cardiovascular events or death.

A genuine effort must be made to accurately follow this stepwise assessment and to pursue hospital admission and/or further testing only in appropriately selected patients. Besides

standardization of assessment, the use of EGSYS-2 online interactive decision-making software and utilization of syncope units are the only interventions known to further improve the diagnostic yield and rate of hospitalization and/or testing.

E. **Need for further testing.** Additional testing is generally not needed when an underlying cause for syncope has been identified by initial assessment. Further workup is recommended when there is a suggestion of cardiac cause or uncertain etiology. Investigations should be individualized to be cost-effective (Fig. 32.1).

FIGURE 32.1 Schematic algorithm for the evaluation of patients presenting with syncope. ECG, electrocardiogram; EGSYS, Evaluation of Guidelines in Syncope Study; ELR, external loop recorder; HCT: hematocrit; EPS, electrophysiologic study; ICD: implantable cardiac defibrillator; ILR, implantable loop recorder; LHC, left heart catheterization; T-LOC, transient loss of consciousness.

TABLE 32.3 Causes of Syncope in the Evaluation of Guidelines in Syncope Study 2 Trial

Neurally Mediated	OH	Cardiac Arrhythmia	Structural Cardiopu
• Vasovagal	• Drug induced	• Brady	• AMI
• Carotid sinus	• ANS failure	• Sick sinus	• Aortic stenosis
• Situational	• Primary	• AV block	• HOCM
• Cough	• Secondary	• Tachy	• Pulmonary HTN
• Micturition	• Volume depletion	• VT	• Others
• Defecation		• SVT	
• Swallow		• Inherited	
• Others			
66%	10%	11%	5%

Unknown cause: 2%.

AMI, acute myocardial infarction; ANS, autonomic nervous system; AV, atrioventricular; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension; OH, orthostatic hypotension; SVT, supraventricular tachycardia; TIA, transient ischemic attack; VT, ventricular tachycardia.

Adapted from Brignole M. Diagnosis and treatment of syncope. *Heart*. 2007;93(1):130–136. With permission from BMJ Publishing Group Ltd.

1. **Echocardiography** is recommended when **structural cardiac disease is suspected**. It is useful in diagnosing valve pathology and myocardial processes that may contribute to syncope (i.e., aortic stenosis and cardiac tumors). It has a low diagnostic yield in the absence of clinical, physical, or ECG findings, suggesting a cardiac abnormality.
2. **Stress testing** is recommended in patients with exertional syncope or with presentation suggestive of coronary artery disease. In addition to ischemia assessment, stress test helps in the detection of exertional arrhythmias.

3. **Patients with pacemakers** should undergo **pacemaker interrogation** for possible malfunction (battery depletion, lead malfunction, lead dislodgement, or R-on-T phenomenon).

4. **Tilt table testing** works via orthostatic stress induced by upright position with or without chemical stimulation which provokes a reflex-mediated syncope. Isoproterenol is needed in >50% of cases to trigger the reflex but at the expense of a higher false-positive rate. The following are **indications for tilt testing**:

a. **Single unexplained syncope** at increased risk of traumatic injury or with occupational hazard during subsequent events (e.g., driver, pilot)

b. **Unexplained recurrent syncope in patients with no heart disease or in those with heart disease after ruling out a cardiac cause**

c. Also used to **differentiate vasovagal syncope from OH**

A positive test is defined by hypotension and/or relative or absolute bradycardia. **Bradycardia** (cardioinhibitory response) translates into a **higher risk of subsequent asystolic syncope**. Tilt table testing has a sensitivity of 70% and specificity of 35% to 92% with isoproterenol. **The sensitivity increases with higher angle of tilt and longer duration**. It appears that **tilt table testing, when used in the appropriate setting, is beneficial in diagnosing previously unexplained syncope**.

5. **Electrocardiographic monitoring** encompasses a variety of ECG-monitoring techniques with different recording times. It is indicated when there is **suspicion for arrhythmia-induced syncope.** Guidelines also recognize the **early use of implantable loop recorders (ILRs)** in the workup of **unexplained and recurrent syncope with low risk for cardiovascular events. High-risk patients** can be considered for ECG monitoring **only after a complete comprehensive work fails to reveal a cardiac cause** because a delay in diagnosis could pose harm to the patient. The main goal of this monitoring strategy is to detect a correlation between **symptoms and the arrhythmia**. Yet, certain rhythms are considered **diagnostic even if asymptomatic:**

a. **Asystole** > 3 seconds

b. **SVT** with rate higher than 160 beats/min for 32 or more beats

c. **VT**

d. **Second-degree AV block (type II) or complete AV block, and runs of nonsustained ventricular tachycardia (NSVT)** should be taken seriously

Even a normal cardiac rhythm during a syncopal episode helps exclude an arrhythmia-induced event suggesting a good prognosis. The main disadvantages of monitoring strategies include **delayed diagnosis and variable diagnostic yield based on event frequency.** Therefore, the selection of recording device is based on risk of cardiovascular event and frequency of symptoms.

e. **In-hospital telemetry** is the ECG monitoring of choice in patient with **high risk for major cardiovascular events or sudden death requiring admission.**

f. **Holter monitor** offers generally 24- to 48-hour monitoring with a diagnostic yield for arrhythmia of 24% and correlation of a cardiac arrhythmia with a syncopal spell of 4%. It can be considered **when symptoms occur on a daily basis.**

g. **External loop recorders** are capable of monitoring the heart's electrical activity for up to 4 weeks, thus they are **only indicated if symptoms frequency is greater than monthly**. They continuously record and delete electrical activity in a loop until it is

activated by the patient to record activity during symptoms. When activated by the patient, loop recorders permanently record the previous 5 to 15 minutes of rhythm data. The recorder can capture arrhythmias during a syncopal episode even if the patient activates it after regaining consciousness. Reported diagnostic yield is better than Holter monitoring (50% at 2 weeks and 90% at 4 weeks), but is significantly reduced by operator error.

h. **ILRs** offer a long recording time with battery life up to 3 years. They are **implanted subcutaneously** via a minor surgical procedure. They can be manually or automatically activated with wireless transmission. **Early use of ILR enhances diagnostic yield and time to diagnosis** in an unselected population with **recurrent and unexplained syncopal events** compared with conventional management. Pooled analysis from available studies revealed a **diagnostic yield of 32% at 18 months**. Reports suggest that diagnostic yield **can increase up to 80% with extended monitoring for 2 years**. Early ILR use also **decreases the number of hospitalizations and testing** without impact on mortality. **ILR** allows earlier initiation of ECG-targeted therapy with associated **reduction of syncopal recurrences in selected cases** (e.g., documented asystolic pauses). Nonetheless, no evidence exists to support the use of ILR as a first-line diagnostic tool in all patients with syncope. ILR is recommended during the following scenarios:

1. 1 Recurrent unexplained syncope at low risk for cardiovascular event or sudden death. **In high-risk patients it may be used only after prompt cardiac evaluation failed to reveal the cause of the event.**
2. 2 Patients with **recurrent reflex-mediated syncope** despite appropriate medical management **when identification of underlying mechanism might change management.** (e.g., identification of asystolic pauses)
3. 3 Other suggestions include **differentiation of seizure from syncope** when anticonvulsive therapy failed to control episodes.

i. **Mobile cardiac outpatient telemetry (MCOT)** provides continuous ambulatory ECG monitoring with continuous recording or 24-hour loop memory. MCOT offers live wireless reporting to a center, which is able to record the event and contact the patient and/or physician. Therefore, it provides higher diagnostic yield compared with patient-activated systems.

6. **Signal-averaged electrocardiography (SAECG)** is a collection of 100 to 300 single QRS complexes, which are amplified, filtered for noise, and averaged to determine the presence of late potentials. Late potentials **seem to identify the presence of a reentrant substrate and may indicate an independent risk for the development of future life-threatening ventricular arrhythmias**. SAECG is useful in **predicting inducibility of ventricular arrhythmias by an electrophysiology study (EPS)**, especially in patients with **ischemic heart disease with structurally normal hearts**. SAECG may also be helpful in identifying patients with arrhythmogenic right ventricular dysplasia or infiltrative cardiomyopathies.

a. **A positive SAECG finding suggests the need for further EP testing**, especially in individuals with known heart disease.

b. The **absence of late potentials has a high negative predictive value.**

7. **EPS** in the assessment of syncope is **mainly recommended** in patients with **coronary artery disease and syncope of suspected arrhythmic etiology with**

otherwise no indication for implantable cardiac defibrillator (ICD) implantation. Conversely, EPS is not indicated in patients with a structurally normal heart, normal ECG, and no palpitations preceding the syncope. Sensitivity and specificity of EPS are generally poor. EPS should also be considered in the following scenarios:

a. Uncertainty about the origin of wide QRS tachycardia, including bundle branch blocks after nonrevealing noninvasive cardiac testing

b. Patient with syncope at high risk of cardiovascular event or with occupational implications that could translate into harm if diagnosis is delayed

c. Known or suspected VT, especially to guide therapy

d. NSVT, mild-moderate left ventricular dysfunction, and late potentials on SAECG, used to stratify prognosis and guide therapy

e. Drug-refractory malignant VT in candidates for ablative therapy

Induced arrhythmia during **EPS does not usually produce syncope in the laboratory**; therefore, a cause-and-effect relationship often has to be assumed. **EPS findings** considered diagnostic in the cause of syncope include

f. Sustained monomorphic VT

g. Sinus bradycardia with corrected sinus node recovery time over 525 ms

h. Spontaneous or pacing-induced infranodal block or infrahisian block

i. Baseline His-ventricle (HV) interval >100 ms or significant prolongation after procainamide challenge

j. Paroxysmal SVT with symptomatic hypotension

The limitations and disadvantages of EPS are high cost, invasive nature, lower specificity if a more aggressive electrical stimulation protocol is used, and poor prediction of bradyarrhythmias.

8. **Adenosine triphosphate (ATP) test** has been suggested to aid in the diagnosis of unexplained syncope. Patients are injected with a 20-mg bolus of ATP and are kept in a supine position with continuous electrocardiographic monitoring. Asystole lasting >6 seconds or AV block lasting >10 seconds is considered abnormal. ATP test may be able to diagnose syncope caused by transient AV block. However, it has not been able to reproduce sinus arrest. This test remains in the investigational phase, and outcome data are not yet available.

V.TREATMENT. The treatment of syncope hinges on preventing recurrent episodes, decreasing physical harm from syncopal events, and lowering mortality. Therapy must be individualized to the underlying cause or mechanism.

A. **Reflex-mediated syncope.** The **first step** involves **reassurance about the benign prognosis and patient education to avoid triggers.** It should also include **adjustment of medication regimen** (e.g., chronic vasodilator therapy).

1. **Nonpharmacologic treatment:** may be sufficient for those with infrequent and predictable syncopal episodes

a. **Blood volume expansion (probably helpful). All patients should be counseled to liberalize salt (10 g salt per day) and fluid intake (2 to 3 L/d) unless contraindicated** (e.g., hypertension, heart failure).This increases orthostatic tolerance evidenced in the negativization of previously positive tilt test with intravenous fluid expansion. However, there exists no randomized trial assessing the impact of salt tablets in syncope prevention.

b. **Exercise training (debatable effect)** seems to increase blood pressure and orthostatic tolerance, but a small trial failed to detect reduction in syncopal recurrences.

c. **Tilt training (debatable effect)** exposes patients to progressively longer periods of upright posture in order to condition the neural and vascular systems to counter gravitational stress. In one small study on neutrally mediated syncope, tilt training resolved symptoms in 85% of patients during the period of training. However, four randomized trials reported no reduction in the rate of positive tilt test.

d. **Counterpressure maneuvers (probably helpful)** should be **recommended in all patients with predictable episodes**. They include isometric arm and leg exercises (e.g., crossing leg or hand grip) performed at the first sign of a syncopal episode. They raise peripheral vascular resistance and blood pressure and can prevent the syncopal spell. A recent trial reported a significant risk reduction of 36% in syncope recurrence when these measures were added to conventional therapy.

2. **Medical therapy** is **recommended in patients with frequent and/or unpredictable syncopal episodes as an add-on regimen to lifestyles changes**. The majority of long-term randomized studies have failed to show any benefit from most of the medications. These treatments are generally considered second line in reflex-mediated syncope.

a. **α-Agonists (probably helpful): Guidelines favor use of midodrine as "pill in the pocket" strategy** in anticipation of known syncope triggers over **chronic use**. Few small open label studies have reported that midodrine reduces symptoms and increases likelihood of tilt test negativization. Midodrine may decrease syncope recurrence based on one pediatric open label trial. **Etilefrine consistently provides no** benefit in the prevention of neuromediated syncope.

b. **Fludrocortisone (debatable effect)** in pediatric studies has shown inconsistent benefit with two trials actually reporting harm. **No trial** to date has assessed benefit **in adult** population, but results of Prevention of Syncope Trial (POST) II will further clarify the role of fludrocortisone in adults.

c. **Selective serotonin reuptake inhibitor (SSRI) (probably helpful).** Specifically **paroxetine** showed promising reduction of syncope recurrence in highly symptomatic patients. Results have not been confirmed by other trials. Conversely, fluoxetine provides no benefit compared with propranolol or placebo based on one small study.

d. **β-Blockers (probably unhelpful).** Initial low-quality evidence showed inconsistent benefits, but POST I trial reported that **metoprolol provides no benefit** in the treatment of reflex-mediated syncope at moderate risk of recurrence.

3. **Device therapy** has been extensively studied in reflex-mediated syncope. Asystolic pauses are detected in a significant proportion of neuromediated syncope events, whereas carotid hypersensitivity is known to predict the occurrence of sinus pauses. A recent meta-analysis of randomized double-blind studies revealed **no benefit of pacing in an unselected population with vasovagal syncope.**Nonetheless, International Study on Syncope of Uncertain Etiology 3 trial **reveals that pacing patients with vasovagal syncope with symptomatic asystolic pauses (>3 seconds) or asymptomatic pause (>6 seconds) provides a risk reduction in syncope recurrence (57%)** at 2 years. Similarly, **pacing is thought to be**

helpful for carotid syncope with bradycardia. In this setting, dual-chamber pacing is preferred over single ventricular lead pacing, whereas atrial pacing is not recommended.

B. Orthostatic hypotension. The management of OH benefits from **education and lifestyle changes** as outlined above. Emphasis must be made on **discontinuation of potentially offending drugs, avoidance of sudden changes in position, liberalization of fluid and salt intake, utilization of counterpressure maneuver** if events are predictable, and **use of compression stocking** to prevent orthostatic pooling of venous blood.

1. Contrary to reflex-mediated syncope, **chronic use of midodrine (5 to 20 mg TID) is recommended** in patients with OH that failed nonpharmacologic regimen.
2. Weaker evidence exists on fludrocortisone suggesting a decrease in symptoms and higher blood pressure. Additional treatment includes desmopressin in nocturnal polyuria, octreotide in postprandial hypotension, and erythropoietin in severe anemia.

C. Cardiac syncope. The management of cardiac syncope **starts with the correction of electrolyte abnormalities** (e.g., prolonged QT from hypomagnesaemia or hypocalcaemia). Further therapy depends on the underlying mechanism and/or cause of syncope as follows:

1. **Symptomatic bradyarrhythmias and AV blocks require pacemaker implantation**. Patients with an HV interval of >100 ms are at a high risk for **progression to heart block** and may benefit from a pacemaker. Single- and dual-chamber pacemakers decrease risk of recurrence and sudden death in patients with syncope caused by bradyarrhythmias.
2. **Implantable defibrillators** are the best option for patients with malignant or life-threatening ventricular arrhythmias, sustained monomorphic VT, and/or unexplained syncope in the setting of severe left ventricular dysfunction.
3. **Antiarrhythmic therapy** appears to decrease the frequency of syncope; however, it has not been shown to improve survival.
4. Patients with **left or right heart outflow obstruction**, such as HOCM, should be instructed to **avoid exertional activities** that precipitate syncope and **should be considered for surgical repair**.
5. Coronary revascularization is strongly indicated in **patients with life-threatening arrhythmias (usually polymorphic VT) because of myocardial ischemia**.

VI. PROGNOSIS. Among all syncope cases presenting to ED, only 14% will have nonfatal severe outcome and 0.7% will die within a month. Reflex- and OH-mediated syncope are not associated with increased mortality, but harm may occur in association with a syncopal event. Conversely, **patients with cardiac syncope or unknown etiology have higher rates of mortality and sudden death**. Unexplained syncope has a mortality rate of 6% to 10% over 3 years and 24% over 5 years. Meanwhile, cardiac syncope confers mortality rate of 50% over 5 years and 30% in the first year after diagnosis.

Syncope presents usually as a single event with **only 20% recurring.** The best predictor of recurrence for vasovagal episode is the number of events in the prior year (e.g., 7%, 22%, and 69% for patients with 0, <2, or >6 syncopal episodes, respectively). **Cardiac syncope has a higher risk of recurrence** compared with other syncope etiologies.

VII. POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS). This is a poorly understood syndrome characterized by exaggerated increase in heart rate with tilt and exercise. Patients may also feel fatigue, dyspnea, and lightheadedness on standing,

but do not typically experience OH or syncope. Patients typically present at age 14 to 45 years and it predominantly affects females. They often have multisystem complaints such as fibromyalgia, chronic fatigue syndrome, sleep disorders, and gastrointestinal symptoms.

A. Etiology. POTS is thought to be a syndrome with multiple overlapping etiologies, with each etiology having varying importance in individual patients. There is also suggestion of different genetic forms of the disease.

1. **Partial dysautonomia** refers to autonomic impairment in some parts of the nervous system, with efforts by the still-functioning nervous system to compensate.
2. **Increased sympathetic activity.** Studies have shown that patients with POTS have elevated arterial norepinephrine levels and decreased norepinephrine clearance.
3. **Hypovolemia.** Studies have shown reduced blood volume and reduced erythrocyte volume. The cause of these findings is not clear, but some have postulated problems with the renin–angiotensin–aldosterone axis, possibly because of renal denervation.
4. **Changes in venous function.** Patients with POTS have been shown to have increased venous pooling and a decrease in stroke volume on standing.
5. **Primary baroreflex abnormalities** may also cause the increase in heart rate without change in blood pressure that is seen on standing.

In clinical practice, two main forms of the disease have been identified: the dysautonomic or peripheral form with inability to increase systemic vascular resistance with orthostatic stress and the hyperadrenergic or central form with abnormal biofeedback mechanism above the baroreceptor level.

B. Diagnosis. There are no established criteria for the diagnosis of POTS. The characteristic finding is an **increase in heart rate of >30 beats/min or a rise in heart rate to >120 beats/min in the first 10 minutes of tilt as their diagnostic criterion**. OH does not typically occur. It is important to rule out other conditions, such as autonomic neuropathy, central dysautonomia, dehydration, and medication effects.

C. Treatment. Because of the heterogeneous etiologies of POTS, treatment can be very challenging and often requires multiple attempts with different regimens. There are no large controlled studies of therapy.

1. **Volume expansion** using oral fluid intake, a high salt diet, and fludrocortisone may improve symptoms.
2. **Adreno-receptor agonists** such as midodrine may improve symptoms in patients with mainly peripheral autonomic denervation; studies have shown improvement in heart rate response and symptoms during tilt testing.
3. Patients with **mainly hyperadrenergic symptoms** may see improvement with **β-Blockers**. In one placebo-controlled, randomized crossover study, low-dose propranolol (20 mg) improved tachycardia and reduced symptoms, but high-dose propranolol (80 mg) did not change or worsened symptoms.
4. **Pyridostigmine**, an acetylcholinesterase inhibitor, has been used to attenuate tachycardia.
5. **Other centrally acting drugs**, such as SSRIs, clonidine, methyldopa, and phenobarbital, have been used with some success, but experience with their use is very limited.

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CHAPTER 33

Assessing and Managing Cardiac Risk in Noncardiac Surgical Procedures

Donald Clark III

I. INTRODUCTION

A. Background. The risk of perioperative cardiac events varies considerably depending on the patient's baseline risk and the type of operation. Over the last four decades, much work has been done to improve our understanding of a patient's individual perioperative risk. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force Committee developed practice guidelines aimed at providing an evidence-based approach to perioperative evaluation. These guidelines were most recently updated in 2014.

B. Objective. The purpose of preoperative evaluation is to **assess current medical status and cardiac risks posed by the planned operation** and **recommend strategies that may influence short- and long-term outcomes**.

1. The physician should obtain as much information as possible by means of **history and physical examination**. It is not prudent to order noninvasive tests for every patient. Noninvasive tests are requested only if the results are likely to influence treatment and outcome.
2. **As a general rule, preoperative intervention is rarely needed unless it is indicated in the absence of the proposed surgery.** Patients with clinically stable heart disease may not need extensive preoperative testing.
3. **An emergency procedure** is one in which there is limited time for clinical evaluation prior to surgery because of a life-threatening condition, usually <6 hours. In most cases, proceeding with surgery while optimizing perioperative care is preferred to delaying for additional testing.
4. Communication is vital among primary physicians, consulting physicians, anesthesiologists, and surgeons for short- and long-term care of patients.

II. CLINICAL PRESENTATION

A. History

1. The clinician needs to identify cardiac conditions that place a patient at increased risk. Pertinent symptoms include angina, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, palpitations, and syncope.
2. Attention is directed at serious **comorbid conditions** such as diabetes mellitus, peripheral vascular disease, history of stroke, renal disease, and pulmonary disease.

3. **Functional capacity** is determined on the basis of the patient's ability to perform certain daily tasks (Table 33.1).

B. Physical examination

1. The physical examination includes checking blood pressure in both arms (supine and standing) and evaluation of carotid arterial pulse (character, volume, and upstroke), jugular venous pulsation, cardiac rhythm, heart sounds (murmurs, gallops, or rubs), and extremity pulses.

TABLE 33.1 Estimated Energy Requirements for Various Activities

1–4 METs
Eat, dress, or use the toilet
Walk indoors around the house
Walk on level ground at 2 mph (3.2 km/h)
Do light housework such as washing dishes
4–10 METs
Climb a flight of stairs
Walk on level ground at 4 mph (6.4 km/h)
Run a short distance
Heavy work such as vacuuming or lifting heavy furniture
Play games such as golf or doubles tennis
More than 10 METs
Participate in strenuous activities such as swimming, singles tennis, basketball, or skiing

MET, metabolic equivalent; mph, miles per hour.

2. Lung fields are auscultated, and the abdomen is palpated for a possible aneurysm.

3. **High-risk findings** include severe aortic stenosis murmur, elevated jugular venous pressure, pulmonary edema, or S_3 gallop.

C. Active cardiac conditions warrant intensive evaluation and management before proceeding with elective noncardiac surgery and may result in delay or cancellation of the scheduled surgery. Such conditions include unstable coronary syndromes, decompensated heart failure, high-grade atrioventricular block, symptomatic ventricular arrhythmias, supraventricular arrhythmias with uncontrolled ventricular rate, symptomatic bradycardia, and severe symptomatic valvular heart disease.

III. RISK PREDICTION TOOLS. Cardiac risk is a function of patient characteristics and the proposed operation. Two contemporary risk calculators have been incorporated into the guidelines to estimate perioperative cardiac risk. In addition to informing patient–physician discussion, these risk calculators serve to stratify patients. To simplify risk stratification, current guidelines recommend identifying low- and elevated-risk groups.

Procedures with a risk of major adverse cardiac events ≥1% are considered ***elevated risk***. Further testing is not recommended for patients with low risk of major adverse cardiac events.

A. **Revised Cardiac Risk Index (RCRI)**, developed in 1999 by Lee et al. (1), is well validated, simple, and widely used. It has six predictors of risk for major cardiac complications (Table 33.2). A patient with 0 to 1 risk factors is considered low risk.

B. **American College of Surgeons NSQIP Myocardial Infarction and Cardiac Arrest risk prediction rule**, developed in 2011 by Gupta et al. (2), assesses risk of postoperative myocardial infarction (MI) or cardiac arrest. This tool includes adjusted odds ratios for different surgical sites and was shown to have superior discriminative power to the RCRI, particularly for patients undergoing vascular surgery. The calculator is available online: http://surgicalriskcalculator.com/miorcardiacarrest.

IV. SUPPLEMENTAL PREOPERATIVE EVALUATION

A. **Routine laboratory tests** such as serum creatinine, hemoglobin, platelets, potassium, liver profile, and oxygen saturation are important in determining whether a patient needs special attention. Such patients include those with bleeding risk, renal failure, or liver disease.

B. A 12-lead electrocardiogram **(ECG)** is reasonable for patients with known coronary heart disease, significant arrhythmia, peripheral arterial disease, cerebrovascular disease, or other significant structural heart disease. Routine preoperative resting ECG is not recommended for asymptomatic low-risk patients.

TABLE 33.2 Revised Cardiac Risk Index

Six Independent Predictors of Major Cardiac Complications
High-risk surgery (intrathoracic, intraperitoneal, or suprainguinal vascular procedures)
History of ischemic heart disease (history of MI or a positive exercise stress test, current complaint o use of nitrate therapy, or ECG with pathologic Q waves; do not count prior coronary revascularizati criteria for ischemic heart disease is present)
History of heart failure
History of cerebrovascular disease
Diabetes mellitus requiring insulin therapy
Serum creatinine > 2.0 mg/dL (177 μmol/L)
Rate of Cardiac Death, Nonfatal MI, and Nonfatal Cardiac Arrest according to the Number of Pr
No risk factors: 0.4% (95% CI 0.1%–0.8%)
One risk factor: 1.0% (95% CI 0.5%–1.4%)
Two risk factors: 2.4% (95% CI 1.3%–3.5%)
Three or more risk factors: 5.4% (95% CI 2.8%–7.9%)
Rate of Cardiac Death and Nonfatal MI, Cardiac Arrest or Ventricular Fibrillation, Pulmonary

TABLE 33.2 Revised Cardiac Risk Index

according to the Number of Predictors and the Nonuse or Use of β-Blockers

No risk factors: 0.4%–1.0% vs. < 1% with β-blockers

One to two risk factors: 2.2%–6.6% vs. 0.8%–1.6% with β-blockers

Three or more risk factors: > 9% vs. > 3% with β-blockers

C. CI, confidence interval; ECG, electrocardiogram; MI, myocardial infarction.

D. Adapted with permission from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043–1049.

E. Echocardiography. Echocardiograms can provide information about certain pathologic conditions (left ventricular dysfunction and aortic stenosis) that predispose to increased perioperative cardiac risk. Routine use of echocardiography is not recommended. However, assessment of left ventricular function is reasonable for patients with dyspnea of unknown etiology, physical examination concerning significant valvular disease, or patients with known heart failure and change in clinical status.

V. STEPWISE APPROACH TO PREOPERATIVE CARDIAC ASSESSMENT. The ACC/AHA Task Force developed an **algorithm for preoperative cardiac evaluation** to help physicians systematically identify clinical predictors and determine if noninvasive testing is indicated prior to the noncardiac surgery (Fig. 33.1).

VI. NONINVASIVE CARDIAC STRESS TESTING. There is no evidence that noninvasive diagnostic testing improves surgical outcomes. A patient's baseline functional capacity should guide the decision to pursue additional preoperative stress testing. Overall, **preoperative noninvasive cardiac stress testing should be reserved for patients who are candidates for these tests regardless of the planned surgery**.

The recommendations from the 2014 ACC/AHA guidelines are summarized as follows:

A. Patients with elevated risk and **moderate to good function capacity** (≥4 to 10 metabolic equivalents [METs]) may **proceed to surgery** without further exercise testing (class IIb).

B. Patients with elevated risk and **poor functional capacity** (<4 METs) may reasonably undergo **noninvasive pharmacologic testing if it will change management** (class IIa).

C. Routine noninvasive testing is not recommended in patients who are undergoing low-risk surgery.

The **different modalities for stress testing** are detailed in Section IX.

FIGURE 33.1 A stepwise approach to preoperative cardiac evaluation of a patient undergoing a noncardiac surgery. CPG, clinical practice guideline; GDNT, guideline-directed medical therapy; MACE, major adverse cardiovascular events; METs, metabolic equivalents. (Adapted from Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll*

Cardiol. 2014;64(22):e77–e137. Copyright © 2014 American College of Cardiology Foundation and the American Heart Association, Inc. With permission.)

VII. PREOPERATIVE CORONARY REVASCULARIZATION. There are **no prospective randomized controlled trials (RCTs) supporting "prophylactic" coronary revascularization** prior to noncardiac surgery. The **Coronary Artery Revascularization Prophylaxis trial** randomized 510 patients with established CAD at high risk for perioperative cardiac complications to undergo either revascularization (PCI or CABG) or no revascularization before elective major vascular surgery. There were no differences in perioperative and long-term cardiac outcomes between groups, excluding those with left main disease, LVEF < 20%, and severe aortic stenosis.

A. Indications for revascularization before noncardiac surgery are the same in which revascularization is recommended in the general population:

1. Stable angina with left main disease
2. Stable angina with three-vessel disease (especially with ejection fraction [EF] <50%)
3. Stable angina with two-vessel disease with significant proximal left anterior descending artery stenosis and either EF < 50% or ischemia on noninvasive testing
4. High-risk unstable angina or non–ST-segment elevation MI
5. Acute ST-elevation MI

B. Patients with **asymptomatic ischemia** (based on functional study) do not appear to benefit from preoperative revascularization prior to noncardiac surgery.

C. Routine prophylactic revascularization should not be performed in patients with stable CAD before noncardiac surgery.

D. Small observational studies suggest that patients who undergo **CABG** should wait for at least 4 weeks before proceeding with noncardiac surgery.

VIII. MANAGEMENT OF PATIENTS WITH PRIOR PCI ON DUAL ANTIPLATELET THERAPY (DAPT). The risks of bleeding, ischemic events (i.e., stent thrombosis), and consequences of surgical delay must be considered in patients with prior PCI scheduled to undergo noncardiac surgery. In 2016, the ACC/AHA released a focused update providing recommendations incorporating recent data demonstrating the safety of shorter duration DAPT with newer generation drug-eluting stents. Recommendations for timing of surgery are incorporated into a treatment algorithm outlined in Figure 33.2.

If $P2Y_{12}$ inhibitor therapy needs to be held in patients being treated with DAPT following stent placement, **continuation of aspirin therapy is recommended if possible**. $P2Y_{12}$ inhibitor therapy should be resumed postoperatively as soon as possible. There is **no convincing evidence demonstrating the efficacy of "bridging" therapy** with intravenous antiplatelet or anticoagulant therapy during temporary discontinuation of DAPT.

IX. MANAGEMENT OF SPECIFIC PREOPERATIVE CONDITIONS

A. Valvular heart disease. In general, the indications for evaluation and treatment of valvular heart disease are similar to those in the non-preoperative setting. Symptomatic stenotic lesions are associated with increased perioperative morbidity, whereas symptomatic regurgitant valve diseases can usually be managed medically and with close monitoring perioperatively.

1. **Severe aortic stenosis**, if stable and asymptomatic, can be managed with perioperative hemodynamic monitoring and close attention to avoidance of significant periprocedural hypotension. For symptomatic patients, management options include surgical valve replacement, TAVR, or balloon valvuloplasty as a short-term bridge. The management strategy should be individualized, because there are no data regarding the efficacy and safety of these options for patients undergoing noncardiac surgery.
2. **Mitral stenosis** when asymptomatic is managed medically with heart rate control and hemodynamic monitoring. When mitral stenosis is severe and symptomatic, mitral valvuloplasty or valve replacement is considered before a high-risk operation is performed.
3. For patients with **aortic or mitral regurgitation**, the medical regimen is optimized with diuretics and afterload reduction.
4. Appropriate **prophylaxis for bacterial endocarditis** is administered for patients with valvular disorders according to the guidelines.

Perioperative anticoagulation management for patients with prosthetic heart valves is detailed in Chapter 18.

FIGURE 33.2 Timing of elective noncardiac surgery in patients with coronary stents. BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug eluting stent. (Adapted from Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation.* 2016;134(10):e123–e155.)

B. Arrhythmias. High-risk conduction disorders listed above as active cardiac conditions require further evaluation before proceeding with noncardiac surgery. The following points are important to remember when evaluating arrhythmias in the preoperative setting:

1. Identification of any **underlying cardiac disease, drug toxicity, or metabolic disturbances** that could be the cause of the arrhythmia is very important.
2. Patients with a preoperative history of **atrial fibrillation** who are clinically stable generally do not require special evaluation, other than adjustment of anticoagulation.
3. The indications for antiarrhythmic therapy and cardiac pacing are similar to those in the nonoperative setting.
4. Frequent premature ventricular beats and asymptomatic nonsustained ventricular tachycardia are not associated with increased perioperative cardiac risk.

C. Permanent pacemakers and implantable cardioverter–defibrillators (ICDs). Patients who are completely pacemaker-dependent should have their device checked within 3 to 6 months before surgery. A concern in pacemaker-dependent patients is

the potential for interaction between intraoperative electrocautery and their device. **Electromagnetic interference, usually with monopolar electrocautery, may cause transient inhibition of pacing and/or inappropriate ICD shocks.** These devices should be reprogrammed to an asynchronous mode (VOO or DOO) and tachytherapies inactivated for ICDs. If a device is inactivated during surgery, the patient should remain on a continuous cardiac monitor throughout the procedure with external defibrillator equipment available. It is imperative to ensure that devices are interrogated postoperatively and reprogrammed to the appropriate settings.

D. Cardiomyopathies and pulmonary hypertension. Patients with restrictive cardiomyopathy, hypertrophic obstructive cardiomyopathy, peripartum cardiomyopathy, and pulmonary hypertension represent a high-risk surgical population. Multidisciplinary management including a specialist familiar with these conditions is recommended to optimize management perioperatively.

X.PERIOPERATIVE MEDICAL THERAPY

A. β-Blockers. In 2012, concerns regarding the scientific integrity of work conducted by Poldermans called into question the evidence base for perioperative β-blocker therapy. The revised 2014 ACC/AHA clinical practice guidelines took this into account, excluding data from the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography and PeriOperative ISchemic Evaluation trials in a systemic review, which did not substantially affect the estimates of risk or benefit. Overall, preoperative β-blockers appear to reduce the risk of cardiac events but are consistently associated with bradycardia and stroke. Based on current evidence, the guidelines are summarized as follows:

1. **Patients on chronic β-blocker therapy should be continued on β-blockers perioperatively** (class I).
2. It may be reasonable to begin perioperative β-blockers in patients with intermediate- or high-risk myocardial ischemia on noninvasive stress testing (class IIb).
3. It may be reasonable to begin β-blockers prior to surgery in patients with three or more RCRI risk factors (class IIb).
4. If β-blockers are initiated, it may be reasonable to begin therapy in advance to assess safety, preferably more than one day before surgery (class IIb).
5. **Do not begin β-blocker therapy on the day of surgery** (class III).

B. **α_2-Agonists** are **not recommended** to prevent cardiac events in patients undergoing noncardiac surgery.

C. The role of **calcium channel blockers** is not well defined and requires further research. Calcium channel blockers with negative inotropic effects, including diltiazem and verapamil, should be avoided in patients with depressed EF or clinical heart failure.

D. Statins. Current evidence, limited to small RCTs and observational studies, suggests statin therapy reduces cardiac events in patients undergoing noncardiac surgery. Patients already taking statins should continue therapy at the time of surgery. Guidelines state that it may be reasonable to initiate perioperative therapy in statin-eligible patients undergoing vascular surgery or other high-risk procedures. The timing and duration of perioperative therapy remains unclear.

E. **Aspirin.** In patients without stents, the value of perioperative aspirin is unclear. It may be reasonable to continue aspirin therapy in patients with high-risk CAD or cerebrovascular disease where risks of potential ischemic events outweigh risks of bleeding.

XI. PERIOPERATIVE HEMODYNAMIC MONITORING

A. **Pulmonary artery catheters** are occasionally used in high-risk patients (severe valvular disease, combined shock states, advanced heart failure) who are undergoing procedures associated with significant hemodynamic stress. The ACC/AHA guidelines advise to assess the benefit versus risk when considering the use of pulmonary artery catheters. Catheter-guided volume optimization is not routinely recommended because multicenter randomized trials have not shown an outcome benefit with the use of pulmonary artery catheters.

XII. POSTOPERATIVE MONITORING AND MANAGEMENT OF EVENTS

A. **Postoperative MI.** Perioperative tachycardia, hypertension, bleeding, hypovolemia, vasodilatation, hypoxia, and hypercarbia lead to increased myocardial stress. Myocardial injury, as defined by elevated cardiac troponin, is common following noncardiac surgery and is predictive of increased morbidity and mortality. However, **only a small proportion (<5%) of these events are type 1 MIs** (primary coronary event, such as a plaque rupture or thrombotic occlusion). **The majority of cases are secondary to type 2 MIs** related to myocardial oxygen supply–demand mismatch, of which there is no specific therapy beyond supportive care and risk factor management. Differentiating the two conditions can be difficult in the postoperative setting, particularly when patients are intubated, sedated, and/or receiving pain medication. Nonspecific findings, such as CHF, hypotension, nausea, or ST-segment depression, may be the only clues to myocardial ischemia. Current guidelines only recommend measurement of troponin levels in the presence of **signs or symptoms suggestive of myocardial ischemia or MI**.

B. The management of **postoperative heart failure and pulmonary edema** is similar to that in nonoperative settings. ECG and troponin should be checked to rule out MI.

C. **Arrhythmias.** Perioperative arrhythmias are common, especially among elderly patients and after thoracic surgeries. For patients with arrhythmias, the metabolic profile and medications should be reviewed, and any underlying reversible conditions should be corrected, including hypoxia, fever, bleeding, pain, and infection. β-Blockers and calcium channel blockers can reduce postoperative tachyarrhythmias.

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CHAPTER 34

Hypertensive Crisis

Jeffrey Rossi

I. INTRODUCTION

A. Epidemiology. More than 50 million people in the United States are diagnosed with systemic hypertension, many of whom are inadequately treated. Approximately 1% of those poorly treated progress to a crisis phase, accounting for more than 50% of all cases of hypertensive crisis. Unless promptly recognized and treated, hypertensive crisis can lead to acute central nervous system, renal, and cardiovascular dysfunction, and, possibly, death.

B. Definitions. Hypertensive crisis is defined as having either a **hypertensive emergency or hypertensive urgency**. According to the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, normal blood pressure is defined as a systolic blood pressure <120 mm Hg and a diastolic blood pressure <80 mm Hg. Severe hypertension is defined as a systolic blood pressure >180 mm Hg and/or diastolic blood pressure >120 mm Hg.

1. Hypertensive emergency. Hypertensive emergency is defined as severe hypertension with evidence of acute end-organ damage, which can be manifested by a variety of syndromes (Table 34.1). Severe hypertension in the presence of chronic organ damage without associated acute manifestations does not constitute an emergency. Delineating hypertensive emergency from urgency is important because it implicates the need for immediate parenteral blood pressure lowering therapy in a monitored setting (typically intensive care unit [ICU]) to minimize tissue damage and long-term complications.

2. Hypertensive urgency. Hypertensive urgency, on the other hand, is generally defined as **severe hypertension without acute end-organ damage**. In the absence of symptoms or acute organ dysfunction, severe hypertension can be lowered over a period of days to weeks. Patients can be treated with oral medications and usually managed as outpatients.

3. Pseudoemergencies. Pseudoemergencies are acute rises in blood pressure attributed to **a physiologic trigger, causing a massive sympathetic or catecholamine surge**. These are typically seen as the result of pain, hypoxia, hypercarbia, hypoglycemia, anxiety, or a postictal state.

II. PATHOPHYSIOLOGY

A. Autoregulation. Understanding autoregulation is the cornerstone of managing hypertensive crises safely while minimizing the risk of iatrogenic complications. The kidney, brain, fundi, and heart all possess **autoregulatory mechanisms that maintain blood flow at near-constant levels despite fluctuations in blood pressure**.

There is a range of pressures for which the autoregulatory mechanism functions normally. In **normotensive patients** or in those with adequate hypertension management, this range of mean arterial pressures (MAPs) is approximately between 60 and 120 mm Hg. Loss of autoregulatory control at an MAP of 120 mm Hg in patients without preexisting chronic hypertension explains why a seemingly trivial elevation in blood pressure (160/100 mm Hg) can have severe end-organ damage. Classic examples of this phenomenon occur with acute illnesses such as acute glomerulonephritis, preeclampsia, and cocaine abuse. However, in **chronically hypertensive patients** the autoregulatory range is shifted to the right from arteriolar smooth muscle hypertrophy. This hypertrophy minimizes the transmission of pressure to the capillary bed, allowing tissue tolerance of higher blood pressures, but at the same time places the patient at risk for hypoperfusion if treated to normotensive pressures (Fig. 34.1). **This is the reason that blood pressure should not be reduced too quickly in chronically hypertensive patients because this will result in relative hypotension causing tissue hypoperfusion**. Gradual reduction in blood pressure allows the rightward-shifted autoregulatory curve to normalize as the arteriolar hypertrophy slowly regresses. Treatment must be tempered by the fact that **abrupt overzealous blood pressure reduction may lead to hypoperfusion and ischemia, with potential for irreversible neurologic damage**. Cerebrovascular accidents, blindness, paralysis, coma, myocardial infarction (MI), and death have been reported as consequences of overaggressive blood pressure reduction.

TABLE 34.1 Hypertensive Emergencies

Severe hypertension (>180/120 mm Hg) with any of the following:
Encephalopathy
Acute stroke, intracranial hemorrhage, head trauma
Acute aortic dissection
Pulmonary edema
Myocardial ischemia and/or infarction
After coronary artery bypass surgery
Postoperative bleeding at vascular suture lines
Acute renal failure and/or hematuria and proteinuria
Retinal hemorrhages, exudates, papilledema
Eclampsia

B.

FIGURE 34.1 Autoregulatory cerebral blood flow response to changes in mean arterial pressure. Rightward shift of the autoregulation curve in chronically hypertensive patients. (Adapted from Strandgaard S, Olesen J, Skinhoj, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J.* 1973;1:507–510. With permission from BMJ Publishing Group Ltd.)

C. **Endothelial damage.** The abrupt increase in systemic vascular resistance (SVR) caused by elevated levels of circulating vasoconstrictors (e.g., norepinephrine and angiotensin II) during hypertensive crises leads to **arteriolar fibrinoid necrosis and endothelial damage**. This endothelial damage causes loss of autoregulatory function and the accumulation of necrotic fibrinoid debris that narrows and obliterates the vascular lumen. Target organ dysfunction ensuing from these two processes leads to further release of vasoactive substances, producing a cycle of increasing SVR, elevated systemic blood pressure, vascular injury, and tissue damage.

D. **Manifestations.** The endothelial damage and escape from autoregulatory control during a hypertensive crisis leads to the classic acute end-organ complications. Because the brain is encased in a finite space in the skull, the excess blood flow results in cerebral edema and elevated intracranial pressure (ICP), leading to encephalopathy and seizures. In the kidney, the fibrinoid necrosis and the excess blood flow destroy glomeruli, resulting in proteinuria, hematuria, and acute renal failure. The acute injury to the fundi is manifested by exudates, hemorrhage, papilledema, and potentially blindness. The cardiovascular system can suffer from myocardial ischemia and pulmonary edema from the increased afterload state as well as aortic dissection and hemolysis from the shear stress.

III. ETIOLOGY.

It is estimated that 30% to 40% of patients with a hypertensive crisis have an identifiable underlying cause compared with <5% of those with hypertension who have not had a crisis. **Evaluation for such secondary causes and precipitants is indicated in all patients with a hypertensive crisis**.

A. A common scenario is that of a patient inadequately treated for chronic hypertension or one that is medically nonadherent.

B. Risk factors for progression to hypertensive crisis include male gender, black race, low socioeconomic status, cigarette smoking or other tobacco abuse, and oral contraceptive use. Unlike primary hypertension, the incidence of which increases with age, the peak incidence of hypertensive crisis occurs among people aged 40 to 50 years.

C. Underlying pathologic states that can precipitate hypertensive crises include renal parenchymal disease, renovascular hypertension, collagen vascular disease and scleroderma, pheochromocytoma, vasculitis, preeclampsia, and neurologic disorders (Table 34.2).

D. A number of **medications and illicit drugs** can cause marked elevations in systemic blood pressure. The most common offenders are **cocaine**, oral contraceptives, sympathomimetic agents (e.g., diet pills and amphetamines), cold remedies (especially pseudoephedrine), nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, and monoamine oxidase inhibitors. Withdrawal from medications and illicit drugs can also precipitate severe hypertension. Examples include alcohol, benzodiazepine, and clonidine withdrawal.

IV. CLINICAL PRESENTATION

A. History

1. **Symptoms.** The history should focus on the organs that are known to suffer from end-organ damage: cardiovascular, neurologic, renal, and ocular. Cardiopulmonary symptoms include shortness of breath and chest pain. Neurologic symptoms include headache, confusion, lethargy, altered mental status, nausea, and vomiting. Oliguria and change in urine color to suggest hematuria may be the symptoms volunteered by the

patient if there is renal damage. Blurred vision or change in vision suggests ocular involvement.

2. **Symptom chronology.** Among patients with severe hypertension, symptom chronology and the duration of uncontrolled blood pressure should be elicited, because this will guide the aggressiveness of blood pressure control.

3. **History of hypertension.** Most patients with hypertensive crises have an underlying history of chronic primary hypertension; however, a significant proportion have secondary forms of hypertension. Age of onset of hypertension as well as other potential clues to a secondary form of hypertension should be assessed.

4. **Contributory medication history** may include NSAIDs, oral contraceptives, erythropoietin, psychotropic agents, monoamine oxidase inhibitors, ephedrine, cyclosporine, tacrolimus, over-the-counter cold remedies, and many other medications. Withdrawal from clonidine is always a risk factor for a crisis in hypertensive patients to whom this medication has been previously prescribed. For those on antihypertensive medications, it is crucial to elicit administration history, because a frequent, and potentially catastrophic complication occurs when severe hypotension is induced by initiation of all outpatient medications in a patient with nonadherence.

5. **History of use of recreational drugs** such as **cocaine** and amphetamines, nonprescription stimulants including sympathomimetic weight loss pills, and performance-enhancing substances for athletes is important to elicit.

6. **Smoking history.** Smokers are at increased risk for progression to severe hypertension, perhaps because of endothelial dysfunction and dysfunctional autoregulation.

TABLE 34.2 Conditions That May Precipitate a Hypertensive Crisis

Essential hypertension from undiagnosed or poorly controlled hypertension (most common)
Nonadherence to antihypertensive medication regimen
Renovascular disease
Acute, as well as chronic, renal parenchymal diseases
Acute central nervous system insults (e.g., ischemic stroke and intracranial hemorrhage)
Drug induced (e.g., interactions, idiosyncratic reactions, exaggerated effects, and abrupt withdrawal)
Collagen vascular disease and vasculitis (classically scleroderma)
Preeclampsia
Pheochromocytoma
Obstructive sleep apnea

B. Physical findings

1. **Vital signs.** Blood pressure is measured in both upper and lower extremities to evaluate for stenosis or dissection of the aorta or great vessels. Severe hypertension is confirmed by taking two blood pressure measurements separated by 15 to 30 minutes. **No absolute level of blood pressure differentiates an emergency from an urgency.** ***The distinction is based upon the assessment of acute end-organ damage***.

2. **Optic fundi** are examined for signs of retinopathy, including exudates, hemorrhages, or papilledema.
3. **Neurologic assessment** is performed to assess mental status and neurologic motor deficits. Patients with hypertensive encephalopathy may manifest neurologic signs of confusion or seizure activity.
4. **Cardiovascular and pulmonary systems** are examined for the presence of an S_3, S_4, new murmur, and/or pulmonary edema. Total volume status should be assessed, because certain treatments can cause severe hypotension in the setting of volume depletion and other medications are less effective in the setting of fluid overload.
5. **Vascular system** is examined by palpation of pulses and auscultation for bruits, especially renal bruits.

V.DIAGNOSTIC EVALUATION. If a hypertensive emergency is suspected, appropriate arrangements for ICU admission and parenteral treatment should not be delayed while waiting for the results of further tests. Chest pain, shortness of breath, headache, blurred vision, signs of altered mental status, focal neurologic deficits, retinal exudates and hemorrhages, crackles, an S_3 gallop, and pulse deficits all point toward an emergency. Diagnostic testing can be performed after treatment has been instituted.

A. **Complete blood count and blood smear.** The presence of anemia with schistocytes should raise concerns for hemolysis and microangiopathic hemolytic anemia.

B. **Blood chemistries** to evaluate for renal function and electrolyte levels. Hypokalemia and other electrolyte disturbances may give a clue to a secondary cause of hypertension (e.g., primary hyperaldosteronism and Cushing syndrome).

C. **Urinalysis** to look for proteinuria, hematuria, and casts. **Hematuria** and moderate to severe **proteinuria** are surrogate markers for glomerular damage.

D. **Finger-stick glucose test** should be performed to exclude hypoglycemia as the cause of altered mental status in the setting of suspected hypertensive encephalopathy as well as a cause of pseudoemergency.

E. **Electrocardiogram** to evaluate for myocardial ischemia and chronicity of hypertension with evidence of left ventricular hypertrophy. **Cardiac markers** of ischemia (creatine kinase and troponin) should be checked, but troponin is a very sensitive marker and will commonly be slightly above the upper limit of normal in severely hypertensive patients. This, in isolation, should not be considered acute end-organ damage.

F. **Chest radiograph** assesses heart size, can confirm auscultatory findings of pulmonary edema, and may show a widened mediastinum to suggest an aortic dissection.

G. **Computed tomography and/or magnetic resonance imaging (MRI) of the brain** may be indicated to evaluate neurologic deficits and altered mental status, especially in the setting of suspected primary stroke, hemorrhage, or trauma.

H. A urinary **toxicology screen** should be collected, because cocaine and other illicit drugs frequently cause severe hypertension.

I. Prior to initiating treatment, especially in hypertensive urgencies, obtaining **renin and aldosterone** level measurements as well as serum and urine **metanephrine** samples assists with retrospective analysis for a secondary cause of hypertension. Many of the medications used to treat hypertension (β-blockers, diuretics, and angiotensin-converting enzyme [ACE] inhibitors) confound the interpretation of these tests. This diagnostic

evaluation should never delay treatment of a patient presenting with hypertensive emergency.

J. After appropriate management and resolution of the crisis, workup for common **secondary causes of hypertension should be performed**. Renovascular hypertension is very commonly seen in these patients. In addition, primary hyperaldosteronism, coarctation of the aorta, obstructive sleep apnea, and Cushing syndrome are frequently undiagnosed and should be investigated if the particular patient has suggestive features.

VI. THERAPY.

The presence of **acute or rapidly progressive end-organ damage, and not the absolute blood pressure reading, determines whether the situation is an emergency or an urgency**. This determination dictates the type of treatment (i.e., parenteral or oral) and the setting (i.e., ICU, hospital ward, or outpatient) in which it is implemented. Management of acute hypertensive syndromes should be tailored to each patient and based on the presence, absence, and type of end-organ damage. For example, a blood pressure of 130/90 mm Hg may represent a hypertensive emergency for a patient with an aortic dissection, whereas a blood pressure of 200/120 mm Hg for a patient with asymptomatic chronic hypertension without acute end-organ dysfunction does not necessitate emergent parenteral therapy.

A. Hypertensive emergencies

1. Goals of therapy include immediate but controlled reduction of the MAP. The pharmacologic characteristics and potential toxic side effects of antihypertensive agents must be understood and anticipated.

a. Patients are **treated in an ICU**, where clinical status and vital signs can be constantly monitored with the aid of an intra-arterial line.

b. **Blood pressure is reduced in a controlled and predictable manner**. It is recommended that **blood pressure be reduced initially by no more than 25% of MAP over minutes to hours**. After the first 24 hours, further reductions should occur over days to weeks in order to allow the autoregulatory mechanisms to reset. **Exceptions include aortic dissection, postoperative bleeding, and pulmonary edema, all of which demand more aggressive blood pressure reduction to prevent catastrophic complications**.

2. Medical therapy. A number of parenteral antihypertensive medications are available to manage hypertensive emergencies. Characteristics of an ideal agent include rapid onset and cessation of action, a predictable dose–response curve, and minimal side effects. Table 34.3 lists parenteral antihypertensive agents, dosages, side-effect profiles, and specific indications.

a. **Sodium nitroprusside is the drug of choice** for most hypertensive emergencies. This is due to its favorable hemodynamic profile, rapid onset, and rapid cessation of action. A potent, direct vascular smooth muscle relaxant, nitroprusside decreases afterload and preload by means of dilating arterioles and increasing venous capacitance. Hemodynamic effects include a decrease in MAP, afterload, and preload; renal blood flow and renal function may improve if cardiac output improves. Although the direct cerebral vasodilation by nitroprusside may cause an adverse increase in cerebral perfusion, this is counteracted by a potent effect on MAP. Most patients with a neurologic crisis who need blood pressure control tolerate nitroprusside without a worsening of neurologic status. Unlike intravenous nitroglycerin, nitroprusside does not raise ICP or cause headaches. However, the

theoretical possibility of an increase in cerebral blood flow as well as increased ICP must be kept in mind if there is further clinical deterioration despite a decrease in the MAP when using this agent.

1. **1 Administration.** Sodium nitroprusside must be administered by constant intravenous infusion in an intensive care setting with invasive arterial blood pressure monitoring. It has a very rapid onset of action, and its effect ceases within 1 to 5 minutes of stopping the infusion.
2. **2 Side effects.** Red blood cells and muscle cells metabolize nitroprusside to cyanide, which is converted to thiocyanate in the liver and excreted in the urine. **Thiocyanate levels rise in patients with renal insufficiency, and cyanide accumulates in patients with hepatic disease**. Signs of thiocyanate toxicity include nausea, vomiting, headache, fatigue, delirium, muscle spasms, tinnitus, and seizures. Monitoring for signs and symptoms of toxicity and maintaining thiocyanate levels at <12 mg/dL allow safe use of nitroprusside. Risk factors for cyanide poisoning include treatment time >48 hours, renal insufficiency, and doses greater than 2 µg/kg/min. Severely affected patients can be treated with a sodium thiosulfate infusion. Thiocyanate toxicity is extremely rare in the extensive experience with nitroprusside at our institution.

TABLE 34.3 Parenteral Medications Used to Manage Hypertensive Emergencies

Drug	Dosage	Onset/Duration	Indications	Side
Nitroprusside sodium (Nipride, Nitropress)	Infusion: 0.25–10 µg/kg/min	Immediate/3–5 min	Most emergencies	Nause and
Nitroglycerin (a.k.a. glyceryl trinitrate) (Nitro-Bid)	Infusion: 5–200 µg/min	Immediate/3–5 min	Myocardial ischemia, MI, left ventricular failure	Heada tole
Labetalol (Normodyne, Trandate)	Bolus: 20 mg/5 min until desired effect (max 80 mg) Infusion: 1–2 mg/min	5–10 min/1–8 h	Most emergencies except those complicated by left ventricular failure	Heart
Nicardipine (Cardene)	Infusion: 5–15 mg/h	5–10 min/1–4 h	Most emergencies except those complicated by left ventricular failure	Reflex flus Avoid
Clevidipine (Cleviprex)	Bolus: 1–2 mg/h with potential doubling every 90 s for desired effect	2–4 min/5–15 min	Most emergencies except those complicated by left ventricular failure	Avoid
Phentolamine (Regitine)	Bolus: 5–15 mg IV Infusion: 0.2–5.0 mg/min	1–2 min/3–10 min	Pheochromocytoma crisis Crisis because of catecholamine excess	Tachy
Hydralazine (Apresoline)	Bolus: 10–20 mg IV every 30 min until desired effect	10–20 min/3–8 h	Eclampsia	Marke flus isch

TABLE 34.3 Parenteral Medications Used to Manage Hypertensive Emergencies

	achieved or side effects occur				ele
Enalaprilat (Vasotec IV)	1.25–5 mg every 6 h		15 min/6 h	Scleroderma crisis, left ventricular failure	Marke high hyp
Fenoldopam (Corlopam)	Infusion: 0.1–0.3 µg/kg/min		<5 min/30 min	Most emergencies, renal insufficiency	Tachy Cauti

ICP, intracranial pressure; IV, intravenous; MI, myocardial

arction.

c. **Labetalol** is useful in most hypertensive crises. The main disadvantage is its relatively long duration of action. Labetalol is an α-blocker and nonselective β-blocker. When given through continuous intravenous infusion, the relative β- to α-blocking effect of labetalol is 7:1.

1. **1** The **hemodynamic effects** of labetalol include a decrease in SVR, MAP, and heart rate and a decrease or no change in cardiac output. Cardiac output is often spared because the decrease in stroke volume from the β-blockade is offset by the decrease in afterload from the α-blockade. Labetalol has little direct effect on cerebral vasculature, does not increase ICP, and is **considered by some to be the drug of choice in situations characterized by markedly elevated ICP**. Labetalol begins to lower blood pressure within 5 minutes, and its effects can last 1 to 3 hours after cessation of the infusion.

2. **2 Contraindications.** Labetalol is contraindicated for patients with acutely decompensated heart failure, cardiogenic shock, bradycardia, second- or third-degree heart block, and severe reactive airway disease known to be exacerbated by β-blockers. Labetalol should not be used without prior α-blockade in patients with heightened adrenergic tone including pheochromocytoma and cocaine overdose because inadequately blocked α-activity can increase blood pressure when β-blockade is incomplete.

d. **Nitroglycerin** is an important drug for managing hypertension in the setting of myocardial ischemia, acute MI, and acute cardiogenic pulmonary edema (ACPE). It is primarily a venodilator and has modest effects on afterload at high doses. The decrease in preload and afterload decreases myocardial oxygen demand. Nitroglycerin also dilates the epicardial coronary arteries, inhibits vasospasm, and favorably redistributes blood flow to the endocardium. **Nitroglycerin directly increases cerebral blood flow, raises ICP, and is not used in situations initially characterized by high ICP**. Tachyphylaxis to nitroglycerin is well known, and it is not uncommon for the blood pressure to rebound after prolonged administration. Headache is the most frequent side effect. Tachycardia resulting from reflex sympathetic activation may also occur.

e. **Fenoldopam** is a selective peripheral dopamine-1-receptor agonist approved for the management of severe hypertension. Fenoldopam is an arterial vasodilator with a rapid onset of action and a relatively short half-life when administered intravenously. It may be of particular benefit in patients with renal insufficiency, because it has been shown to improve renal perfusion. Fenoldopam may cause reflex tachycardia, which can be blunted by the concomitant use of a β-blocker. Fenoldopam is contraindicated in patients with glaucoma,

because it can increase intraocular pressure. It is a potent systemic vasodilator and is used primarily by anesthesiologists to control blood pressure intraoperatively.

f. **Nicardipine.** As a dihydropyridine calcium channel blocker, nicardipine inhibits vascular smooth muscle contraction but has little to no activity on the heart's atrioventricular or sinus nodes. It is particularly useful in the setting of postoperative hypertensive crises and neurologic scenarios, because it does not raise ICP and directly reduces cerebral ischemia. It is contraindicated in advanced heart block, acute MI, and renal failure. It is administered via a continuous intravenous infusion. In headtohead comparisons, nifedipine has shown similar safety and efficacy to labetalol, although nifedipine appears to provide more predictable and consistent BP control. **Clevidipine** is a short-acting dihydropyridine calcium channel blocker administered as a continuous infusion that does not cause reflex tachycardia. Its benefit over nicardipine is that the half-life is shorter and thus relative hypotension can be reversed quickly with cessation of the infusion. Clevidipine is contraindicated in patients with disordered lipid metabolism and should be used with caution in combination with propofol because it is administered in a lipid-laden emulsion.

g. **Enalaprilat.** This is a short-acting intravenous ACE inhibitor that lowers blood pressure abruptly. It is not widely used in hypertensive emergencies, because it can precipitate hypotension, particularly in volume-depleted patients or those with renal artery stenosis. ACE inhibitors are first-line therapy for the management of scleroderma renal crisis.

h. **Hydralazine.** Although very commonly administered, the role of intravenous hydralazine in hypertensive emergency should be limited to the treatment of pregnant women with preeclampsia and eclampsia. Hydralazine is a direct arterial vasodilator with no effect on venous capacitance. It crosses the uteroplacental barrier but has minimal effects on the fetus. It is usually administered in intravenous boluses of 10 to 20 mg and has a long duration of action. Hydralazine decreases SVR, induces compensatory tachycardia, and increases ICP. It can exacerbate angina and is **contraindicated in the care of patients with ongoing coronary ischemia, aortic dissection, or increased ICP**.

i. **Clonidine.** Clonidine should be used primarily in cases where the cause of hypertensive emergency is clonidine withdrawal.

B. Oral agents. Once the blood pressure is controlled parenterally, switching to an oral regimen that benefits the patient in the long term, based on their particular comorbidities, is recommended. In chronically hypertensive patients, this usually requires at least two antihypertensive medications. Increasing the dose of existing medications or reinitiating therapy in nonadherent patients is appropriate.

C. Management of specific emergencies

1. **Neurologic emergencies.** Patients with neurologic findings and severe hypertension present a particular challenge. Neurologic emergencies can be the result of a hypertensive emergency that will then be exacerbated by the elevated blood pressure or the result of a primary neurologic insult that causes markedly elevated blood pressures to maintain necessary perfusion. One key differentiating point is that **neurologic alterations caused by severe hypertension are reversed when blood pressure is controlled appropriately**, **whereas primary neurologic disorders typically do not improve with blood pressure control**.

a. **Hypertensive encephalopathy.** This condition occurs when cerebral edema is induced by markedly elevated blood pressures that overwhelm the

autoregulatory capabilities of the brain and is characterized by headache, irritability, and an altered state of consciousness. The treatment of choice is **sodium nitroprusside or labetalol**. Agents that depress the sensorium or increase ICP (i.e., intravenous nitroglycerin) should be avoided. Mental status will classically revert to normal within hours of blood pressure reduction. **If there is no improvement despite an appropriate decrease in blood pressure, the diagnosis must be reconsidered and concern should be for a primary neurologic insult causing secondary hypertension**. During the neurologic workup, an MRI of the brain may reveal white matter edema in the parieto-occipital regions, termed reversible posterior leukoencephalopathy syndrome. Occasionally, hypertensive encephalopathy will manifest as seizures. Along with appropriate blood pressure control, concurrent anticonvulsive therapy to terminate active seizures is appropriate; however, chronic antiepileptic therapy is not necessarily indicated because treatment of the hypertension prevents further events.

b. Ischemic stroke. Although hypertension is a risk factor for ischemic strokes, the management of hypertension in the setting of an acute stroke is controversial. The elevated blood pressure is thought to be protection from hypoperfusion because of vasodilation in the peri-ischemic regions. In general, patients should not be treated unless their blood pressure is >220/120 mm Hg or they have evidence of acute end-organ damage elsewhere (e.g., aortic dissection and myocardial ischemia). In addition, in those that are eligible for thrombolytic therapy, a blood pressure < 185/110 mm Hg is required. The goal reduction is 15% in the first 24 hours. Labetalol is the preferred agent, with calcium channel blockers being acceptable alternatives.

c. Intracranial hemorrhage. Intracerebral hemorrhage and subarachnoid hemorrhage (SAH) are often associated with severe hypertension. Similar to an ischemic stroke, the increased blood pressure is thought to be protective. Because of the blood within the skull, ICP increases. In order to maintain the necessary cerebral perfusion pressure (CPP) of 60 to 80 mm Hg in the setting of elevated ICP, an increase in MAP is necessary (CPP = MAP − ICP). Neurology consultation along with neuroimaging and intracerebral pressure monitoring is frequently used to guide blood pressure management. Nimodipine is considered the standard of care for SAH, because it prevents vasospasm commonly seen in this condition.

2. Cardiovascular emergencies

a. Aortic dissection. As opposed to most other presentations of hypertensive emergency when appropriate care requires that blood pressure be normalized slowly, in the setting of an acute aortic dissection, **blood pressure must be corrected immediately**. Patients with a **type A dissection** have a mortality rate of 1% per hour in the first 48 hours unless medical therapy is instituted rapidly and the patient is referred for **emergency surgical intervention**. In the setting of an uncomplicated **type B dissection, antihypertensive therapy** aimed at reducing vascular resistance and shear force on the vessel wall is the treatment of choice. Aortic dissections require decreased vascular shear force by means of reducing the inotropic state of the heart and the ratio of change in ventricular pressure to the change in time (dP/dt). **This should be accomplished via β-blockade prior to vasodilation** in order to prevent reflex tachycardia and increases in dP/dt. **Aggressive blood pressure reduction** is indicated, even for patients with normal blood pressure, because shear force and afterload must be maximally reduced to prevent extension of the dissection and/or aortic rupture. A systolic blood pressure between 100 and 110 mm Hg (or lower if tolerated) with a heart rate between 50 and 60 beats/min is the goal. Suspect hemopericardium with tamponade or aortic rupture if hypotension

is present prior to initiating therapy. **Sodium nitroprusside with an intravenous β-blocker** (metoprolol) is the treatment of choice at our institution. Continuous infusion with labetalol is sometimes used because of its combined effects on myocardial contractility as well as SVR but the fixed β-blockade to α-blockade ratio makes independent titration of blood pressure and heart rate challenging. Fenoldopam, esmolol, and diltiazem infusions are other options.

b. Acute cardiogenic pulmonary edema. Often termed flash pulmonary edema, **ACPE because of severe hypertension** is best treated with **sodium nitroprusside or nitroglycerin**. Because of the pulmonary edema, a common reflexive action is to administer intravenous loop diuretics; however, this may have deleterious effects downstream. Accepting this seemingly paradoxical statement requires insight into the pathophysiology of pulmonary edema in this particular setting. The patients at risk for ACPE tend to be older in age with long-standing hypertension or diabetes, all of which impair diastolic function. The **acutely** elevated blood pressure results in left ventricular afterload mismatch; left ventricular end-diastolic pressure suddenly rises with concomitant elevation of the pulmonary venous pressure. On the pulmonary capillary level, increased Starling forces cause transcapillary leak and, ultimately, pulmonary edema. If the patient is euvolemic prior to the acute pressure change, then the pulmonary edema is due to maldistribution of the intravascular volume and not due to total body volume overload. Intravenous loop diuretics may have an initial beneficial venodilatory effect, but the subsequent volume depletion can cause future hemodynamic side effects. Thus, **treatment should be aimed at decreasing the acute pressure overload and afterload mismatch**, which will reverse the fluid shift in a time frame similar to the rate of decompensation. If nitroprusside or nitroglycerin infusions are not immediately available in this setting, **nitroglycerin tablets can be given sublingually** with repeated administration until goal blood pressure is achieved. Because the ACPE is often due to rapid onset of pressure overload and not due to chronically elevated blood pressure, normalization of the blood pressure in this hypertensive emergency is well tolerated without ischemic risks. It is not uncommon to see immediate relief of dyspnea and hypoxia in a patient with florid pulmonary edema once the blood pressure is lowered. β-Blockers and calcium channel blockers must be avoided in the decompensated state because the impaired inotropy and chronotropy will exacerbate the already afterload-burdened ventricle.

c. Myocardial ischemia. Preload, afterload, contractility, and heart rate determine myocardial oxygen consumption. Elevated blood pressure, and thus afterload, can induce ischemia from the increased oxygen demand. In addition, the significantly elevated blood pressure can rupture stable coronary plaques, resulting in an MI. Blood pressure reduction with nitroglycerin is the treatment of choice. Nitroprusside is added if further blood pressure reduction is required. Heparin infusion should not be started with uncontrolled systolic blood pressures (190 mm Hg or greater), because the risk of intracerebral bleeding is significant.

d. Postoperative bleeding. Postoperative bleeding from vascular suture lines should be treated with immediate normalization of blood pressure, similar to an aortic dissection. Parenteral treatment with sodium nitroprusside, nicardipine, or labetalol is preferred. **After coronary bypass grafting, nitroglycerin** is considered the initial drug of choice to maximize cardiac perfusion.

3. Pregnancy. In addition to delivery of the fetus and placenta in preeclampsia, **intravenous magnesium** therapy is the treatment of choice to prevent progression to eclampsia. Labetalol or hydralazine, combined with a β-blocker to prevent

reflex tachycardia, can be used safely in pregnancy. ACE inhibitors and angiotensin receptor antagonists are contraindicated. Target blood pressures in pregnancy are 130 to 150 systolic and 80 to 100 diastolic.

4. **Pheochromocytoma.** **Phentolamine** is an intravenous α-adrenergic blocker useful in cases of pheochromocytoma because it is effective in cases of catecholamine excess. β-Blockers should never be used in isolation because they can cause a paradoxical increase in blood pressure because of the effects of unopposed α-receptor stimulation from circulating catecholamines.

D. **Hypertensive urgencies.** Most patients diagnosed with hypertensive urgency actually have chronically severe hypertension and **are not in any immediate danger of progressing to hypertensive emergency**. They are often people with chronic hypertension who are suboptimally treated or nonadherent. As previously mentioned, the key to distinguishing hypertensive emergency from urgency is to assess whether there is evidence of acute end-organ damage.

1. **Goal of therapy**

a. Hypertensive urgencies can often be managed with **oral medication without admission to the hospital**. End-organ damage is not imminent, and blood pressure can be lowered modestly over a period of hours as long as adequate follow-up care is ensured. **The greatest danger lies in overtreating these patients and inciting hypotensive complications**. However, even in the absence of acute end-organ dysfunction, hospital admission should be considered for patients with a diastolic blood pressure >140 mm Hg, those with a high risk of cardiovascular complications (known coronary disease or previous stroke), or those with uncertain outpatient follow-up.

b. Because hypertensive urgencies can have significant morbidity if treated aggressively, lower initial doses of antihypertensive medications are used to treat patients with known cerebrovascular disease or coronary artery disease or who are volume depleted. These patients tend to have exaggerated responses to drug therapy. In addition, they are also especially vulnerable to the effects of hypotension. Monitoring for 4 to 6 hours is necessary to judge treatment effect and to look for complications. Urgent follow-up care is mandatory within 24 to 48 hours. In general, blood pressure should be lowered to <160/<100 without overly rapid correction as noted above. Patient-specific optimal blood pressure goals can then by achieved over the next 2 to 3 months.

2. **Drug therapy.** In adherent patients already prescribed with antihypertensive medications, increasing the dose of a current medication is usually sufficient. If initiation of a new agent is required, the choice should be a medication that benefits the patient in the long term; therefore, underlying comorbidities should be taken into account. The medications commonly used for hypertensive urgencies include captopril, long-acting nifedipine, and oral labetalol.

a. **Captopril.** Considered by some to be the drug of choice, captopril is the **fastest acting oral ACE inhibitor**. At small doses, it rarely causes marked hypotension, although this potential exists in patients who are markedly volume depleted or who have renal artery stenosis. Captopril begins to work within 15 to 30 minutes of ingestion and the duration of activity is 4 to 6 hours. An initial dose of 6.25 mg should be given and if hypotension does not occur within 1 to 2 hours, the patient will tolerate doses of 12.5 to 25 mg three times daily.

b. Nifedipine. ***The short-acting and sublingual forms of nifedipine should not be used, because profound hypotension is easily precipitated***. The long-acting form is a potent antihypertensive medication and should be initiated at 30 mg daily with uptitration as an outpatient. The onset of action is not as quick as labetalol or captopril but the daily dosing is favorable for adherence.

c. Labetalol. A combined α-blocker and β-blocker, labetalol taken orally has a relative β-blocking to α-blocking effect of approximately 3:1. Dosage begins at 100 mg (taken orally twice daily) and is titrated to the desired response. The onset of action is 30 minutes to 2 hours after administration; the duration of action is 8 to 12 hours.

VII. PROGNOSIS. The prognosis of a patient with an untreated hypertensive crisis is poor. Before the introduction of effective antihypertensive agents, 1-year mortality exceeded 80% and 5-year mortality was approximately 99%. In the modern era of effective antihypertensive medications, 10-year survival has improved to 70%. However, patients presenting with hypertensive crises have increased risk for future cardiovascular events despite a lower prevalence of overall cardiac risk factors. Therefore, appropriate recognition of these clinical syndromes coupled with the treatment of blood pressure in a safe and controlled manner is paramount to significantly improve outcomes for these once mortal conditions.

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CHAPTER 35

Cardiac Trauma

Jeffrey Rossi

I. INTRODUCTION.

Trauma represents the leading cause of death in males younger than 40 years in the United States. Cardiothoracic injuries are a primary or contributing factor in up to 75% of all traumatic deaths. Cardiac trauma occurs most commonly in the setting of motor vehicle accidents, interpersonal violence, cardiopulmonary resuscitation (CPR), falls from great heights, as well as sporting and industrial accidents. Cardiac trauma can be easily overlooked in the presence of distracting injuries, because it can occur in the absence of chest pain or visible wounds.

A. Cardiac trauma is divided into blunt trauma (i.e., motor vehicle accidents and falls) and penetrating trauma (i.e., primarily, knife and gunshot wounds).

B. As many as 50% of people with cardiac injuries die in the field, but advances in diagnostic testing and surgical techniques have improved the prognosis of patients who reach emergency centers alive. Definitive management requires rapid mobilization of the surgical team and transport to the operating room.

C. Initial attention is focused on the airway, breathing, and circulation, and the primary survey is performed according to the published Advanced Trauma Life Support guidelines. The cardiac physical examination should assess vital signs, peripheral pulses, murmurs, signs of heart failure, distended neck veins, and the presence of pulsus paradoxus. Routine laboratory evaluation should include cardiac biomarkers, and a portable chest radiograph should be performed rapidly. **Transthoracic echocardiography (TTE) at the bedside is the preferred modality for the initial assessment of cardiac trauma.** Focused Assessment with Sonography for Trauma is a widely applied technique using bedside ultrasound to rapidly assess blunt trauma at multiple body sites, including the heart. An electrocardiogram (ECG) is indicated to evaluate for suspected coronary dissection or traumatic coronary thrombosis. The role for cardiac computerized tomography (CT) using intravenous contrast is expanding, and it remains the diagnostic study of choice to evaluate suspected trauma and/or dissection of the aorta and great vessels, along with transesophageal echocardiography (TEE).

II. BLUNT TRAUMA

A. Blunt cardiac trauma generally occurs in the setting of motor vehicle accidents, but it may also be related to falls, blows from blunt objects, or CPR.

B. Blunt trauma may injure the **pericardium**, **myocardium**, **valves or subvalvular apparatus**, **coronary arteries**, or the **great vessels**. The clinical presentation is generally one of **tamponade** or **hemorrhage**, depending on whether the pericardium is intact.

Although hypotension and tachycardia are seen in both scenarios, tamponade is suggested by elevated neck veins, muffled heart sounds, and pulsus paradoxus and is easily confirmed by a bedside echocardiogram. A new murmur coupled with signs of heart failure should raise clinical suspicion for injury to the valves or subvalvular apparatus.

C. Angiography has traditionally been the criterion standard for diagnosing significant blunt trauma–associated cardiac injury. However, current guidelines recommend initial evaluation with CT scan of the chest with intravenous contrast because of comparable sensitivity and ready availability.

1. **Pericardium.** Increased shear forces during blunt trauma may lead to lacerations or tears in the pericardium. Clinically, the patient may experience pleuritic chest pain, and an ECG may reveal the typical findings of pericarditis. Management is with analgesics. Late cases of constriction occasionally develop after traumatic injury to the pericardium.

2. **Myocardium**

   a. **Myocardial rupture.** The myocardium can be injured by several mechanisms in sudden deceleration injuries. Compression between the sternum and the spinal column, as well as sudden overdistention with blood after abdominal injuries, may lead to myocardial rupture. The thin walls and large diameter of the right atrium predispose it to rupture, and **more than 50% of cases of cardiac rupture involve the right atrium**. The left atrium may be involved in as many as 25% of cases, with the remainder involving the thicker walled right and left ventricles. Most victims die immediately, but some series suggest that survival may approach 50% if patients arrive with intact vital signs. Management requires prompt thoracotomy and definitive surgical repair. Emergency pericardiocentesis is relatively contraindicated, because it can lead to pericardial reaccumulation and arrest, and is generally only considered as a desperate measure in an arresting patient when trained personnel are unavailable to perform a thoracotomy.

   b. **Myocardial contusion.** Blunt chest wall trauma may lead to focal injury and necrosis of cardiac myocytes, known as myocardial contusion. Definitive diagnosis is based on histology, and, therefore, the true incidence and clinical significance of myocardial contusion remain controversial. Patients may complain of precordial pain, but symptoms are usually difficult to interpret in the setting of chest wall trauma and associated injuries. A number of studies have investigated the use of ECG, cardiac enzymes, and TTE in diagnosing myocardial contusion, but none of these tests has been found to be sensitive or specific for the diagnosis. The ECG may be normal or may show nonspecific ST–T wave changes or findings consistent with pericarditis. Elevations in serum troponin levels and creatine kinase–myocardial band (CK-MB) isoenzymes are observed in some patients, but CK-MB may be masked by skeletal muscle CK-MM release, especially when total CK >20,000 U/L. TTE may reveal a small effusion or

focal wall motion abnormalities. Patients with contusion are thought to be at increased risk for arrhythmic death during the recovery period, because the injured, inflamed myocardium behaves much like a scar tissue as a substrate for slowed conduction and unidirectional block in the development of reentry cycles. However, findings on ECG, TTE, or laboratory tests are insensitive in predicting outcomes. From a practical standpoint, the diagnosis of cardiac contusion does not generally alter management, because treatment is mostly supportive care, observation, and analgesia. However, making the diagnosis should alert physicians to the potential for arrhythmias. Most centers perform a baseline ECG and monitor patients with blunt chest wall trauma for at least 12 hours before discharge.

3. **Valvular insufficiency.** Injury to cardiac valves, papillary muscles, or chordae tendineae during blunt cardiac trauma may lead to acute valvular regurgitation. A review of 546 autopsies after blunt trauma suggested that valvular injury may occur in as many as 9% of cases, with a slight increase in frequency in patients with preexisting valvular heart disease. The **aortic valve is most commonly involved**, followed in decreasing frequency by the mitral and tricuspid valves. A new murmur, hypotension, and fulminant pulmonary edema should suggest the diagnosis. The differential diagnosis of a new holosystolic murmur (occasionally with a new right bundle branch block or right-axis deviation on the ECG) should also include a traumatic ventricular septal defect. An emergency transthoracic echocardiogram and rapid transport to the operating room are generally required. Acute tricuspid regurgitation is generally well tolerated with lower extremity edema and fatigue as the presenting symptoms, although it occurs relatively rarely.
4. **Coronary arteries.** Blunt trauma occasionally leads to **thrombosis** or **dissection** of a coronary artery and subsequent myocardial infarction. In general, the prognosis after a traumatic myocardial infarction is better than that of the usual acute coronary syndrome because patients tend to be younger and have less atherosclerotic burden and less comorbidity. Nevertheless, patients with infarctions related to trauma are at risk for all the mechanical complications associated with atherosclerotic disease, such as left ventricular aneurysm or pseudoaneurysm formation, ischemic mitral regurgitation, and ventricular septal defect. In rare cases, blunt trauma contributes to the formation of an arteriovenous fistula between the coronary artery and another structure, such as the coronary sinus, great cardiac vein, right atrium, or right ventricle. Clinically, the patient may have a loud, widely radiating murmur, and ligation of the coronary artery or bypass surgery may be necessary. Multidetector CT has been shown to be helpful in differentiating blunt cardiac injury from acute myocardial infarction, a distinction that is important regarding possible initiation of anticoagulation and need for urgent cardiac catheterization.
5. **Commotio cordis.** Case reports of sudden cardiac death in children and adolescents after relatively low-impact chest wall trauma (most commonly, a baseball or hockey puck striking the chest) have received significant media attention in the past. The mechanism is unclear, but it appears that a blow to the chest during an electrically vulnerable period of cardiac repolarization may induce ventricular tachycardia or ventricular fibrillation. Victims have

been surprisingly refractory to cardiac defibrillation, and few of them survive. Autopsy reports consistently show no evidence of underlying structural heart disease.

6. **Great vessels.** The aorta may also be injured in motor vehicle accidents and falls when sudden deceleration leads to tears or disruption of the vessel. Not surprisingly, most patients with aortic rupture die immediately, but 10% to 20% may reach emergency centers alive if the bleeding is limited by clot or by the pleura. Aortic rupture typically occurs at the proximal portion of the descending aorta, where the aorta is tethered against the spine by intercostal arteries and the ligamentum arteriosum. Patients frequently present with chest or back pain and hypotension, but a high index of suspicion is often needed to make the diagnosis. Increased pulse pressure in the upper extremities and diminished pulse pressure in the lower extremities may be found on examination. The chest radiograph may reveal a widened mediastinum, large left pleural effusion, loss of the aortic knob contour, or deviation of the esophagus to the right. A normal chest radiograph, seen in as many as 25% of patients, does not rule out acute aortic pathology.

   CT scan with intravenous contrast is generally the first-line imaging modality for the diagnosis of ascending aortic dissection and other suspected traumatic injury to the aorta. TEE is also useful and has the advantage that it can be performed rapidly at the bedside in a critically ill patient who is not suitable for transport. TEE requires sedation and may not be feasible in patients with maxillofacial or cervical spine injures. Although TTE cannot be used to exclude the diagnosis of aortic dissection, a limited and focused study can be performed more rapidly at the bedside than any other test, and visualization of a flap in the aortic root or ascending aorta can clinch the diagnosis. Magnetic resonance angiography is an alternative modality, but is not well suited for unstable patients because of the time required to perform the study. Aortography, once the gold standard, is now rarely performed out of concern for procedural complications in the setting of acute aortic injury. Definitive surgical repair is indicated for ascending aortic dissection or traumatic aortic rupture. Recent guidelines suggest a preference toward endovascular repair when institutional expertise and anatomy are suitable. If possible, the timing of surgery should be delayed until adequate resuscitation and heart rate and blood pressure control have been achieved. Given the risk of rupture and exsanguination, aggressive reduction of systolic blood pressure to less than <100 mm Hg is recommended. Heart rate should be maintained at <100 bpm. Patients with persistent hemodynamic instability despite aggressive measures should be taken emergently to the operating room.

III. PENETRATING TRAUMA

A. Gunshot wounds and stabbings are the most common types of penetrating trauma. The prognosis depends entirely on the extent of injury and the number of chambers involved. Overall mortality is estimated at 60% to 93% for gunshot wounds, 22% to 62% for knife injuries, and 25% for bolting instruments (i.e., nail guns). Less frequently, iatrogenic catheter-induced injury can occur in the setting of temporary or permanent pacemaker placement.

B. As with blunt cardiac trauma, the clinical presentation tends to be one of **tamponade** or exsanguinating **hemorrhage**, depending on the integrity of the pericardium. **However, unlike the case of blunt trauma, tamponade carries a favorable prognosis in penetrating trauma.** One series described a survival rate of 73% among patients with penetrating trauma with tamponade versus 11% among those without. Thrombus within the pericardium is thought to stabilize the rapid hemorrhagic shock associated with penetrating

injuries. Pericardial lacerations may also seal spontaneously. Bleeding from the muscular, thicker walled left ventricle is also more likely to be self-limited, whereas injury to the relatively thin right ventricle or right atrium is more likely to be catastrophic and fatal. Knife wounds tend to be smaller and focal, whereas gunshot wounds tend to be larger and extensive and more likely to present with frank hemorrhage.

C. **The right ventricle is the chamber most often involved in penetrating trauma** because of its anterior location in the chest. As described for blunt trauma, penetrating trauma may result in laceration of the pericardium or myocardium, valves, coronary arteries, or the aorta.

D. **Diagnosis.** In an unstable patient, a TTE should be obtained rapidly at the bedside. Although images may be suboptimal, both the sensitivity and the specificity of TTE for identifying cardiac abnormalities in this setting are 85% to 90%. A portable chest radiograph may reveal the presence of a pneumothorax or hemothorax.

E. **Management.** After the diagnosis of penetrating cardiac trauma has been made, the patient should be transported as rapidly as possible to the operating room for definitive surgical repair. The infusion of saline and blood products should be continued as needed. Warming of fluids is often needed to prevent hypothermia associated with massive volume resuscitation. There is no role for serial pericardiocentesis in patients with trauma and pericardial effusion, but emergency pericardiocentesis is occasionally necessary if there are delays in reaching the operating room. Injuries in close proximity to coronary arteries may be repaired using biocompatible glues to avoid vessel injury.

IV. SPECIAL CONSIDERATIONS

A. **Indwelling foreign bodies and missile embolization.** Missile embolization from bullet fragments, air gun pellets, or shrapnel is an extremely rare complication from gunshot wounds or battlefield injuries. Data from the Vietnam conflict suggest that this phenomenon complicates 0.3% to 0.4% of all vascular missile injuries. Clinical suspicion for embolization should be raised in a scenario of multiple penetrating entrance wounds or a single penetrating entrance wound without a corresponding exit wound. The majority of patients with right heart or pulmonary embolization are asymptomatic, but up to 17.4% of patients develop chest pain, dyspnea, or hemoptysis. Up to 4% of patients may exhibit cardiac arrhythmias. Patients with undiagnosed indwelling foreign bodies may also develop subacute bacterial endocarditis as a latent presentation. Metallic missile fragments are usually radiopaque and detected on plain x-rays or a noncontrast CT scan. Intracardiac indwelling foreign bodies should be evaluated by TEE, especially when endocarditis is suspected. Ultimately, the decision to remove asymptomatic indwelling foreign bodies is made on a case-by-case clinical basis considering operative logistics and weighing the risk against the potential benefit.

B. **Device implants.** An awareness of device-related complications in the setting of cardiac trauma is important, given the expanding patient population with pacemakers and/or implantable defibrillators. Common complications in the setting of blunt trauma would include pocket hematoma, lead dislodgement, or fracture. Penetrating trauma could expose the generator and/or tunneled leads and lead to bleeding or secondary infection. Lead perforation is an uncommon but life-threatening complication manifested as tamponade. Hypotension and bradycardia should prompt concern for lead fracture or dislodgement, especially if the patient is known to be pacemaker dependent. Emergent transcutaneous or

transvenous pacing is indicated if the underlying bradyarrhythmia is not hemodynamically tolerated. Device interrogation can also be performed at the bedside to assess pacer dependence and the functional status of all leads using computer equipment provided by the major manufacturers.

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CHAPTER 36

Cardiovascular Manifestations of Systemic Disease

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I. INTRODUCTION. Several systemic diseases involve the cardiovascular system, with important therapeutic and prognostic implications. It is vital for cardiologists to recognize, manage, and prevent cardiovascular involvement in various systemic diseases. This chapter reviews the cardiovascular manifestations of various systemic disorders.

II. RHEUMATOLOGIC DISORDERS

A. Rheumatoid arthritis (RA) is one of the commonest forms of chronic inflammatory polyarthritis resulting in joint destruction and deformation. It affects 1% to 3% of the population and is more common in women. The most common cardiovascular manifestations of RA are as follows:

1. **Pericarditis** can present in nearly 50% of patients with RA. It can vary from acute pericarditis and chronic asymptomatic effusive pericarditis to cardiac tamponade or chronic constrictive pericarditis, with significant hemodynamic consequences. Most cases with uncomplicated acute pericarditis will respond to nonsteroidal anti-inflammatory drugs (NSAIDs). Corticosteroid therapy may be needed for patients with severe pericarditis.
2. **Coronary artery disease (CAD).** Cardiovascular disease is the leading cause of death in patients with RA because of accelerated atherosclerosis, likely a result of chronic systemic inflammation and use of corticosteroids. After controlling for traditional risk factors of atherosclerosis, patients with RA have been shown to have two to three times greater risk of CAD compared with controls. In the large prospective Nurses' Health Study, women with RA were found to have a twofold higher risk of myocardial infarction compared with controls. In a more recent study, ischemic heart disease was found in 16.6% of RA patients compared with 12.8% of controls. In addition to disease-modifying drugs to reduce systemic inflammation, aggressive lifestyle modification, including tight control of blood pressure and low-density lipoprotein cholesterol, is warranted.
3. **Cardiomyopathy.** RA can cause granulomatous inflammation of the myocardium leading to cardiomyopathy or involve the conduction system resulting in varying degrees of heart block. Rarely, secondary amyloidosis can occur in RA, leading to an infiltrative cardiomyopathy.

4. **Valvular disease.** A small proportion of patients with RA can have valvular involvement in the form of rheumatoid nodules; however, clinically significant valve disease is very rare.

B. Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that occurs more commonly in women and is characterized by a wide range of organ involvement, including arthritis, dermatitis, glomerulonephritis, serositis, and hematologic abnormalities. Drug-induced lupus can occur with various cardiac medications, including procainamide, quinidine, and hydralazine, and this is associated with the development of antihistone antibodies. SLE can affect the cardiovascular system in various ways:

1. **Valvular disease** is the most common type of cardiac involvement in SLE. The characteristic valvular lesions in SLE are nonmobile, noninfectious vegetations on the atrial aspect of the mitral valve or the arterial aspect of the aortic valve, referred to as Libman–Sacks endocarditis (Fig. 36.1). Studies have shown that valvular involvement is very common in SLE and occurs in >50% of patients. The most common valvular abnormality is valvular thickening, followed by vegetations and valvular regurgitation or stenosis. Serial echocardiography should be performed to monitor for progression of valve disease. The vegetations can embolize and cause stroke or myocardial infarction in rare cases (Fig. 36.1).
2. **Pericarditis** is very common in SLE and has been shown to occur in >50% to 60% of patients. Associated pericardial effusion is usually exudative, with elevated protein and low glucose concentration, and infection must be ruled out in the setting of concomitant immunosuppressive therapy. Cardiac tamponade and chronic constrictive pericarditis can also occur. NSAIDs can be tried first in mild cases of pericarditis. Colchicine can be tried alongside NSAIDs. Systemic steroids can be considered in patients that are not responsive to NSAIDs and colchicine.
3. **Coronary artery disease.** Premature coronary atherosclerosis has been shown to occur commonly in patients with SLE compared with age-matched controls. CAD can also manifest as coronary arteritis, thrombosis in the presence of antiphospholipid antibody (APLA) syndrome (see Section II.C), or, rarely, embolism from Libman–Sacks endocarditis.
4. **Myocardial dysfunction** in patients with SLE can result from ischemia, valve disease, or long-standing hypertension. Patients with peripheral skeletal myositis have an increased risk of lupus myocarditis.
5. **Conduction system disease** with complete heart block can occur in infants born to mothers with SLE, particularly those with anti-Ro and anti-La antibodies. Women with SLE contemplating pregnancy should undergo screening for these antibodies prior to pregnancy and, if present, should undergo fetal echocardiography to screen for conduction abnormalities and myocardial dysfunction. There is some evidence suggesting a role for intrauterine dexamethasone in reversing fetal myocarditis and slowing conduction disease.

C. Antiphospholipid antibody syndrome is characterized by the presence of antiphospholipid antibodies or lupus anticoagulant, recurrent venous or arterial thrombosis, and miscarriages. APLAs can occur independently, referred to as primary APLAs, or can be associated with other autoimmune diseases such as SLE (10% to 30%) and are then referred to as secondary APLAs. Valvular disease is common in APLAs and is characterized by noninfectious vegetations similar to those seen in SLE (Libman–Sacks endocarditis).

Management of arterial or venous thrombosis or significant valvular vegetations includes anticoagulation therapy with warfarin. Monitoring anticoagulant effect while on heparin or warfarin may be difficult, because these patients can have prolonged partial thromboplastin time or international normalized ratio at baseline, in which case monitoring of anticoagulant effect can be done using activity levels of factors II and X.

FIGURE 36.1 Transesophageal echocardiogram demonstrating vegetations (Libman–Sacks endocarditis) on the atrial aspect of anterior and posterior mitral valve leaflets in a patient with systemic lupus erythematosus. **A:** Zoom view of the valve leaflets. **B:** A less detailed image of the leaflets. LA, left atrium; LV, left ventricle.

D. Scleroderma or systemic sclerosis is a rare autoimmune disorder, characterized by vasospasm, microvascular occlusion, and fibrosis of skin and multiple organs. Cardiovascular involvement can occur in progressive as well as limited scleroderma.

1. **Pericardial disease** in the form of fibrinous pericarditis is present in over 70% of patients on autopsy studies, although it is clinically manifest as symptomatic pericarditis in only about 15% to 30% of patients. Small pericardial effusions can be detected in about 40% of patients by echocardiography, but are rarely significant. Acute pericarditis may be treated with NSAIDs, with close monitoring of renal function. Corticosteroids carry the risk of inducing scleroderma renal crisis.
2. **Pulmonary hypertension (PH)** is responsible for significant morbidity and mortality in patients with scleroderma and is more common in the limited type. Autopsy studies have shown histopathologic changes consistent with PH in 65% to 80% of patients with scleroderma; however, <10% of patients manifest PH clinically. Patients with scleroderma and PH appear to have a worse prognosis compared with those with primary PH, with a 2-year survival of <50%. Drugs for PH, such as prostacyclins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan and ambrisentan), and phosphodiesterase inhibitors (sildenafil and tadalafil), have been studied in patients with scleroderma and PH. Combination therapies including the use of warfarin may improve survival in patients with PH from systemic sclerosis. Echocardiography should be used to screen for asymptomatic PH.
3. **Myocardial involvement** with patchy fibrosis can occur in patients with scleroderma. Epicardial coronary arteries are usually normal on angiography; however, ischemia can occur secondary to microvascular vasospasm. Diastolic dysfunction has been commonly found in these patients. Electrical abnormalities such as frequent ectopy, supraventricular arrhythmias, and nonsustained ventricular tachycardia (VT) can occur in patients with progressive systemic sclerosis. The risk of sudden cardiac death is higher in those with a history of syncope.

E. Seronegative spondyloarthropathies include HLA-B27 antigen–associated arthropathies such as ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease–associated arthritis. These disorders occur more commonly in males. Proximal aortitis with or without aortic regurgitation and conduction disturbances are most commonly associated with ankylosing spondylitis and reactive arthritis. Proximal aortitis can lead to thickening, stiffness, and dilatation of the aortic root with aortic regurgitation. Aortic or mitral valve thickening with nodularities of the aortic cusps and thickening of the anterior mitral valve leaflet resulting in a characteristic subaortic bump are

commonly observed valvular abnormalities in patients with ankylosing spondylitis. Extension of the subaortic inflammation and fibrotic process into the basal septum can result in conduction abnormalities such as heart block, which is usually at the level of the atrioventricular (AV) node. Other less common cardiac abnormalities include pericarditis, diastolic dysfunction, and supraventricular arrhythmias.

F. **Dermatomyositis (DM) and polymyositis (PM)** are idiopathic inflammatory myopathies characterized by proximal skeletal muscle weakness and elevated levels of muscle enzymes, such as creatine kinase and aldolase. Cardiovascular manifestations of DM and PM include pericarditis, conduction abnormalities, and congestive heart failure secondary to myocarditis that can be focal or generalized and may be steroid responsive. Cardiac magnetic resonance imaging (MRI) with delayed gadolinium enhancement may be useful in monitoring response to therapy. Coronary vasculitis is a rare manifestation. Management of DM and PM includes corticosteroids, and adjunctive therapies include methotrexate, azathioprine, and intravenous immunoglobulin (IVIg).

III.SYSTEMIC VASCULITIDES

A. **Giant cell arteritis (GCA)**, also referred to as temporal arteritis, is the most common vasculitis in patients older than 50 years. It is more prevalent in women compared with men and in those of Northern European descent. GCA usually affects the extracranial branches of the aorta, sparing the intracranial vessels. Transmural inflammation of the vessels is followed by intimal hyperplasia, luminal occlusion, and end-organ ischemia. Branches of the external and internal carotid arteries are particularly susceptible, and the typical clinical presentation of GCA includes new-onset headache, scalp and temporal artery tenderness, jaw pain, acute visual loss, and polymyalgia rheumatica. Concomitant elevation in erythrocyte sedimentation rate (ESR) is almost always present. Temporal artery biopsy is the gold standard for diagnosis and shows transmural chronic granulomatous inflammation with destruction of elastic laminae. Treatment with corticosteroids should be initiated as soon as possible, without waiting for temporal artery biopsy. GCA is associated with thoracic and abdominal aortic aneurysms. According to one study, patients with GCA are 17 times more likely to develop thoracic aortic aneurysm and 2.4 times more likely to develop abdominal aortic aneurysm compared with age-matched controls. Rare cardiovascular manifestations include pericarditis, myocarditis, and coronary vasculitis. Studies have shown that MRI or fluorine-18-deoxyglucose positron emission tomography (FDG PET) can be useful for the detection of large vessel vasculitis. Transthoracic echocardiography and abdominal ultrasonography are useful in screening for thoracic and abdominal aortic aneurysms. Low-dose aspirin should be added to corticosteroids, because it has been shown to reduce the rate of blindness and stroke in patients with GCA.

B. **Takayasu arteritis (TA)** is also a large vessel vasculitis like GCA, but it occurs in young women, particularly of Indian, Japanese, and African-American descent. It typically affects the aorta and its major branches (Fig. 33.2). In TA, arterial stenoses are more common than aneurysms. Clinically, TA is characterized by claudication (upper extremities more common compared with lower extremities), “pulselessness” or asymmetric pulses, and blood pressure. Systemic symptoms such as fever, malaise, arthralgias, myalgias, night sweats, and elevated ESR may indicate active disease. Renal artery stenosis can be associated with hypertension. Cardiac manifestations include aortic regurgitation secondary to aortic root dilatation and rarely coronary arteritis. Diagnosis is based on

imaging studies that show vascular involvement typical of TA. Imaging modalities such as MRI and PET enable visualization of inflammation in the vessel wall. Therapeutic strategies include corticosteroids, immunosuppressants such as cyclophosphamide or methotrexate in steroid-resistant cases, and anatomic correction using an endovascular or surgical approach when feasible.

FIGURE 36.2 Magnetic resonance angiogram in a patient with Takayasu arteritis demonstrating severe diffuse narrowing of both common carotid arteries and severe disease in the left subclavian artery (arrows).

C. **Kawasaki disease** is an acute febrile illness that affects children, usually below the age of 5 years, with the highest incidence in those of Asian descent. Cardiovascular manifestations include pericarditis, myocarditis, aortitis, aortic regurgitation, and arrhythmias. Coronary vasculitis can occur, which if left untreated can lead to coronary aneurysm formation in about 4 weeks. Aneurysms larger than 8 mm are referred to as giant aneurysms, and these can thrombose acutely, leading to myocardial infarction as well as sudden death. Treatment with aspirin and single-dose IVIg (dose 2 g/kg) reduces the formation and progression of coronary aneurysms. Recommendations by the American Heart Association include long-term follow-up and consideration of anticoagulation for children with multiple giant coronary aneurysms or known obstructive lesions, chronic low-dose aspirin therapy, and coronary artery bypass or percutaneous intervention if lesions are severe and symptomatic.

D. **Idiopathic aortitis** is commonly associated with disorders such as TA and GCA in addition to rheumatologic diseases such as SLE, Behçet disease, seronegative spondyloarthropathies, antineutrophil cytoplasmic antibody–associated vasculitides, Cogan syndrome, and sarcoidosis. Although most cases of aortitis are noninfectious in etiology, infectious causative agents such as staphylococcus, streptococcus, salmonella, and syphilis must be considered. Aortitis can be diagnosed for the first time in surgically excised specimens after aortic surgery. In a 20-year review of over 1,200 aortic surgical specimens at Cleveland Clinic, 52 (4.3%) were clinically and pathologically classified as idiopathic aortitis. Of these, 67% were women. In 96% of cases with idiopathic aortitis and aneurysm formation, aortitis was limited to the thoracic aorta. In 96% of cases, signs of systemic illness were not present at the time of aortic surgery. In 31% (16 of 52), aortitis was associated with a remote history of vasculitis and a variety of other systemic disorders such as GCA, TA, SLE, and Wegener's granulomatosis. Over a mean follow-up of 41 months, new aneurysms were found in 6 of 25 patients not treated with corticosteroids. It is prudent to follow these patients with serial imaging to identify new aneurysms. Treatment with corticosteroids requires evidence of an ongoing systemic inflammatory disease.

E. **Churg–Strauss syndrome (CSS)** is a rare small vessel vasculitis characterized by asthma, peripheral eosinophilia, pulmonary infiltrates, and varying degrees of cutaneous, renal, neurologic, and cardiac involvement. Cardiovascular manifestations are common in CSS and are responsible for significant morbidity and mortality in these patients. The most common cause of death is congestive heart failure secondary to cardiomyopathy, the cause of which may be small vessel vasculitis or eosinophilic infiltration of the myocardium followed by fibrosis or a combination of both pathologic processes. Other cardiac

manifestations include myocarditis and pericarditis with or without pericardial effusion. Therapy mainly includes corticosteroids but other immunosuppressants may be needed.

F. **Polyarteritis nodosa** is a rare nongranulomatous disease affecting medium-sized arteries that leads to weakening of the vessel wall secondary to necrotizing changes with aneurysm formation or intimal proliferation and stenosis. Cardiac manifestations include angina, myocardial infarction, congestive heart failure, and arrhythmias such as supraventricular tachycardia. Treatment is similar to CSS and primarily includes corticosteroids.

IV.CONNECTIVE TISSUE DISEASES

A. **Marfan syndrome** was first described over 100 years ago by Antoine-Bernard Marfan, a French pediatrician. It is an autosomal dominant connective tissue disease secondary to mutations in the fibrillin-1 gene (*FBN1*) that encodes major constituent proteins of microfibrils, which form a significant component of the extracellular matrix. It is a common heritable condition with an estimated prevalence of 1 per 3,000 to 5,000 individuals. About 25% cases have no family history and are a result of de novo mutations. However, genetic evaluation of first-degree relatives is recommended in all instances. The diagnosis of Marfan syndrome is based on the Ghent criteria, based on the consensus by an international expert panel, which have been revised recently with more weight on cardiovascular manifestations. In the absence of family history, the presence of aortic root aneurysm or aortic dissection and ectopia lentis establishes the diagnosis of Marfan syndrome. In the absence of either of these two, the presence of *FBN1* gene mutation or a combination of systemic manifestations listed above is required. Cardiovascular manifestations of the Marfan syndrome are as follows:

1. **Aortic aneurysm and dissection.** Defect in microfibrils results in degeneration of elastic fibers in the aortic media (sometimes inappropriately referred to as "cystic medial necrosis"), with the resultant aortic aneurysm formation. This typically occurs at the level of the aortic root and involves the sinuses of Valsalva. The aortic root diameter should be serially monitored with echocardiography or computed tomography/MRI. According to the current guidelines, annual imaging is recommended if stability in aortic root size is documented. If the baseline aortic diameter is >4.5 cm or if there is significant growth from baseline, more frequent imaging should be considered. **Elective surgical repair** should be considered if the maximal cross-sectional area in square centimeters of the ascending aorta or root divided by the patient's height in meters exceeds a ratio of 10, because shorter patients have dissection at a small size and 15% of patients with Marfan syndrome have dissection at an aorta size smaller than 5.0 cm. This threshold is smaller than for other disorders with aortic aneurysm, given the greater tendency for aortic dissection at smaller diameters in patients with Marfan syndrome. Indications for earlier repair at sizes <5.0 cm include rapid growth defined as >0.5 cm/y, family history of aortic dissection at a diameter <5.0 cm, the presence of significant aortic regurgitation, or in female patients contemplating pregnancy with an ascending aortic diameter >4.0 cm. If the aortic root is <4 cm, then the risk of dissection is considered low, and pregnancy can be allowed with β-blocker therapy and careful monitoring with serial echocardiography throughout pregnancy. Aortic regurgitation usually occurs secondary to aortic root dilatation. Aortic dissection in Marfan syndrome is usually type A, that is, starts in the ascending aorta and can extend to a variable degree distally. About 10% of dissections in Marfan syndrome begin distal to the origin of the left subclavian artery (type B).

Type A dissection necessitates immediate repair, given the high risk of life-threatening complications if not treated promptly. Medical management in patients with Marfan syndrome includes **β-Blockers**, which have been shown to reduce the risk of aortic dilatation and aortic dissection. The beneficial effect of β-blockers is largely due to the reduction in heart rate and the rate of pressure increase in the aorta, which leads to less stress on the aortic wall. **Angiotensin receptor blockade** with losartan has been shown to slow the rate of aortic root dilatation in animal models of Marfan syndrome, secondary to mitigation of excessive transforming growth factor β-signaling. However, the evidence for its use in humans is less compelling although a trial of its use in children with Marfan syndrome suggested efficacy similar to β-blockade in reducing aortic dilatation. Certainly, it seems appropriate to consider its use in Marfan patients with adequate blood pressure on β-blockade. **Calcium blockers** have been associated with higher risk of dissection and should be avoided. Because of the risk of acute aortic dissection, patients with Marfan syndrome should be counseled to avoid isometric exercise, including heavy weight lifting, contact sports, and competitive athletics.

2. **Mitral valve prolapse** commonly occurs in patients with Marfan syndrome and is more common in women. The incidence is as high as 60% to 80%, and progressive mitral regurgitation occurs in about 25% of patients. The valve leaflets are usually thickened and redundant, and occasionally ruptured chordae or prolapse may be present. Progressive untreated mitral regurgitation can lead to left ventricular dilatation, congestive heart failure, and PH. Tricuspid valve prolapse can occur concomitantly. Standard management for chronic severe mitral regurgitation is indicated in symptomatic patients, with repair of the mitral apparatus if possible, but replacement may be necessary when the leaflets are very redundant or there is severe annular calcification or chordal damage.
3. **Dilated cardiomyopathy** independent of, or out of proportion to, valvular abnormalities can occur in patients with Marfan syndrome. This has been hypothesized to be secondary to a potential role of fibrillin mutations in the reduction of myocardial function.
4. **Arrhythmias**, both supraventricular and ventricular, can occur in patients with Marfan syndrome.

B. Loeys–Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with similarities to the Marfan syndrome but with important genotypic and phenotypic differences. It is caused by mutations in the genes encoding transforming growth factor β receptors 1 and 2 (*TGFBR1* and *TGFB2*). Type I LDS is characterized by arterial tortuosity and aneurysms, most often in the aortic root but can involve other arteries, hypertelorism (widely spaced eyes), and bifid uvula or cleft palate or both. Patients are predisposed to more **aggressive and widespread vascular disease**, including aneurysm formation and dissection, compared with Marfan syndrome, with a mean age of death of 26 years. Patients with LDS can develop aortic dissection at aortic diameters <5 cm; hence, **elective repair is recommended at much smaller aortic root dimensions (4.2 cm) compared with Marfan syndrome**. Surgical repair has not been associated with tissue fragility in patients with LDS. More than 50% of patients with LDS can develop aneurysms of other vessels; hence, yearly surveillance imaging of the entire vascular tree has been recommended.

C. Ehlers–Danlos syndrome, type IV or vascular form, is a rare autosomal dominant disorder associated with mutations in the gene for type III procollagen (*COL3A1*).

Arterial rupture or dissections are the major causes of mortality in these patients and can occur in the thoracic or abdominal vessels, including aortic rupture or dissection. The median age of survival was about 48 years in a study of 220 patients with this disorder. In the same study, 25% of patients had a medical or surgical complication by the age of 25 years and >80% had such complications by the age of 40 years. In contrast to LDS, tissues are friable in Ehlers–Danlos syndrome, and surgical repair after ruptured aneurysm or dissection can be complicated by hemorrhage or poor wound healing. The role of prophylactic surgical repair for unruptured aneurysms is unclear. Pregnant women have a 50% chance of transmitting the disorder to the child and about 11.5% risk of mortality. Pregnancy should be considered high risk, and women should be counseled against it.

V.OTHER SYSTEMIC DISEASES

A. Sarcoidosis is an idiopathic systemic granulomatous inflammatory disease affecting mainly the lungs, but can involve the lymph nodes, skin, eyes, heart, kidneys, musculoskeletal system, nervous system, and endocrine system. **Cardiac involvement is found in 25% of patients with sarcoidosis on autopsy, but only 5% of patients have clinically apparent cardiac involvement**. The most common sites of cardiac involvement are the basal interventricular septum, AV node and the His bundle, focal regions in the ventricular free walls, and the papillary muscles. Cardiovascular manifestations of sarcoidosis are as follows:

1. **Arrhythmias** can vary from conduction disturbances, including heart block to fatal ventricular arrhythmias. Complete heart block is the most common abnormality in patients with clinically evident sarcoidosis and is found in 20% to 30% of patients. First-degree heart block and bundle branch blocks are also seen. Granulomatous infiltration of the ventricular myocardium can set up foci of automaticity, leading to ventricular arrhythmias. VT is the most common arrhythmia and is reported in about 20% of patients with sarcoidosis. Sudden cardiac death caused by an arrhythmia is one of the leading causes of death (>60%) in patients with sarcoidosis.
2. **Congestive heart failure** may occur secondary to widespread infiltration of the myocardium. It may also occur because of arrhythmias, cor pulmonale from long-standing PH, valvular abnormalities, or a combination of these abnormalities. Progressive congestive heart failure is the second most common cause of death in patients with sarcoidosis.
3. **Pericardial** involvement can manifest as pericarditis, pericardial effusion, and constrictive pericarditis.

Diagnosis of cardiac sarcoidosis may be difficult. Endomyocardial biopsy with finding of noncaseating granulomas has high specificity, but poor sensitivity owing to the patchy nature of myocardial involvement particularly in the basal septum, whereas the location of biopsy is often the apical septum. Electrocardiogram often reveals conduction abnormalities but has poor sensitivity. Echocardiographic findings include increased ventricular septal thickness (secondary to granulomatous expansion) or wall thinning (because of fibrosis), aneurysms, regional wall motion abnormalities, and eventually ventricular dilatation. Contrast-enhanced MRI and 18-FDG PET are more sensitive modalities for detecting early cardiac involvement, and findings correlate with disease severity. These imaging modalities can be used in evaluating response to therapy. Corticosteroid therapy can halt cardiac disease progression and improve survival; however, it does not prevent sudden cardiac death. Pacemaker implantation

is often necessary in cases of symptomatic heart block or asymptomatic high-grade conduction disease. Implantable cardioverter defibrillator implantation is recommended for primary prevention in patients with cardiac sarcoidosis at risk for sudden cardiac death, such as those with a history of nonsustained VT or low ejection fraction. Cardiac transplantation for cardiac sarcoidosis is rarely used, because the disease can recur in the transplanted heart. However, it may be considered in young patients with severe end-stage heart failure or resistant VT.

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CHAPTER 37

Pericardial Disease

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I. INTRODUCTION. The pericardium is a double-layered, flask-shaped sac containing the heart and the initial part of the great vessels. The outer fibrous layer adjoins adjacent intrathoracic structures, whereas the inner mesothelial portion forms a parietal and a visceral layer, between which lies the pericardial cavity. Normally, this contains <50 mL of serous pericardial fluid but this may expand substantially in pathologic states. The pericardium serves as a barrier to infection and injury. It also permits the unimpeded expansion, within a protective range, of the ventricle during diastole. Normally, the pericardium readily transmits changes in intrathoracic pressure to the heart with important hemodynamic consequences. Finally, the pericardium can modulate cardiac reflexes and coronary tone via secretion of prostaglandins. The most common pericardial diseases identified in clinical practice include acute pericarditis, pericardial effusion, cardiac tamponade, and constrictive pericarditis. They may result from local or systemic processes.

II. ACUTE PERICARDITIS. It is a pericardial syndrome presenting with inflammation of the pericardium. It most often affects males 16 to 65 years old. It accounts for 0.2% of cardiovascular admissions. Despite relatively generally good prognosis, pericarditis usually recurs in one-third of patients without proper treatment with risks for deleterious complications along with a decrease in quality of life. Etiologies of acute pericarditis are shown in Table 37.1.

A. Clinical presentation. Clinical diagnosis of acute pericarditis is made when two of the following criteria are met—chest pain, pericardial rub, electrocardiogram (ECG) changes, and pericardial effusion. In doubtful situations, magnetic resonance imaging (MRI) with gadolinium enhancement may be value in illustrating pericardial uptake.

1. **Chest pain** (>85% of cases) is usually affected by respiration and is retrosternal **improved by sitting up and leaning forward**.
2. **Pericardial rub** (<33% of cases) is described as a scratchy and high-pitched sound—often evanescent with changes in quality and intensity on serial exam. Commonly, there is a biphasic rub consisting of atrial and ventricular systolic components. It is best heard during inspiration with the patient leaning forward while placing the diaphragm of the stethoscope at the left lower sternal border.

3. **ECG** changes (up to 60% of cases) evolve through four stages. These may be absent in tuberculosis and neoplastic pericarditis. In the setting of a large effusion, ECG may show **electrical alternans or low voltage** or both.

a. **Stage 1:** Diffuse—usually upsloping and concave ST-segment elevation with upright T-waves and PR-segment depression in all leads except V_1 and aVR. There is often reciprocal PR-segment elevation with ST-segment depression in aVR—the "knuckle" sign (Fig. 37.1).

b. **Stage 2** occurs several days later with the resolution of previous PR- and ST-changes accompanied by T-wave flattening.

c. **Stage 3** is characterized by T-wave inversion.

d. **Stage 4** follows after several days to weeks with upright T-waves again.

TABLE 37.1 Causes of Acute Pericarditis

	Causal Agent	Presentation	S
Infectious			
Viral	Coxsackievirus B and Echovirus are the most common causal agents	Most common cause of acute pericarditis Prodromal upper respiratory symptoms	R
Bacterial	Staph and strep usually following pneumonia or empyema	Patient looks toxic Chest pain and rub is not necessarily present	U E
Tuberculosis (TB)	Pericardial involvement occurs in 1% of pulmonary TB	Immunocompromised Patient from TB-endemic area High rates of pericardial constriction	C S T P
Fungal	*Histoplasma*, *Aspergillus*, *Blastomyces*, *Candida*ssp.	Histoplasma more likely in immunocompetent patients	P F S
Noninfectious			

TABLE 37.1 Causes of Acute Pericarditis

Idiopathic	Unknown, although many of them are viral	Self-limited	
Post-myocardial infarction (post-MI)	Myocardial necrosis	Usually 2–4 d after MI Post-MI pericarditis is surrogate of extensive myocardial necrosis	E
Dressler syndrome	Unknown, but thought to be an autoimmune reaction	Usually 6–8 wk after MI	
Postpericardiotomy	Unknown, also believed to be autoimmune	6–8 wk after surgery Incidence varies from 10% to 40%	
Uremic	Unknown, likely retention of uremic toxins	ESRD before or within 8 wk of dialysis Majority of cases have rub and large pericardial effusion	
Neoplastic	Usually metastatic (lung, breast, lymphoma and leukemia)	Highly suspicious for tamponade	C E P
Autoimmune	LES, RA, Sjogren, vasculitis, FMF, TRAPS	Rarely first manifestation of autoimmune disease Poor response to	A

TABLE 37.1 Causes of Acute Pericarditis

		therapy
Inflammatory	Sarcoidosis, Still disease	A
		F
Drugs	Hydralazine, procainamide, doxorubicin, phenytoin, penicillin	

4. ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; ASA, acetylsalicylic acid; CT, computed tomography; ENA, extractable nuclear antigens; ESRD, end-stage renal disease; FMF, familial Mediterranean fever; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; TRAPS, tumor necrosis factor receptor-1 syndrome.

5. **Pericardial effusion—**new or worsening effusion.

A pericarditis illness that persists beyond 4 to 6 weeks is called incessant pericarditis, whereas chronic pericarditis is reserved for cases lasting longer than 3 months.

B. Management. Patients with acute pericarditis must be managed in the hospital if there exists a poor prognostic factor and/or concerns of underlying condition driving the illness.

1. **Major prognostic factors.** The following are the **major poor prognostic factors**:

a. Fever >38°C
b. Subacute symptoms
c. Large pericardial effusion (echo-free space around the heart > 20 mm)
d. Cardiac tamponade
e. Failure to respond to medical therapy

Other **minor prognostic factors** include myopericarditis, immunosuppression, trauma, and oral anticoagulant therapy.

2. **Testing in suspected pericardial disease**

In all cases with suspicion for pericardial disease, it is recommended to obtain the following:

FIGURE 37.1 Stage 1 electrocardiographic changes in acute pericarditis. Note PR-segment elevation in lead aVR ("knuckle" sign), and diffuse ST-elevation and the upsloping nature of ST-segments when compared with acute myocardial infarction. (Adapted from Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: endorsed by the Society for Cardiovascular Magnetic Resonance and Society of Cardiovascular Computed Tomography. *J Am Soc Echocardiogr*. 2013;26(9):965–1012.e15. Copyright © 2013 Elsevier. With permission.)

a. **Routine blood tests:** white blood cells (WBC), renal and liver function tests

b. **ECG**

c. **Chest x-ray**—enlarged bottle-like cardiac silhouette occurs with large pericardial effusion (usually >300 mL). X-ray may also reveal underlying mediastinal, pleural, or pulmonary disease.

d. **Transthoracic echocardiogram** within a day of presentation to assess for effusion (only in 40% of cases), tamponade/constrictive physiology, increased pericardial brightness, and wall motion abnormality (if myocardium involved)

e. **Inflammatory markers and markers of myocardial injury.** Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP/ultrasensitive CRP [usCRP]) are supportive of the diagnosis of acute pericarditis and can help in monitoring the disease process.

f. **Routine testing to identify underlying cause is not recommended.** Testing should be conducted only if the clinical scenario suggests an underlying etiology. Such testing includes bacterial culture, tuberculin test, viral serologies, fungal tests, thyroid function tests, autoimmune panel, cardiac biomarkers, and/or cytology.

C. General indication for imaging

1. **Echocardiography is the first-line imaging** modality and is routinely indicated in acute pericarditis.

2. **Advanced imaging with cardiac MRI or computed tomography (CT)** (Table 37.2) may be considered in the following scenarios:

a. Atypical presentation

b. Equivocal echocardiogram with poor prognostic features

c. Failure of medical therapy

d. Concern for chronic pericarditis

TABLE 37.2 Pericarditis Findings per Imaging Modality

Echocardiography

- Many cases have normal echocardiogram
- Pericardial effusion with/without tamponade physiology (3% of cases)
- Increase pericardial brightness
- Intrapericardial masses
- Wall motion abnormalities (5% of cases of myopericarditis)

Cardiac Computed Tomography

- Noncalcified thickened pericardium with effusion
- Irregular pericardium is a sign of severe inflammation
- Iodine contrast enhancement supports inflammation
- Pericardial effusion can be classified as transudative or exudative based on Hounsfield units

Cardiac Magnetic Resonance Imaging

- Noncalcified thickened pericardium with effusion
- Exudative effusion present with high T1W signal intensity on SE images

TABLE 37.2 Pericarditis Findings per Imaging Modality

- Increased T2 STIR suggests pericardial edema
- Increased LGE suggests organizing pericarditis
- Increased T2 STIR signal suggests an acute process with ongoing edema and neovascularization, wh chronic inflammation
- Signal intensity on SE tends to inversely correlate with chronicity of pericardial inflammation
- Loss of normal sliding motion of parietal layer over visceral layer may suggest adhesions

e. LGE, late gadolinium enhancement; SE, spin-echo; STIR, short-tau inversion recovery time.

f. Chest trauma–associated pericarditis

g. Investigation of secondary cause of pericarditis—concomitant ischemia, neoplasm, lung infections, and so on

D. Differential diagnosis. Chest pain from acute pericarditis can mimic aortic dissection, pulmonary embolism, pneumothorax, or acute coronary syndrome. ST-elevations in pericarditis are usually upsloping and concave with upright T-waves in contrast to horizontal or downsloping convex ST-elevation seen in acute ST-elevation myocardial infarction. Echocardiography may help in making the distinction by assessing for wall motion abnormalities, which are usually absent in acute pericarditis.

E. Medical therapy

1. **Physical activity should be limited** until resolution of symptoms and normalization of CRP, ECG, and echocardiogram. In addition, athletes should restrict exertion for a minimum of 3 months.
2. **The first-line treatment** for acute pericarditis is **nonsteroidal anti-inflammatory drugs (NSAID)/aspirin and colchicine** as an adjunct therapy until resolution of symptoms and normalization of CRP (Table 37.3). The choice of NSAID/aspirin is based on patient tolerance, side effects, comorbidities, and physician expertise. Ibuprofen is the preferred agent with a reasonable safety profile. **The addition of colchicine speeds resolution of symptoms and decreases risk of incessant or recurrent episode by half.** For etiology-specific treatments see Table 37.1.
3. **Steroid use during the first episode increases the odds of recurrence by fourfold.** Therefore, **this is not recommended as first-line treatment** for acute pericarditis. Low-dose corticosteroids (prednisone 0.2 to 0.5 mg/kg for a month) in combination with colchicine should be considered only in the setting of aspirin/NSAID contraindication or another indication for steroid therapy such as a steroid-sensitive autoimmune condition.

TABLE 37.3 First-Line Treatment for Acute Pericarditis

Medications	Dose
Ibuprofen	• 600–800 mg orally three times a day until symptoms resolution and CRP normalizatio wk • Favored NSAID in general given best safety profile
Aspirin	• 750–1,000 mg orally three times a day until symptoms resolution and CRP normalizatio

TABLE 37.3 First-Line Treatment for Acute Pericarditis

	wk • Favored in patients with concurrent indication for ASA (e.g., coronary artery disease)
Colchicine	• 0.6 mg orally twice a day for 3 mo if first episode or 6 mo if recurrence. In patient <70 kg • Taper is not mandatory

4. ASA, acetylsalicylic acid; CRP, *C-reactive protein;* NSAID, nonsteroidal anti-inflammatory drug.

5. Most patients with idiopathic or viral pericarditis should have a 1-month follow-up to ensure resolution of symptoms and assess for constrictive changes. Patients with pericardial effusion should have serial echocardiograms to follow the size and resolution of the effusion.

F. Complications. Complications usually relate to the underlying cause and not the number of recurrences. For instance, the overall rate or constrictive pericarditis is lower than reported after a first episode of pericarditis.

1. **Recurrent pericarditis:** This is defined as a **recurrent episode of pericarditis after a symptom-free period of at least 4 to 6 weeks** (following taper of medication) from the initial episode. **Rate of recurrence after an episode of acute pericarditis is 15% to 30%.** The recurrence rate increases to 50% after the first recurrence. The proposed pathophysiology for recurrence is autoimmune or auto-inflammatory, whereas a viral cause is identified in up to 20%.

a. **Independent factors for recurrence** identified in trials include **steroid use and CRP elevation** at presentation. Other risk factors proposed include fever, subacute presentation, immunosuppressed host, myopericarditis, large effusion, tamponade physiology, prior chest trauma, incomplete treatment course, and delayed response to therapy.

b. Clinical presentation and management are similar to acute pericarditis. Exercise limitation is recommended similar to acute pericarditis.

c. The **combination of aspirin/NSAID** (weeks to months) **and colchicine** (6 months) **halves rate of subsequent recurrent episode of pericarditis**.

d. **Triple therapy with low–moderate-dose corticosteroids** (prednisone 0.2 to 0.5 mg/kg), **aspirin/NSAID, and colchicine is only considered after first-line regimen failure**. A very slow taper is recommended once symptoms have resolved and CRP has normalized. Intrapericardial steroids have occasionally been used to minimize systemic effect of corticosteroids.

e. Steroid-sparing alternative therapies currently under investigation include disease-modifying antirheumatic drugs (e.g., azathioprine and methotrexate), immunomodulators (e.g., intravenous immunoglobulin G), and biologic anti-inflammatory drugs (e.g., anakinra) (Fig. 37.2).

f. Pericardiectomy is considered as a last resort for refractory severe symptoms.

2. **Pericarditis with myocardial involvement:** Myopericarditis is defined as acute pericarditis with secondary elevation of myocardial biomarkers in the absence of new

left ventricular (LV) impairment. If either new focal or diffuse myocardial impairment is identified, then the event is defined as perimyocarditis.

FIGURE 37.2 Medical therapies for recurrent pericarditis. (Adapted by permission from Nature, Imazio M, Lazaros G, Brucato A, et al. Recurrent pericarditis: new and emerging therapeutic options. *Nat Rev Cardiol*. 2016;13(2):99–105. Copyright © 2016 Springer Nature.)

a. **Hospitalization is recommended for patients with myocardial involvement.**

b. **Cardiac MRI should be obtained, beyond the routine pericarditis workup to further characterize myocardial involvement.**

c. Coronary angiogram should be pursued in those cases with convincing angina and/or increased risk of coronary events.

d. **Activity restriction for at least 6 months** is recommended in those patients with myopericarditis given increased risk of ventricular arrhythmias.

e. **Empiric treatment with lowest efficacious dose of aspirin/NSAIDs** is recommended. There is no enough evidence to support the use of colchicine in this setting.

f. If LV systolic function is depressed (LV ejection fraction <40%), optimal heart failure management is recommended.

g. In general, myopericarditis seems to have good prognosis with no increased risk of death or heart failure.

h. **Cardiac tamponade: occurs in up to 11% of cases**, mostly in neoplastic and postsurgical cases. It should be suspected in any patient with acute pericarditis presenting with dyspnea, tachycardia, and hemodynamic instability.

3. **Constrictive pericarditis.** Acute pericarditis evolves into constrictive pericarditis only in 1% to 2% of cases, but rarely follows recurrent pericarditis. It is more commonly seen in purulent and tuberculous pericarditis (20% to 30% of cases).

III. PERICARDIAL EFFUSION.

Any process that interferes with the production and/or reabsorption of pericardial fluid may lead to the **accumulation of >50 mL within the pericardial cavity** leading to a pericardial effusion. Effusions can be classified based on onset, size, localization, composition, and hemodynamic compromise as described in Table 37.4.

Effusions with inflammatory signs are likely related to **acute pericarditis**. **Neoplastic process** is more likely the **cause of effusions causing tamponade** without systemic inflammation. **Large effusions without tamponade or inflammatory signs** are usually due to **chronic idiopathic etiology**.

TABLE 37.4 Classification of Pericardial Effusion

Onset
Acute (<3 mo)
Chronic (>3 mo)
Size

TABLE 37.4 Classification of Pericardial Effusion
Mild (50–100 mL)—Echo-free space < 10 mm
Moderate (100–500 mL)—Echo-free space 10–20 mm
Large (>500 mL)—Echo-free space > 20 mm
Localization
Circumferential
Loculated
Composition
Transudate
Exudate Hemopericardium Pyopericardium
Hemodynamic Impact
None
Effusive–constrictive
Tamponade

The **most common causes** of pericardial effusion in developed countries **include idiopathic (50%), neoplastic (10% to 25%), infections (15% to 30%), iatrogenic (15% to 20%), and autoimmune (5% to 15%)** (Table 37.5).

A. Clinical presentation

1. Clinical presentation ranges **from asymptomatic to tamponade**.

2. **Major determinants of clinical presentation are underlying etiology of pericardial effusion, volume of effusion, and rate of accumulation.**

3. Rapid accumulation of a small pericardial effusion (80 to 200 mL) tends to lead to early symptoms including tamponade, whereas a slowly developing effusion may lead to the development of large amounts of pericardial fluid before the onset of symptoms.

4. Often pericardial effusions are incidentally identified on imaging.

5. When symptomatic, the most common complaints are

a. Chest discomfort/fullness

b. Progressive dyspnea

c. Orthopnea

d. Patients can also complain of compressive symptoms such as dysphagia (esophagus), hoarseness (recurrent laryngeal nerve), hiccups (phrenic nerve), and/or nausea/vomiting.

6. Physical examination may reveal muffled heart sounds with large effusions. **Ewart sign** can be identified in some patients (dullness to percussion, bronchial breath sounds, and egophony below the angle of left scapula).

7. Sinus tachycardia and low blood pressure are ominous signs of tamponade.

8. Patients with tamponade have **pulsus paradoxus** (>10 mm Hg) and **Beck triad** (jugular venous distention, muffled heart sounds, and hypotension).

B. Management. Most pericardial effusions can be managed as an outpatient. Initial **assessment for tamponade** should assess for signs of tamponade such as tachycardia, tachypnea, and hypotension. **Hospital admission is recommended** in those patients with **high-risk features**.

TABLE 37.5 Causes of Pericardial Effusion

Idiopathic

Infections
- **Viral infections**—Coxsackieviruses A, B5, and B6, echovirus, adenovirus, mumps virus, hepatiti influenza, varicella, human immunodeficiency virus
- **Bacterial (purulent)**—*Staphylococcus, Streptococcus, Haemophilus influenzae, Salmonella, meningitidis, Mycoplasma pneumonia, Legionella pneumophila, Rickettsia*, psittacosis, Lyme disea
- **Tuberculosis**
- **Fungal infections**—Histoplasmosis, aspergillosis, blastomycosis, coccidioidomycosis, fungal endo
- **Other infections—***Amebiasis, Echinococcus*

Immunologic/inflammatory disorders
- Rheumatic fever
- Systemic lupus erythematosus, ankylosing spondylitis, rheumatoid arthritis, scleroderma
- Polymyositis, dermatomyositis
- Polyarteritis nodosa, granulomatosis with polyangiitis, giant cell arteritis
- Sarcoidosis, amyloidosis
- Inflammatory bowel disease, Whipple disease
- Behçet syndrome, Reiter syndrome, familial Mediterranean fever

Acute myocardial infarction
- Delayed post-myocardial–pericardial injury syndromes
- Post-myocardial infarction syndrome (Dressler syndrome)

Metabolic
- Uremia, myxedema, hypoalbuminemia

Trauma
- Postpericardiotomy syndrome
- Indirect trauma to the chest
- Percutaneous cardiac interventions
- Perforation of the heart by indwelling catheters

Neoplastic
- **Primary—**Mesothelioma, teratoma, fibroma, leiomyofibroma and sarcoma, lipoma and angioma
- **Metastatic—**Breast carcinoma, bronchogenic carcinoma, lymphoma, leukemia, melanoma

Drugs

TABLE 37.5 Causes of Pericardial Effusion

- Hydralazine, minoxidil, heparin, warfarin, phenytoin, phenylbutazone, cromolyn sodium, dan procainamide, penicillin, colony-stimulating factor, interleukin-2

Radiation

Dissecting thoracic aneurysm

1. **High-risk features.** The following are the **high-risk features**

a. **Concern for tamponade**

b. **Large effusion, chronic effusion**

c. **Suspicion for underlying bacterial or neoplastic process**

2. Workup for suspected pericardial effusion should include

a. **Routine workup** for pericardial disease as described before

b. An echocardiogram is essential in the assessment of tamponade physiology.

c. Rule out chronic medical conditions based on clinical presentation (e.g., hypothyroidism, chronic kidney disease, cancer screening). If pericarditis is identified, there is no need to pursue workup for chronic conditions.

C. **General indication for imaging**

1. **Transthoracic echocardiogram** is the modality of choice and routinely recommended in patients with suspicion for or known effusions to diagnose and risk-stratify the patients. The following are the echo findings of pericardial effusion:

a. **Persistent intrapericardial echo-free space throughout the cardiac cycle** on M-mode is associated with effusions >50 mL. Conversely, an echo-free space seen only during systole may represent a normal amount of pericardial fluid (trivial effusion).

b. **Small effusions** tend to localize posteriorly distal to the atrioventricular ring with echo-free space <10 mm.

c. **Moderate effusions** surround the heart with an echo-free space of 10 to 20 mm.

d. **Large effusions** are circumferential with greater anterolateral expansion and echo-free space width >20 mm. Anteroposterior or lateral heart swings can be seen in large effusions.

e. **Loculated effusions** with echo densities, stranding, or adhesions suggest exudate over transudate.

f. Two-dimensional echocardiography parasternal long-axis image with echo-free space between the descending aorta and heart helps differentiate a pericardial effusion from left pleural effusion.

g. Anterior epicardial fat is differentiated from an anterior effusion based on higher echo density than myocardium and movement in synchrony with heart.

h. Cardiac tamponade physiology is described later in this chapter.

2. **Advanced imaging with CT or MRI may be considered as an adjunct in equivocal cases with suspicion for complex effusion, pericardial thickening, or pericardial masses.** Both studies provide better assessment of localization, size, and characteristics of the fluid than echocardiography.

a. **Cardiac CT is able to further characterize effusions based on CT attenuation**: <10 HU suggests simple transudate; 20 to 60 HU suggests purulent, malignant, or myxedematous effusions; and 60 to 80 HU supports chylopericardium or hemorrhage. Features of pericardial thickening on CT are similar attenuation to effusion, high-attenuation nodularities, lack of movement with position changes, and pericardial enhancement with contrast.

b. **Cardiac MRI can better differentiate pericardial thickening from small pericardial effusion** compared with cardiac CT. Transudative effusions have low-intensity signal on standard dark-blood images and exhibit high-intensity signal on bright-blood cine images. Meanwhile, exudative collections have high-intensity signal on both T1 and T2 images.

D. Medical therapy

1. **Treatment should be targeted to underlying etiology.** Cases with evidence of acute pericarditis should be treated accordingly. Unfortunately, anti-inflammatory therapies in isolated effusion with no sign of inflammation (e.g., elevated ESR, CRP/usCRP, and late gadolinium enhancement [LGE]) are generally ineffective.
2. **Pericardiocentesis is recommended if there**

a. Are significant symptoms
b. Is suspicion for bacterial/neoplastic etiology
c. Is large chronic effusion
d. Is tamponade physiology.

3. Slow pericardial drainage (30 mL/24 hours) has shown to decrease the risk of re-accumulation.
4. Pericardiectomy or **pericardial windows** are indicated in effusions with recalcitrant symptoms, loculated effusion, or when biopsy is needed.

E. Prognosis and follow-up. Recent evidence suggests that the presence of a small effusion is associated with a worse prognosis when adjusted for age and gender. Prognosis is further impacted by the underlying condition. Moderate and large effusions carry a worse prognosis because they are often caused by bacterial or neoplastic conditions. Up to 30% of large chronic effusion progress to tamponade. Similar to acute pericarditis, idiopathic effusions even if recurrent have a low risk of progression to constriction.

The following is the recommended echocardiographic follow-up for pericardial effusions:

1. No follow-up for small asymptomatic effusions
2. Moderate idiopathic effusions should be monitored with echocardiography every 6 months.
3. Large effusions should have follow-up with echocardiography every 3 to 6 months.

IV. CARDIAC TAMPONADE. It is a potentially fatal condition characterized by impaired ventricular diastolic filling caused by an increase in intrapericardial pressures because of the accumulation of pericardial fluid, pus, blood, or gas. The spectrum of tamponade ranges from compensated tamponade to cardiogenic shock.

The development of cardiac tamponade is determined by the **interplay** between **pericardial stiffness** (infiltrations, calcification, or fibrosis), **size of effusion, and rate of fluid accumulation** (Fig. 37.3).

A. Pathophysiology

1. The pericardium is able to distend in response to fluid accumulation until a limit on its ability to stretch is reached. Beyond this, small increments in pericardial fluid volume result in large increases in intrapericardial pressure.
2. **Intracardiac volume becomes fixed** and there is equalization of intracardiac diastolic pressures with those within the pericardium. This causes an absolute reduction in intracardiac volumes, **ventricular diastolic filling, and stroke volumes.**
3. The **cardiac output is initially maintained** by a heightened adrenergic tone, resulting in a resting tachycardia and peripheral vasoconstriction.
4. The **right and left ventricles compete for the fixed cardiac volume**. On inspiration, the negative intrathoracic pressure increases the right ventricle venous return, albeit reduced compared with normal, with concomitant reduction in left ventricle filling via a **reduction of pulmonary vein to left ventricle pressure gradient**. This causes a delay in mitral valve opening, a decrease in mitral inflow velocity, left septal bulge, and **further stroke volume reduction** causing a drop in systolic blood pressure **(pulsus paradoxus)**. The opposite changes occur in expiration.

FIGURE 37.3 Pericardial pressure–volume curves. Accumulation of pericardial fluid over time causes minimal changes in intrapericardial pressures until the pericardial stretch limit is reached (flat line) causing exponential increase in intrapericardial pressure. A slower fluid accumulation rate (solid line) takes longer to reach limit contrary to a rapid filling (dashed line) because there is more time for the pericardium to stretch and activate compensatory mechanisms. The pericardial compliance (dotted line) plays a key role in pericardial tamponade because a decrease in compliance moves the curve to the left. (Adapted from Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26(9):965–1012.e15. Copyright © 2013 Elsevier. With permission.)

5. Finally, in **severe tamponade**, **compensatory mechanisms fail**, resulting in a **decreased cardiac output**. Reduced coronary perfusion may cause **subendocardial hypoperfusion**, further compromising cardiac output.

B. Clinical presentation

1. The signs and symptoms of cardiac tamponade all reflect a low cardiac output: restlessness, agitation, drowsiness, or stupor; decreased urine output; dyspnea; chest discomfort and syncope or near syncope; and weakness, anorexia, and weight loss with a chronic effusion.
2. Physical examination usually reveals **Beck triad** (jugular venous distention, distant heart sounds, and hypotension). The following findings are commonly seen in cardiac tamponade:

a. Compensatory **tachycardia** because of low output state and decreased diastolic filling
b. Tachypnea that reflects elevated pulmonary venous pressure
c. **Elevated central venous pressure** is characterized by a prominent *x* descent and an attenuated or absent *y* descent.
d. **Diminished heart sounds** because of decreased transmission through the fluid-filled pericardium. A pericardial friction rub may be present in some cases.

e. **Pulsus paradoxus (inspiratory drop in systolic blood pressure >10 mm Hg)** as described above. Pulsus paradoxus is **not specific to cardiac tamponade** but may be seen in severe obstructive pulmonary disease, right ventricular (RV) infarction, pulmonary embolism, or asthma.

f. **Hypotension** (in severe cases)

C. **Management.** It is recommended that all patients with suspected or confirmed tamponade physiology be admitted to hospital and to an intensive care unit setting if hemodynamic compromise is present. All patients should complete routine pericardial disease workup. Transthoracic echocardiogram must be performed emergently when the diagnosis of cardiac tamponade is suspected.

D. **General indication for imaging**

1. **Transthoracic echocardiography (TTE) with Doppler** is the initial imaging method of choice. A transesophageal echocardiogram (TEE) is indicated in the postoperative patient with clinical signs of tamponade and inadequate surface images or in whom fluid is not present in the pericardium. Echocardiographic signs of cardiac tamponade include the following:

a. Presence of pericardial effusion

b. **Right atrial diastolic collapse** (Fig. 37.4) typically in late diastole (near peak of R wave) and continues into ventricular systole (sensitive, but specificity only 82%). It is best seen in the parasternal short-axis view, the subcostal view, and the apical four-chamber view. **The longer the duration of diastolic collapse, the more specific it is for tamponade.**

c. **RV early diastolic collapse** or inversion (Fig. 37.4). Most commonly seen in the anterior RV free wall and infundibulum near the end of T-wave with patients in the supine position. The parasternal long-axis and short-axis views of the heart are the best for evaluating this sign. M-mode recording through the right ventricle helps to outline the timing and duration of the event. **Isolated RV diastolic collapse appears to occur before the onset of clinical tamponade.** Conditions that raise RV intracavity volume and RV pressure delay the occurrence of RV diastolic collapse until higher intrapericardial pressures are reached. It has p**oor sensitivity in surgical patients** because of the loculated nature of their effusions and the presence of adhesions.

d. **Left atrial diastolic collapse**—a rare but specific sign of tamponade

e. **Abnormal inspiratory increase of RV dimensions** and decrease of LV dimensions

f. **Exaggerated respiratory variation of atrioventricular inflows** detected on pulsed Doppler (Fig. 37.4): **Expiratory reduction in tricuspid peak E-wave velocity of >60%** and i**nspiratory reduction in mitral peak E-wave velocity of >30%**. The respirophasic variation of atrioventricular inflow must be considered only in the context of chamber collapse, inferior vena cava (IVC) dilatation, and/or abnormal hepatic vein flow.

FIGURE 37.4 Two-dimensional subcostal view of the heart and pulsed Doppler recordings of mitral and tricuspid inflow in a patient with cardiac tamponade. **A:** Atrial collapse is signaled by arrow occurring at end of diastole (near top of QRS). **B:** RV collapse is signaled by arrow in early diastole. **C:** Doppler recording of mitral inflow with a respirometer (white line) showing

respirophasic flow velocity variation (white dots), with expiratory decrease in peak mitral E-wave velocity exceeding 30%, as is typical in significant tamponade. **D:** Doppler recording of tricuspid inflow with a respirometer (white line) showing respirophasic inflow velocity variation (white dots). These respiratory changes are opposite to those seen in mitral flow velocity. LA, left atrium; LV, left ventricle; PEff, pericardial effusion; RA, right atrium; RV, right ventricle; insp, inspiration; exp, expiration. (Adapted from Klein AL, Abbara S, Agler DA. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26(9):965–1012.e15. Copyright © 2013 Elsevier. With permission.)

g. **Expiratory blunting or reversal of diastolic hepatic vein flow**

h. **IVC plethora**

2. **TEE** is highly sensitive for detecting hematoma in this setting. Following cardiac surgery, a localized pericardial hematoma rather than fluid may impair filling of the heart. It commonly occurs around the right atrium and is difficult to diagnose using TTE. **TEE should be considered** in cases where **pericardial hematoma is suspected** but TTE images are non-diagnostic.

3. **Advanced imaging with cardiac CT and MRI** are second-line imaging modalities reserved for subacute complex cases (equivocal postsurgical cases, regional tamponade, or concern for loculated effusions).

4. **Right heart catheterization** is occasionally used in "borderline" cases to confirm the diagnosis of tamponade, quantify the hemodynamic compromise, and assess conditions after pericardiocentesis. Classic diagnostic finding is the **equalization (within 4 mm Hg) of average diastolic pressure in the cardiac chambers,** which is raised usually between 10 and 30 mm Hg.

E. Medical therapy

1. Prompt **drainage of pericardial fluid is the most important intervention**. The timing and method of drainage ultimately depend on the etiology of the effusion, the patient's level of acuity, and the availability of trained physicians.

2. The options include pericardiocentesis under echocardiographic or fluoroscopic guidance and surgical drainage. The latter is preferred if there is a high likelihood of recurrence, in purulent effusions, in loculated effusion, or with urgent bleeding into pericardium. Generally, if the patient is hemodynamically compromised percutaneous drainage is performed because induction of anesthesia may lead to a further drop in cardiac output and complete hemodynamic collapse.

3. If the fluid is loculated and not easily accessible through a pericardial window, CT-guided needle drainage is occasionally helpful.

4. Additional management includes volume expansion, inotropic support if the patient is hypotensive, and avoidance of diuretics or vasodilators.

V. CONSTRICTIVE PERICARDITIS.

This is the result of a noncompliant pericardium, usually as a consequence of inflammation, fibrosis, or calcification, which encases the heart leading to heart failure because of impaired diastolic ventricular filling. Pericardial thickening is commonly seen; however, up to 20% of cases have a normal pericardial thickness.

Constrictive pericarditis can be caused by any pericardial process (Table 37.6). The most common cause of constrictive pericarditis in developed countries is viral or idiopathic

pericarditis (42% to 49%) followed by postcardiac surgery (11% to 37%) and radiation therapy (9% to 31%). Meanwhile, in developing countries tuberculosis pericarditis is the leading cause of constriction.

A. Pathophysiology

1. Constrictive pericarditis can be classified into the following specific subforms:

a. **Transient constrictive pericarditis usually follows an episode of acute pericarditis with effusion**, but can also follow any pericarditis, pericardiectomy, and chemotherapy or be associated with autoimmune diseases. **It accounts for 9% to 17% of all constrictive pericarditis**. It is defined as a transient form of **constriction because of inflammation rather than scarring that resolves by itself or with 3 to 6 months of anti-inflammatory therapy.** Therefore, symptoms of constriction may be accompanied by those of pericarditis with signs of inflammation (ESR, CRP/usCRP, LGE). Prompt recognition and treatment may be important to prevent potential evolution into chronic constrictive pericarditis.

b. **Effusive–constrictive pericarditis** is described in patients with pericardial tamponade in whom intracardiac pressures remain elevated (right atrial pressure fail to decrease by 50% or to less than 10 mm Hg) despite pericardiocentesis. There is predominant involvement of the visceral pericardium (epicardium), called constrictive epicarditis by some authors. Some patients may have resolution with a conservative approach but others require extensive epicardiectomy, which should be performed at experienced centers as it is technically challenging.

TABLE 37.6 Common Causes of Constrictive Pericarditis

Idiopathic	• Accounts for 42%–49% of cases • It is the most common cause of constriction in deve • Rate of progression into chronic constriction is <1%
Infectious diseases Viral (e.g., coxsackievirus B and echovirus), bacterial, tuberculosis, fungal, and parasitic	• Tuberculosis is the main cause of constriction in de • Bacterial and tuberculous pericarditis have the high constriction (20%–30%)
Postcardiac surgery	• Accounts for 11%–37% of cases • Risk factors include intraoperative hemorrhage int pericarditis, and the occurrence of postpericardiot
Radiation	• Risk factors include duration of therapy, total an and volume of the heart in the radiation field • Delay onset up to 20 y after radiation therapy • In contrast to other causes of constrictive pericar dysfunction from radiation damage
Immunologic disorders Rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and sarcoidosis	• Account for 3%–7% of cases of pericardial constric • Only 3%–5% of autoimmune pericarditis evolve int
Neoplastic disease Breast cancer, lung cancer, lymphoma,	• Causes constriction via infiltration of pericardium

TABLE 37.6 Common Causes of Constrictive Pericarditis

mesothelioma, and melanoma	
Miscellaneous	• Accounts for <10% of all cases of constriction • Includes trauma, drug, and uremic pericarditis

c. **Chronic constrictive pericarditis** is defined as persistent constriction after 3 to 6 months duration.

2. The encasement of the heart by **non-distensible pericardium limits the cardiac filling to a fixed volume**. In early diastole, the **ventricles expand normally with rapid early filling** secondary to the elevated pulmonary and systemic pressures. Once the **ventricles reach the confines of the rigid pericardium, diastolic filling comes to an abrupt halt** because of an immediate increase in ventricular pressure. **Nearly all ventricular filling occurs in the second phase of diastole (early filling)** with little contribution from the third phase (diastasis) and the fourth phase (atrial systole). **The hallmark of constrictive pericarditis, although nonspecific, is the ultimate equalization of end-diastolic pressures in all four cardiac chambers.**

3. **The stiff pericardium also prevents the transmission of intrathoracic pressures** to the cardiac cavities during the respiratory cycle (intrathoracic–intracardiac pressure dissociation), which causes significant respirophasic variation of ventricular preload with associated enhanced ventricular interdependence.

4. **During inspiration**, the **right heart preload and tricuspid inflow velocity increase** because of the negative intrathoracic pressure. Conversely, **left heart preload and mitral inflow decrease** as a consequence of full transmission of the negative pressure to pulmonary vein in contrast to partial or no transmission into the left heart chambers. This leads to a **full right ventricle and an emptier left ventricle encased by stiff pericardium**, which causes a **leftward shift of the ventricular septum**.

5. The opposite occurs **on expiration**, a positive intrathoracic pressure **reduces right-sided preload and tricuspid inflow**. Meanwhile, the increased thoracic pressure is fully transmitted to the pulmonary venous circulation but not the left heart, **increasing LV filling pressures and mitral inflow**. This will ultimately lead to a **full left ventricle and emptier right ventricle** causing **rightward septal shift and late diastolic flow reversal in the hepatic veins**.

6. The myocardium is generally normal; and **myocardial relaxation and systolic function are usually spared**. However, myocardial function may occasionally be compromised by tethering of the myocardium to the pericardium.

B. **Clinical presentation.** The **early symptoms** of constrictive pericarditis are often insidious and nonspecific including **malaise, fatigue, and decreased exercise tolerance**. As the **disease progresses**, patients complain predominantly **of right-sided heart failure symptoms**including peripheral edema, hepatic congestion, ascites, and worsening exercise tolerance.

The physical examination in a patient with constriction commonly reveals the following:

1. **Increased jugular venous distension**, on occasions so high that it may only be evident by examining the patient upright. Observation of the jugular venous pulsations reveals a **prominent *y* descent that is produced by the rapid ventricular filling in early**

diastole. Many patients demonstrate a lack of inspiratory fall in venous distention, known as **Kussmaul sign**.

2. **Muffled heart sounds** because of decreased transmission through the thickened pericardium and **soft first heart sound (S1)** because mitral and tricuspid valves are nearly closed by the end of diastole

3. **Occasionally, one may hear a pericardial knock** in early diastole. This represents the abrupt cessation of diastolic filling that occurs when further ventricular relaxation is impeded by the rigid pericardium. The pericardial knock **must be differentiated from other early diastolic sounds** such as an opening snap, third heart sound (S_3), and tumor plop. In general, the pericardial knock is of a higher frequency, is heard best with the stethoscope diaphragm, and occurs slightly earlier than an S_3.

4. **Decreased breath sounds** at the bases, attributed to pleural effusions

5. **Congestive hepatosplenomegaly**. In severe cases, there may be liver dysfunction and **ascites**.

6. **Peripheral edema**

C. **Management.** Confirming the diagnosis of constrictive pericarditis often presents a challenge; the clinician must rely on clinical suspicion and integration of imaging techniques to increase diagnostic accuracy. Perhaps, the greatest challenge lies in differentiating constrictive pericarditis from restrictive cardiomyopathy.

1. **Routine workup for suspected constrictive pericarditis should include the following:**

a. Complete basic workup recommended in all cases of pericardial disease (WBC, liver and renal function, ECG, echocardiogram, inflammatory markers, and cardiac biomarkers).

b. **ECG** usually reveals a low voltage with generalized flattening of the T-waves. Atrial fibrillation is a common finding.

c. **Chest radiograph** reveals pericardial calcification in 30% of cases. It is best appreciated with a lateral film, usually involving the right ventricle and atrioventricular groove. **Pleural effusions** occur frequently.

d. **Inflammatory markers** (ESR, CRP/usCRP) are important in identifying cases with transient constrictive pericarditis.

e. **Echocardiography**

D. **General indication for imaging.**

1. TTE is routinely recommended as first-line imaging in the diagnostic workup of constriction. In patients with a consistent clinical presentation, an echocardiogram with definitive constrictive physiology may be sufficient. Doppler echocardiography also helps **exclude competing diagnoses**, such as restrictive cardiomyopathy. The following are the characteristic echo findings of constrictive physiology:

a. **Pericardial thickening** (only approximately two-thirds of cases) is suggested by parallel motion of parietal and visceral pericardium.

b. Flattening of LV posterior wall endocardium

c. **Septal bounce** "shudder" (M-mode) described as oscillatory diastolic beat-to-beat movement of the ventricular septum

d. **Abnormal respirophasic septal shift** (ventricular interdependence) with septal movement to the left in early diastole with inspiration, whereas on

expiration, the septum shifts back to the right (Fig. 37.5). This is the most sensitive echocardiographic finding.

e. **IVC plethora**

f. **High early E-wave** velocity, short deceleration time, and **decreased A-wave** (E/A > 1) suggesting predominant grade 3 diastolic filling or restrictive filling

g. **Increased respirophasic variation of atrioventricular inflows** with major changes during first beats on inspiration and expiration (Fig. 37.6). Findings suggestive of constrictive physiology are

1. **1 Inspiratory reduction of peak mitral E-wave velocities >25%**
2. **2 Inspiratory increase of tricuspid E-wave velocities >40%**
3. **3** Opposite changes occurs during expiration.

h. Respiratory variation in **pulmonary venous flow during diastole** mirrors peak mitral E-wave changes during respiration. **Pulmonary venous peak diastolic flow velocity variability of >20% is supportive of constriction but not necessary for diagnosis.**

i. **Expiratory hepatic diastolic flow** reversal with **hepatic diastolic reversal-to-forward flow velocity ratio during expiration of >0.79** is characteristic of constrictive physiology. Conversely, hepatic diastolic flow reversal on inspiration is suggestive of restriction (Fig. 37.6).

j. Doppler velocities of the medial mitral valve annulus in early diastole (e′) are **normal or slightly increased** (>8 cm/s). Conversely, restrictive cardiomyopathies have decreased e′ velocities **at both medial and lateral mitral annuli** (<7 cm/s), reflecting abnormal myocardial relaxation (Fig. 37.7).

k. **Annulus paradoxus,** defined as an inverse relationship of E/e′ compared to PCWP in patients with constrictive pericarditis

FIGURE 37.5 Respirophasic ventricular septum movement in a patient with constrictive pericarditis using M-mode echocardiogram with additional respirometric recording. The ventricular septum moves toward the left ventricle with inspiration (upward arrow) and toward the right ventricle with expiration (downward arrow). (Adapted from Klein AL, Abbara S, Agler DA. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26(9):965–1012.e15. Copyright © 2013 Elsevier. With permission.) **FIGURE 37.6** Pulsed Doppler recordings of mitral (**A**), tricuspid (**B**), superior vena cava (SVC) (**C**), and hepatic vein (**D**) inflow velocities, with simultaneous respirometric recording, in a patient with constrictive pericarditis. The peak early diastolic filling velocity (E) to peak late diastolic filling velocity (A) ratio is increased (>1). **A:** Mitral inflow velocities markedly increase during expiration (E_e and A_e) and decrease with inspiration (E_i and A_i). **B:** Tricuspid inflow velocities increase with inspiration (E_i and A_i) and decrease with expiration (E_e and A_e). Similar changes are not observed in normals and those with restrictive disease. Patients with restriction have an increased E/A ratio; but, there is no significant respirophasic variation. **C:**SVC flow velocities showing increased diastolic reversal flow (DR_e) during expiration. **D:** Hepatic vein flow velocity showing increase in both peak systolic (S_i) and diastolic (D_i) flow velocities with inspiration. During expiration, there is marked drop in both velocities (S_e and D_e) and an increase in diastolic

reversal flow. (Adapted from Klein AL, Abbara S, Agler DA. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26(9):965–1012.e15. Copyright

© 2013 Elsevier. With permission.) **FIGURE 37.7** Annular tissue velocities of medial (**A**) and lateral (**B**) mitral annulus in patient with constrictive pericarditis. **A:** The medial E′ velocity is 12 cm/s, and the lateral E′ velocity is 8 cm/s. Lateral E′ is lower than septal E′ in constrictive pericarditis, which is attributable to perimyocardial tethering of the lateral left ventricular free wall. (Adapted from Klein AL, Abbara S, Agler DA. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26(9):965–1012.e15. Copyright © 2013 Elsevier. With permission.)

l. In constrictive pericarditis the relationship between the lateral and medial mitral annuli e′ velocities is often reversed **called annulus reversus. Contrary to normal, e′peak velocity at the medial annulus is typically higher than peak e′ velocity at the lateral annulus**. This is attributed to tethering of the LV lateral free wall to the pericardium in constriction.

m. **Strain imaging** in constrictive pericarditis is characterized by preserved global longitudinal strain but reduced **circumferential deformation with more pronounced involvement of anterolateral wall of the ventricles compared with the septum.** Conversely, restrictive cardiomyopathy commonly presents with a uniform strain reduction affecting longitudinal, radial, and circumferential ventricular deformations. Decreased LV anterolateral strain over septal strain ratio could be used to differentiate constrictive pericarditis from restrictive cardiomyopathy. Regional longitudinal strain ratios are decreased in constrictive pericarditis compared to normal controls or patients with restrictive cardiomyopathy.

n. The **key echocardiographic criteria in the diagnosis of constrictive pericarditis** (Fig. 37.8) include an abnormal septal motion (ventricular interdependence) with either spared or elevated e′ velocity of medial mitral annulus (>8 cm/s) and/or hepatic vein expiration reversal flow ratio of >0.79, in addition to increased respirophasic variation of atrioventricular inflows and IVC plethora.

FIGURE 37.8 Diagnostic algorithm for constrictive pericarditis. AV, atrioventricular; CMR, cardiac magnetic resonance; CRP, C-reactive protein; CxR, chest x-ray; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; IVC, inferior vena cava; LGE, late gadolinium enhancement; LV, left ventricle; usCRP, ultrasensitive C-reactive protein. (Adapted from Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10:165–193; Welch TD, Ling LH, Espinosa RE, et al. Echocardiographic diagnosis of constriction. *Circ Cardiovasc Imaging*. 2014;7:526–534.)

2. **Cardiac MRI** provides both anatomical and hemodynamic information in constrictive pericarditis, without the radiation associated with cardiac CT. MRI may demonstrate features of ventricular interdependence such as septal bounce and respirophasic variation in septal excursion. It can assess pericardial thickening and is the best modality to assess pericardial inflammation. It is excellent at tissue characterization and quantifying LV and RV systolic function, which is of value in patients where there is diagnostic uncertainty. Nonetheless, MRI is inferior to cardiac CT in assessing pericardial calcification.

3. **Cardiac CT** in constrictive pericarditis provides a superior 3D delineation of the pericardium in comparison with echocardiography. A thickened pericardium >4 mm (80% of cases) is supportive of the diagnosis, although normal pericardial thickness does not exclude constrictive pericarditis. Indirect findings include tubular deformation of RV with normal LV and IVC plethora. Cardiac CT is the best modality for assessing pericardial calcification, which may assist in surgical planning.

4. **Cardiac catheterization** assists in both diagnosing constrictive pericarditis and differentiating it from restrictive cardiomyopathy. In general, both right and left heart catheterizations are performed to obtain simultaneous ventricular pressure readings. It is recommended when noninvasive testing fails to provide a definitive diagnosis and in difficult cases.

a. **Right atrial pressure** waveform has been described as having a **W-shaped configuration**. This morphology is produced by a prominent *a*-wave as the atria contract against an elevated ventricular pressure, an exaggerated *x* descent, and a steep *y* descent, because of rapid ventricular filling in early diastole (Fig. 37.9).

b. **Ventricular pressure** waveforms demonstrate the classic **dip-and-plateau** physiology, commonly referred to as the **square root sign** (Fig. 37.9). The **initial downward deflection** reflects the drop in pressure during the isovolumic relaxation period. The subsequent **upward deflection** reflects early diastolic filling. The **terminal plateau** represents the cessation of flow that occurs once the limit of the rigid pericardium has been reached.

c. There is also equalization (within 5 mm Hg) of elevated end-diastolic pressures in both ventricles. The RV systolic pressure is generally <55 mm Hg, with an RV end-diastolic pressure that is more than one-third of RV systolic pressure. These findings assist in **differentiating constrictive pericarditis from restrictive cardiomyopathy, where RV systolic pressure** is often elevated to **>55 mm Hg**.

d. **The ratio of the RV/LV systolic pressure–time area during inspiration versus expiration** (systolic area index) has been shown to be **a useful measure of enhanced interventricular interaction** (Fig. 37.10).

e. **Hypovolemia can mask characteristic features of constrictive pericarditis**, and fluid challenge may be required to unmask ventricular interdependence in patients who are volume depleted.

5. Current recommendations favor a multimodality approach (echocardiography, cardiac MRI, cardiac CT, and cardiac catheterization) based on clinical presentation and patient characteristics to enhance diagnostic accuracy and improve management. The following are suggested situations where integration of imaging may be used:

a. **Equivocal diagnosis of constriction on echocardiogram.** In this scenario, cardiac catheterization is almost always necessary to confirm diagnosis.

b. **Suspicion for transient constrictive pericarditis** (elevated inflammatory markers and constriction symptoms for less than 3 months). Cardiac MRI should be strongly considered in these cases to assess for inflammation. There is emerging evidence supporting anti-inflammatory therapy as an initial strategy in a patient with inflammatory constrictive pericarditis or effusive–constrictive pericarditis.

c. **Cases where assessment of pericardial calcification is warranted**. For instance, recurrent constriction after pericardiectomy or cardiac surgery. Cardiac

CT is the imaging modality of choice for surgical planning. Cardiac CT should be limited otherwise to patients who are unable to undergo cardiac MRI.

FIGURE 37.9 Right atrium (RA), right ventricle (RV), and left ventricle (LV) pressure waveform in constrictive pericarditis. **A:** The preserved *x* descent and the prominent *y* descent contribute to the classic W-shaped atrial waveform. **B:** Note the equalization of left ventricular and right ventricular end-diastolic pressures, generally within 5 mm Hg of one another. The rapid early diastolic filling and subsequent abrupt cessation of flow because of the rigid pericardium produces a dip-and-plateau waveform (square root sign), appreciated best in this waveform following the premature ventricular contraction. ECG, electrocardiogram. (Adapted with permission from Lorell BH, Grossman W. Profiles in constrictive pericarditis, restrictive cardiomyopathy and cardiac tamponade in cardiac catheterization. In: Baim DS, Grossman W, eds. *Angiography and Intervention*. 5th ed. Baltimore, MD: Williams & Wilkins; 1996:801–822.)

FIGURE 37.10 Respiratory ventricular interaction between right ventricle (RV) and left ventricle (LV) systolic area indexes in patients with constriction (**A**) and restriction (**B**). Note that in constrictive pericarditis patients (**A**), there is a rise in the area of RV pressure curve (darker-shaded area) and reduction in the area of LV pressure curve (lighter-shaded area), whereas in restrictive cardiomyopathy patients, there is a drop in the area of RV pressure curve during inspiration, with no change in the area of LV systolic pressure curve. LVA_{exp}, LV systolic area in expirations; LVA_{ins}, LV systolic area in inspirations; RVA_{exp}, RV systolic area in expirations; RVA_{ins}, RV systolic area in inspirations. (Adapted from Talreja DR, Nishimura RA, Oh JK, et al. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. *J Am Coll Cardiol*. 2008;51(3):315–319. Copyright © 2008 American College of Cardiology Foundation. With permission.)

d. Preoperative simultaneous right and left heart catheterization can be done not only to assess ventricular interdependence in order to confirm the diagnosis in complicated cases (radiation heart disease) but also to get an accurate assessment of the cardiac index, which may assist in surgical planning.

E. Differentiating constrictive pericarditis from restrictive cardiomyopathy. Constrictive pericarditis is a potentially curable disease, whereas treatment options in restrictive cardiomyopathy are often limited to medical therapy. There are several key findings by echocardiography, cardiac catheterization, and cardiac MRI that can be used to differentiate these two clinical entities and are described in Table 37.7.

F. Medical therapy. Pericardiectomy is the preferred treatment for constrictive pericarditis, although there are certain clinical scenarios in which medical therapy is appropriate.

1. Patient with **constrictive pericarditis and signs of inflammation** (elevated inflammatory markers and/or evidence of inflammation on cardiac CT or MRI) should be treated initially with trial of **anti-inflammatory therapy for 3 to 6 months** before recommending surgical intervention. This may include NSAIDs and colchicine, reserving steroids for refractory cases.
2. Patient with **effusive–constrictive pericarditis** should have **pericardiocentesis and trial of medical therapy** before recommending pericardiectomy.

TABLE 37.7 Key Findings Used to Differentiate Constriction from Restriction

Investigation	Constrictive Pericarditis
Echocardiography	
Annular tissue velocity (E´)	Preserved except at lateral mitral annulus and righ tricuspid annulus
Diastolic dysfunction	Present
Respirophasic interventricular septal shift	Present
Respirophasic variation in transvalvular/hepatic vein flow	Present
LV wall thickness	Normal
Perimyocardial slippage (motion of LV, RV, and atrial free wall)	Reduced
Cardiac Catheterization	
Elevated LVEDP	Present (equalization of diastolic pressures in all four c that are more suggestive of constriction)
LV/RV discordance	Present
Cardiac Magnetic Resonance Imaging	
Respirophasic shift of interventricular septum	Present
Pericardial thickening or enhancement	Normal or increased
Myocardial scarring detected by post-gadolinium enhancement	Absent unless coexisting cardiomyopathy

3. LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; RV, right ventricular.

4. Patients who have **New York Heart Association class I symptoms** may initially be treated with **diuretics and a low sodium diet. However, some of these patients ultimately require pericardiectomy. Often a metabolic stress test may help assess functional capacity in these patients.**

5. Medical therapy is also appropriate in **patients with severe comorbid illnesses** that limit life expectancy and/or place them at an unacceptably high risk for operative mortality.

6. **Pericardiectomy provides symptomatic improvement in more than 90% of patients**. However, pericardiectomy carries an **operative mortality** that is reported to range from **6% to 12%**. The etiology of constrictive pericarditis can predict perioperative mortality. Patients who have constrictive physiology because of viral or idiopathic pericarditis

have better outcomes than those who have radiation-induced constrictive pericarditis. Those patients with a poor preoperative functional class are at highest risk for perioperative death; therefore, most physicians advocate **early surgical intervention**.

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CHAPTER 39

Common Genetic Issues in Cardiovascular Disease

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I.INTRODUCTION. Genetic abnormalities have been associated with all types of cardiovascular disease, including coronary atherosclerosis, rhythm disorders, aortic disease, and structural heart disease. Since the initial descriptions of familial hyperlipidemia (FH) and the mutations in the low-density lipoprotein receptor (LDL-R), genetic studies have fostered an improved understanding of the underlying pathophysiology of various cardiovascular disease states. Furthermore, the sequencing of the human genome coupled with the advent of new DNA sequencing technologies has increased the expeditious pace of cardiovascular genomics. The ability to efficiently scour through the massive amount of genomic information is improving our understanding of the contributions of genetics to cardiovascular disease.

This understanding would potentially lead to an improved ability to accurately diagnose disease, prevent progression, and risk stratify at the individual level. Furthermore, this information will add to our understanding of the relationship between DNA variants and the response to drugs or other treatment modalities. The **pharmacogenomic** profiles developed may provide a refined approach to treatment with less toxicity. A more comprehensive assessment of future risk for both patient and potentially affected family members would also be feasible.

Although there are some examples within cardiovascular disease of simple **monogenic disorders** explained by principles of Mendelian inheritance, many of the entities, such as coronary atherosclerosis, acute myocardial infarction (MI), and atrial fibrillation (AF), are **complex traits with multiple genes contributing to the phenotype**. As opposed to Mendelian disorders, which are deterministic, complex traits are probabilistic.

It will require extensive time and effort to be able to define all the variations in all the genes that contribute to the susceptibility to or protection from a complex trait. Furthermore, the simple identification of genes involved does not address the issue of gene–gene and gene–environment interactions influencing complex traits. There have been extensive recent reports of genomic variants associated with risk of diseases. These variants are common, often accounting for 20% to 30% of the population attributable risk, but with an odds ratio of 1.2 or 1.3, for example, only 20% to 30% excess risk. These are common variants for common diseases. The hunt to find rare variants that induce susceptibility to common diseases with high risk (or protection) will be more

challenging, but eminently feasible with sequencing technology and ultra high–throughput genotyping. At some point in the future, the major genomic underpinnings for most cardiovascular diseases will be known. Furthermore, the integration of all of the genomic variants for any cardiovascular disease has not been undertaken. What follows is a brief overview of what is known today about the genetic basis for a sampling of disease entities within cardiovascular medicine.

II. METHODOLOGY. The process of discovering relevant genetic underpinnings of generally complex traits requires an extensive analysis of genetic information in large populations. Complex traits without simple Mendelian patterns of inheritance are difficult to analyze, given that there are often multiple genes involved, with many gene interactions being important. However, even before attempting this task, perhaps **the single most significant goal is to accurately and concisely define the phenotype in question**. In addition, many variations often exist within a single category of cardiovascular disease such as hypertrophic cardiomyopathy (HCM) and acute MI. The ability to clearly define cases and controls is paramount to obtaining accurate and reproducible information.

Here are the major methods of identifying DNA variants associated with cardiovascular disease. Of note, some of the single nucleotide polymorphism (SNP) variants that have been found are not in a gene, but **actually in areas of the genome not associated with gene expression**. It is not yet known how these variants exert their effect. Of note, the major variants for MI (at 9p21) and AF (at 4q25) fall into this category of intergene (i.e., not in a gene).

A. Genome-wide association studies. Gene association studies utilize the concept that ***multiple SNPs, where a single nucleic acid substitution results in a different allele, can affect the risk of developing a disease in question***. This is especially true in diseases of complex traits such as coronary artery disease (CAD) and MI. Using genes of interest in a particular disease phenotype, scans are conducted in areas of interest in both cases and controls to compare haplotype frequency to determine if a statistically significant difference between the two groups in the region of interest exists. One of the limitations of this technique is the inability to know whether the SNP of interest is involved in the pathogenesis or simply associated (in linkage disequilibrium) with another SNP that may actually be involved in the process. Utilizing this process of gene association across the entire genome is now possible with high-throughput sequencing technology of up to 1 million SNPs assessed per individual and the term "genome-wide" association has been coined. The SNPs assessed are tagging tiny bins of the genome, such that in a genome of an individual of European ancestry, there are only about 250,000 bins, most of which are sampled by current high–throughput genotyping. **Each bin is typically inherited as a block** (haplotype). The breakdown of the genome into bins via the International Haplotype map was critical in making current genome-wide association studies possible.

Target sequencing of genes at GWAS loci is now commonplace. Using this method the researcher has the opportunity to discover if rare genetic variants in the coding region of any of the genes in the loci may be related. In addition, the era of whole-genome sequencing has arrived. **In whole-genome sequencing the complete DNA sequence of the individual's genome can be determined**. This includes both chromosomal and mitochondrial DNA. Today an entire genome can be sequenced for about $1,000. Also

individual genes can be sequenced cheaply and quickly. These new technologies have increased the speed and lowered the cost of sequencing thereby increasing access to many more researchers and accelerating discovery.

B. Linkage analysis. Linkage analysis is another tool used to identify genes that are possibly involved in the pathogenesis of complex traits. The use of linkage analysis begins without any assumptions as to the potential involvement of various genes. It is based on the idea that during the process of meiosis when recombination events occur, they tend to involve loci on a particular chromosome that are closer together than farther apart. By following the inheritance of certain known loci, assumptions can be made about the presence of alleles that cosegregate with them. Using linkage analysis, the potential exists to identify these known loci as markers and determine the transmission through a pedigree and its relationship to the phenotype in question. In doing so, it may be possible to suggest that an allele in proximity to known loci may be associated with a particular phenotype. The logarithm of odds ratio (LOD score) is used to estimate the (distance) relationship between the known locus of interest and an unknown locus thought to be associated with the disease phenotype. **A LOD score of 3** is used to classify such a statistically meaningful linkage.

C. Gene expression profiling. The identification of certain disease alleles or loci associated with disease-causing genes provides valuable information but remains limited in its scope. The statistical association of genes and disease **does not prove causation or even involvement**in disease. Gene expression profiling takes this concept one step forward in trying to delineate gene expression. The presence of transcription profiles may provide more useful information in terms of relevance of findings made in gene association studies or linkage analysis. Technology now permits the evaluation of large genomes in a rapid fashion to derive expression profiles, which can then be compared between diseased and healthy individuals to draw conclusions about which genes are transcriptionally active in certain phenotypes.

III.GENES INVOLVED IN INDIVIDUAL CARDIAC DISEASE PROCESSES

A. Coronary atherosclerosis and atherothrombosis. Coronary atherothrombosis and atherosclerosis remain significant causes of morbidity and mortality in the population as a whole. There is a great deal of variation in presentation in atherosclerosis and in acute MI. The presence of atherosclerosis is necessary but not sufficient for atherothrombosis. There are separate factors involved that predispose to plaque rupture and thrombosis. Even within the category of plaque rupture, the clinical phenotypes vary significantly, as reflected by the spectrum of diseases that constitute the acute coronary syndromes. These entities are complex traits and are influenced by multiple pathways. Inflammation, endothelial dysfunction, and dyslipidemias are only a few of the pathways influencing the development of atherothrombosis and atherosclerosis. Delineating the genetic basis of specific pathophysiological mechanisms, in most cases, is a work in progress, but it may help to broaden our understanding of the disease.

1. Dyslipidemia: FH and other genetic variants. Dyslipidemia is a known risk factor for the development of atherosclerosis. FH is a well-characterized, albeit relatively uncommon, entity defined by **elevated levels of serum LDL levels**, which predispose to coronary atherosclerosis. Often, these patients can develop atherosclerotic disease between 20 and 30 years of age. In FH, the dyslipidemia is often severe and not responsive to standard lifestyle and pharmacologic interventions.

a. **Autosomal dominant hypercholesterolemia.** Three genes are implicated in causing familial hypercholesterolemia (FH), **the *LDLR*gene (LDL Receptor), the *APOB* gene (apolipoprotein B), and the *PCSK9* gene (proprotein convertase subtilisin/kexin type 9)**. However, a genetic cause for approximately 20% of cases in known loci is unknown. Mutations in any one of these three genes can cause FH and they are inherited in an autosomal pattern.

1. **1** FH resulting from mutations in the ***LDLR gene is the most common form of FH.*** **The *LDLR* gene is located at 19p13.2 and encodes for a protein known as a LDL-R**. These receptors regulate the amount of cholesterol in the blood. There are approximately 1,700 mutations in the *LDLR* gene affecting many aspects of *LDLR* function such as reducing the number of LDL-R produced in the cells or interfering with the receptor when removing LDLs from the blood. Alterations in the gene range from point mutations to gene rearrangements. Homozygotes (two mutant alleles) and heterozygotes (one mutant allele) for FH vary in terms of the severity of lipid levels. The majority of individuals are heterozygous, and those with homozygous patterns of inheritance are more severely affected and are more likely to be diagnosed during childhood. Consanguinity increases the risk of homozygous inheritance and should be noted. Typically, these patients and affected family members develop premature coronary atherosclerosis and MI.
2. **2 The *APOB* gene is located at 2p32.3 and encodes for the production of two forms of the apolipoprotein B protein a component of lipoproteins, the apolipoprotein B-100 and the apolipoprotein B-48**. The mutations in the apolipoprotein B-100 cause familial hypercholesterolemia. The cellular mechanisms involved in cholesterol metabolism are complex, and there are many potential targets where mutations can significantly affect phenotype. One such example is a point mutation in the apolipoprotein B (apo B) component of the LDL molecule. The Arg3500Gln (R3500Q) is the most common substitution in the apo B (*APOB*) gene and results in the inability of LDL to bind to its LDLR. This mutant allele is more common in Northern European populations as a cause of hyperlipidemia, but the phenotype appears to be less severe than in the FH caused by *LDLR*mutations. The R3500 W is another *APOB* gene mutation identified in East Asian populations as a common cause of FH. Mutations in the *APOB* gene occur in 5% to 10% of cases of FH with a country variation in incidence. In some countries such as Japan, Russia, Spain, and Finland the *APOB* genetic mutations have not been identified in FH cases.
3. **3 The *PCSK9* gene, located at 1p32.3, is responsible for increasing degradation of the LDL receptor**. Approximately 1% to 2% of FH involves the *PCSK9 gene.* Mutations in *PCSK9*, such as D129N, D374H, D374Y, E 32K, E670G, F216L, R215H, S127R, D374Y, and R496W, confer gain in function and cause FH. Loss-of-function *PCSK9* mutations such as G236S and N3541 are fairly common and act to reduce serum cholesterol levels, thereby conferring a protection against coronary atherosclerosis. Therefore, loss-of-function mutations do not cause FH. Many new *PCSK9* mutations have been identified, but their effect on *PCSK9* functions and their role in FH in different populations requires further investigation.
4. **4** In 2016, in a large Icelandic study, 13 new rare or low frequency variants with large effects on lipid levels were discovered while 14 previously reported ones were confirmed. Five of these variants were identified within genes associated with CAD including the *PCSK9* and the *LDLR* genes. One of the variants (rs200238879) identified in the *LDLR* gene was determined in a 1997 study as a cause of familial hypercholesterolemia in Iceland. These results indicate the complexity of the genetic picture for dyslipidemia and the power of whole-genome sequencing in detecting rare variants in large global samples.

5. 5 In addition to the FH syndromes, there is a multitude of genes involved in more frequently occurring types of dyslipidemia. Phenotypically, these forms of dyslipidemia are less severe and more amenable to treatment than those observed in the FH population.

b. **Autosomal recessive hypercholesterolemia.** Autosomal recessive hypercholesterolemia occurs as **a result of mutations in the LDL-R adaptor protein 1 gene (*LDLRAP1*) at 1p36.11**. More than 10 mutations are known to cause this condition. These mutations result in either the production of a nonfunctional version of the LDLRAP1 protein or do not make any protein. The phenotype of this form of FH is milder than the autosomal dominant form of the disease and more amenable to treatment with lipid-lowering agents.

2. **Endothelial function.** The ***MEF2a* gene located at 15q26.3 encodes for a transcription factor protein involved in vascular development**. MEF2A localizes to the endothelial cell of coronary arteries and is believed to be important in the function of endothelial cells. Mutations in this gene could be a cause of CAD autosomal 1 (ADCAD1). In 2003, a mutation in the *MEF2a* gene was described in a large family with autosomal dominant transmission of coronary atherothrombosis. A21-bp deletion in exon 11 was thought to result in loss of function. Additional variants in the *MEF2A* thought to be associated with MI and CAD have also been reported. T 21-bp deletion has not been conclusively found in any family apart from that in the original study. This particular mutation may be a "private mutation" for the family in the original study and therefore extremely difficult to replicate. There is much discussion about the role of the MEF2A and its rare variants and their genetic contributions in ADCAD1. Recent genome-wide association studies have failed to identify the *MEF2A* locus on chromosome 15q26 when detecting loci associated with CAD. To add to the debate, scientists point to mixed results linking *MEF2A* mutations to ADCAD1. In 2008, researchers did not find any evidence that the *MEF2A* gene had any linkage or association with MI/CAD in a large German study. In 2010, researchers found that mutations of exon 11 in MEF2A were not involved in sporadic CAD in a Chinese population. However, in 2013, mutations of MEF2A exon 12 were linked to Premature CAD in a Chinese population. In 2014, the mutation in exon 11 was identified in a Chinese population and it was reported that six or seven amino acid deletions and synonymous mutations (147143G→A) may be associated with CAD in this population. These inconsistent results highlight the need for further genetic studies to determine the role of MEF2A's genetic component in ADCAD1.

3. **Inflammation.** The genes, ***ALOX5AP* (arachidonate 5-lipoxygenase–activating protein) located at 13q12.3 and *LTA4H*(leukotriene A4 hydrolase) located at 12q22, encode proteins involved in the leukotriene pathway, particularly in the synthesis of the proinflammatory leukotriene B mediators**.

a. In 2004, the case for inflammation as a significant participant in acute MI was made stronger by the discovery, through linkage analysis to a locus at 13q12-13, of a 4-SNP haplotype known as Hap A (SG13S25, SG13S114, SG13S89, and SG13S32) in the gene *ALOX5AP*. Carriers of the variant had higher levels of leukotriene B4. This variant was found to double the risk of MI and to almost double the risk of stroke. Another haplotype variant, Hap B (*S*G13S377, SG13S114, SG13S41, and SG13S35) of the *ALOX5AP* gene was found to confer a doubling of the risk of MI in a British cohort. In Italy, researchers identified an increased risk for CAD with Hap B only. In a large German study, presence of the haplotype B indicated an association with an increased risk of MI. These studies provide strong evidence of the role of *ALOX5AP* gene for increased CAD risk in Europeans. In a case–control study of a US

Midwestern population with European American ancestry, seven SNPs in the *ALOX5AP* gene along with two haplotypes (Hap A and Hap B) were genotyped. The results indicated that Hap B and one of the SNPs (SG13S377) were significantly associated with increased risk of premature CAD. In a meta-analysis conducted in 2010, the Hap B and SNP (rs1722842) variants in the *ALOX5AP*gene were associated with coronary heart disease, whereas Hap A was associated with the risk of MI. However, lack of correlation between *ALOX5AP* gene variants and CAD, and *ALOX5AP* gene variants and MI have also been reported. Two studies in the United States reported no correlations between *ALOX5AP* gene variants and CAD. Also a study with a Japanese population indicated no relationship between the *ALOX5AP* gene variants and MI. In 2010 a study with a Lebanese population did not find any association between *ALOX5AP* gene variants and CAD or MI. To add to the debate, in 2015, results of a study with a Lebanese population indicated that different SNP variants in the *ALOX5AP* gene yielded a different relationship to CAD. Specifically, the genetic variant rs4769874 is significantly associated with an increased risk of CAD, whereas the rs9579646 SNP is significantly associated with a decreased risk of CAD.

b. The *LTA4H* gene located at 12q23.1 encodes leukotriene A4 hydrolase and is also involved in the inflammation pathway. A haplotype (HapK) in the *LTA4H* gene moderately increased the risk of MI in a cohort from Iceland. A moderate risk was also found in studies of three US cohorts with European Americans, but HapK, although rarer in African Americans, tripled their risk of MI. It is worthy to note that the HapK is very rare in an African population and evidence of HapK in African-American cohorts may be due to European genetic influence. In 2014, researchers in India reported that *LTA4H* is significantly associated with CAD. The results of these studies with the *ALOX5AP* and *LTA4H* gene variants highlight the need for future studies in different populations. However, they provide the basis for further research to develop new drugs targeting the leukotriene pathway, thereby preventing or reducing the risk of MI and CAD in the future.

B. Connective tissue abnormalities and disease of the aorta. Genetic mutations affecting the connective tissue and extracellular matrix typically affect multiple organ systems, but often the most devastating and lethal effects arise from those upon the cardiovascular system. Aortic dissection and rupture are often the consequences of such abnormalities, and what follows is a brief description of three such disorders.

1. Marfan syndrome. This disorder is inherited in an ***autosomal dominant*** fashion with variable penetrance, and it affects the connective tissue, leading to abnormalities of organs of the cardiovascular, skeletal, and ocular systems. In some patients it may be caused by a de novo mutation. The genetic defect is in the **fibrillin-1 (*FBN1*) gene on chromosome 15q21.1**. Often, the diagnosis is made on clinical grounds alone. The classic features of tall stature, arachnodactyly, dolichostenomelia, pectus excavatum, ectopia lentis, and a positive family history all support a diagnosis of Marfan syndrome. The cardiovascular system is affected, and the most common cause of death in these patients is from aortic dissection and aortic rupture. Other common related problems include aortic dilation, aortic valve regurgitation, mitral valve prolapse (MVP), tricuspid valve prolapse, and arrhythmias. When patients with Marfan syndrome present with dissection, they are typically younger and do not have hypertension.

The *FBN1* gene is responsible for producing a key constituent of microfibrils, which are important in the extracellular matrix. Microfibrils add to the elastic properties of extracellular

tissue. Over 1,800 mutations in the *FBN1* gene have been recognized and appear to affect different aspects of cellular processing of fibrillin-1. These mutations can vary from a SNP to a premature stop codon. There are no specific relationships between mutations and phenotypes as of yet. Family members with Marfan syndrome and **the same *FBNI* gene mutation may show wide variation in onset and severity of cardiac symptoms**. The diagnosis of Marfan syndrome is generally made on a clinical basis. However, genetic testing for Marfan syndrome is available.

2. **Ehlers–Danlos syndrome.** Ehlers–Danlos syndrome is a group of connective tissue disorders caused by defects in proteins that are involved in the formation of collagen. It is uncommon and usually has an ***autosomal dominant pattern*** of inheritance but recessive inheritance pattern is seen also. De novo mutations may cause the condition also. In 1997, Villefranche Nosology classified six distinct subtypes of Ehlers–Danlos syndrome. For the most part these subtypes were based on clinical features and linked to mutations in collagen-related genes. In 2017, the International ED Consortium proposed a new classification with 13 subtypes. Each of these subtypes has its own clinical picture. However, **the definitive diagnosis for each of these subtypes, except for the hypermobility type, is based on genetic testing and presence of a causative gene.**

The cardiovascular system is involved in two subtypes: the vascular and the cardio-valvular.

a. The vascular subtype has an autosomal pattern of inheritance. The gene, *COL3A1*, involved in the vascular subtype type of Ehlers–Danlos syndrome, is localized to chromosome 2q32.2 and encodes for type III collagen. Mutations in the gene cause the vascular subtype (vEDS), which accounts for approximately 5% of all Ehlers–Danlos syndrome cases. Vascular complications include dissections of the carotids and the vertebral arteries. There may be arterial rupture of the abdominal vessels such as the renal and hepatic especially at a younger age. Aortic dissections are the primary cause of death and often involve both the thoracic and the abdominal aortas. Up to one-quarter of cases have evidence of aortic aneurysmal involvement. In this vascular subtype hypermobility and skin hyperextensibility are not usually evident. Diagnosis is usually ascertained clinically along with genetic testing for evidence of the mutation in the *COL3A1* gene.

b. The cardiac-valvular subtype has a recessive pattern of inheritance. This *COL1A2* gene, involved in this subtype, is localized to chromosome 7q21.3 and encodes for a component of type I collagen known as the pro-α2(I) chain. Mutations in the gene result in abnormal collagen. This leads to the severe aortic and mitral valve problems seen in this subtype. Skin hyperextensibility and hypermobility are evident in this subtype also. Diagnosis is usually ascertained clinically along with genetic testing for evidence of the mutation in the *COL1A2* gene.

3. **Loeys–Dietz syndrome.** Loeys–Dietz syndrome is a connective tissue disorder characterized by **hypertelorism, cleft palate, and vascular disease in the form of arterial aneurysms and dissection**. It is inherited in ***an autosomal dominant pattern***. In many cases it is the result of a de novo mutation. Clinically, these patients are at high risk for aortic dissection. There are six types of Loeys–Dietz syndrome classified according to the gene involved. Mutations in the *TGFBR1* gene (chromosome 9q22.33) cause Type I, gene mutations in *TGFBR2* (chromosome 3p24.1) result in Type II, mutations in the *SMAD3* gene (chromosome 15q22.33) cause Type III, *TGFB2*(chromosome 1q41) genetic mutations lead to Type IV, mutations in *TGFB3* (chromosome 14q24.3) cause Type V, and mutations in

the *SMAD2* gene (chromosome 18q21.1) cause Type VI. The mutations in these genes produce proteins with reduced function and interfere with the transforming growth factor–β pathway. Phenotypically, the characteristics are similar to those in Marfan syndrome, and also these patients appear similar (with the exception of the craniofacial abnormalities) to Ehlers–Danlos patients with vascular involvement (type IV). The relevance of this distinction is that those with Loeys–Dietz appear to have much lower intraoperative mortality during corrective vascular surgery. Genetic testing to identify the mutation in one of the known genes, and evidence of either aortic root enlargement or type A dissection, or systemic features is needed for definitive diagnosis.

C. Cardiomyopathies. Primary disease of the myocardium affects both systolic and diastolic function and often results in heart failure or other adverse events over time. Many of the nonischemic cardiomyopathies have a strong genetic component to explain their phenotype. Perhaps, the most clinically relevant entities include dilated cardiomyopathy (DCM) and HCM. Cardiomyopathies can also occur as a secondary process in response to a separate unrelated factor (i.e., hypertension), and it is unknown to what degree genetic susceptibility determines the myocardial response/remodeling over time. Until recently, the classification of cardiomyopathies has been based on the phenotype and morphologic characteristics. However, with an improved knowledge of the genetics of these disorders, a new understanding and appreciation for the underlying mechanisms of disease in these disorders will undoubtedly influence how these entities are diagnosed and treated in the future.

1. Dilated cardiomyopathy. DCM is characterized by dilation of one or both of the ventricular chambers resulting in severe systolic dysfunction and characterized by congestive heart failure. A **genetic cause is thought to account for 20% to 50% of DCM** cases, and in many cases, the pattern of inheritance is autosomal dominant. However, recessive, X-linked, and mitochondrial patterns of inheritance are also seen. Many cases of DCM are secondary to other etiologies. Mutations in a large number of genes have been associated with this phenotype. To complicate the picture further each gene has many "private" mutations, that is, mutations unique to a particular family. Also, there are often subtle differences in the various types of DCM, such as age of onset and degree of clinical symptoms, all of which may suggest separate genetic abnormalities are at play. Although the products of most of the genes associated with DCM are important structural proteins, there are others involved in the handling of calcium and regulation of energy within the myocytes. Mutations in the sarcomere protein genes account for approximately 10% of familial and 25% of idiopathic DCM. The *TTN* gene encoding for titin is the most commonly mutated gene in DCM. More than 35 variants of *TTN* have been associated with DCM, many of these are *TTN*-truncating variants with variable penetrance. Many mutations associated with sacromere stability, including *MLP, VCL, CRYAB*, have been linked to DCM. Mutations in *LMNA* gene, which encodes lamin A and lamin C, are seen in DCM with or without conduction system disease. However, when conduction system disease is present it is severe. Although mutations in *SCN5A*, a cardiac sodium channel gene, are also associated with this type of DCM, the clinical picture differs as ventricular dysfunction is usually present. Mutations in the *Dystrophin* and *EMD* genes have been identified in X-linked recessive DCM. Mutations in the *ALMS1* and *GATAD1*genes are transmitted in an autosomal recessive pattern. Genetic

testing is available for many of the gene mutations that have been identified. Table 39.1 lists some of the genetic variants that are believed to be associated with various DCM phenotypes.

2. **Hypertrophic cardiomyopathy.** HCM (see Chapter 10) is a highly variable and heterogeneous disease process that affects the myocardium, with clinical manifestations varying from completely asymptomatic to severe (sudden cardiac death). The broad range of phenotypes and significant selection bias resulted in an overestimation of the mortality rate associated with this disease. The clinical spectrum of the disease is wide, and the ability to accurately predict outcomes remains challenging. The clinical variability of HCM is not only limited to the presenting phenotype but also related to age of presentation, clinical course, and eventual outcomes, making it very challenging to properly identify a phenotype of interest. The characteristic phenotype is an asymmetrically hypertrophied myocardium with a small ventricular chamber and occasionally a left ventricular (LV) outflow tract pressure gradient (with systolic anterior motion of the mitral valve) and/or an intracavitary gradient.

TABLE 39.1 Selected Genetic Variants Associated with Dilated Cardiomyopathy

Gene	Chromosome Location	Mode of Inheritance	Gene Product and Function
ACTC1	15q11-q14	Autosomal dominant	Sarcomeric gene—encodes cardiac actin Vital part of contractile apparatus of myocyte
CSRP3	11p15	Autosomal dominant	Encodes cardiac muscle LIM protein Functions as a stretch sensor in myocyte
DES	2q35	Autosomal dominant	Encodes desmin—cytoskeletal protein invol and mutation may affect contractile force
Lamin A/C (LMNA)	1q22	Autosomal dominant	Encodes lamin A and lamin C Structural proteins—affect structure of nucleu
MYBPC3	11p11.2	Autosomal dominant	Encodes cardiac myosin-binding protein C Mutations may affect contractile mechanism
MYH6	14q12	Autosomal dominant	Sarcomere gene—encodes α-myosin heavy Mutations may affect contractile mechanism
MYH7	14q11	Autosomal dominant	Sarcomere gene—encodes β-myosin hea contractile mechanism
PLN	6q22	Autosomal dominant	Phospholamban—controls muscle relaxatio calcium ATPase
PSEN1/2	14q24.3 (*PSEN1*) 1q31-q42 (*PSEN2*)	Autosomal dominant	Presenilin —*PSEN1* encodes presenilin 1 *PSEN2* encodes presenilin 2 Transmembrane proteins
SCN5A	3p21	Autosomal dominant	Cardiac sodium channel gene

TABLE 39.1 Selected Genetic Variants Associated with Dilated Cardiomyopathy

TMPO	12q22	Autosomal dominant	Encodes thymopoietin—maintains functional
TNNI3	19q13.42	Autosomal dominant	Encodes cardiac troponin I Mutations may affect contractile mechanism
TNNC1	3p21.1	Autosomal dominant	Encodes troponin C1(TnC) Mutations may affect contractile mechanism
TNNT2	1q32	Autosomal dominant	Sarcomere gene—encodes troponin T type Mutations may affect contractile mechanism
TPM1	15q22	Autosomal dominant	Encodes α-tropomyosin Mutations may affect contractile mechanism
Dystrophin (DMD)	Xp21.2	X-linked recessive	Encodes dystrophin Mutations can affect transduction of contracti
EMD	Xq28	X-linked recessive	Encodes for Emerin, a component of the nuc **Autosomal recessive DCM**
ALMS1	2p13.1	Autosomal recessive	Alstrom syndrome Encodes for protein associated with hearing type 2 diabetes
GATAD1	7q21.2	Autosomal recessive	Encodes a protein containing a zinc finger at have a role in regulating gene expression

3. DCM, dilated cardiomyopathy.

4. More than **1,400 known mutations in at least 50 separate genes have been identified, with the majority of mutations in two genes: *MYH7* on chromosome 14 and *MYBPC3* on chromosome 11**. These genes encode proteins of the cardiac sarcomere unit, specifically the product of *MYH7* is β-myosin heavy chain, whereas *MYBPC3* encodes myosin-binding protein C. Mutations in additional sarcomere genes are involved in HCM also. These genes include *TNNT2* (troponin T), *TNNI3* (troponin I), *MYL2* (myosin light chains), *MYL3* (myosin light chain 3), *TPM1* (α-tropomyosin), and *ACTC* (actin). Mutations in non-sarcomeric genes and Z-disc encoding genes have also been identified in HCM. The importance of properly characterizing a phenotype as heterogeneous as HCM has been illustrated by the example of glycogen storage diseases mimicking the appearance of HCM. Mutations in the genes for adenosine monophosphate-activated protein kinase γ2 (PRKAG2) and lysosome-associated membrane protein 2 (LAMP2) were found in phenotypes that closely resembled HCM but were differentiated based on serum protein levels and ventricular preexcitation.

5. **Arrhythmogenic right ventricular cardiomyopathy.** Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a primary abnormality resulting in **fibrofatty infiltration of the myocardium, primarily the right ventricle**. Clinical manifestations include right ventricular dysfunction and lethal ventricular arrhythmias.

Diagnosis often requires a battery of tests, including an electrocardiogram demonstrating repolarization abnormalities and an epsilon wave, magnetic resonance imaging or computed tomography demonstrating fibrofatty infiltration of the right ventricle, and endomyocardial biopsy. Often a positive family history of the disorder is present. ARVC is usually inherited in an ***autosomal dominant*** with incomplete penetrance (in most cases). Thirteen chromosomal locations have been identified for ARVC and mutations associated with ARVC have been identified in specific genes at 11 of these locations. Eleven of these genes encode five desmosomal proteins (desmoplakin, desmoglein, plakophilin-2, desmocollin 2, and plakoglobin), and six non-desmosomal proteins (desmin, Titin, transmembrane protein 43, transforming growth factor β-3, ryanodine receptor 2, and α-catenin). The specific genes for ARVC3 and ARVC6 have not yet been identified although the chromosomal loci are known. Other genes have been reported as being implicated in ARVC: PLN encodes for phospholamban, LMNA encodes lamin A/B, and *SCN5A* gene encodes for sodium channels. In ARVC 8 mutations in the *DSP* gene, encoding desmoplakin, have an autosomal dominant pattern of inheritance, whereas mutations in the same *DSP* gene with an autosomal recessive inheritance result in Carvajal syndrome. Similarly, in ARVC12, mutations in the *JUP* gene encoding plakoglobin have an autosomal dominant pattern of inheritance, whereas mutations in the same *JUP* gene with an autosomal recessive inheritance result in Naxos disease, a variant associated with the triad of ARVC along with dermatological manifestations such as wooly hair and palmoplantar keratoderma. Variants of ARVC are distinguished on the basis of the gene involved and are described further in Table 39.2.

6. **Left ventricular noncompaction**. LV noncompaction (LVNC) is a relatively rare congenital abnormality of the myocardium resulting in a trabeculated appearance of the LV cavity. It **is characterized by spongy myocardium that results from arrest in endomyocardial morphogenesis**. It is seen in <1% of adults. This disorder can occur in isolation or in association with other congenital anomalies or with chromosomal abnormalities. These chromosomal abnormalities are rare and include chromosomal deletion, trisomy, Robertsonian translocation, and mosaicism. When LVNC is present with a congenital abnormality, the cause is related to the gene associated with that abnormality. Over time, it is thought that noncompaction can proceed to DCM with severe systolic dysfunction. LVNC is inherited mainly through an autosomal dominant mode of transmission but X-linked transmission is also seen. Mutations in two sarcomere genes, *MYH7* and *MYBPC3,* are responsible for almost a third of LVNC cases. The genes that have been reported mainly encode for sarcomeric, Z-disc and nuclear-envelope proteins as well as mitochondrial proteins. A mutation in the α-dystrobrevin gene (*DTNA*) on chromosome 18q12.1 has been linked to LVNC1. Mutations for LVNC2 and LVNC3 have been identified on chromosome 11p15 (LVNC2 and chromosome 10q23 (LYNC3) respectively. LVNC variants have been mapped specifically to mutations of the sarcomere genes: LVNC4 is linked to mutation in the *ACTC1* gene (chromosome 15q14), LVNC5 to a mutation in the *MYH7* gene (chromosome 14q12), and LVNC6 caused by mutation in the *TNNT2* gene (chromosome 1q32). Mutation in the *MIB1* gene (chromosome 18q11) is linked to LVNC7, whereas LVNC8 is caused by mutation in the *PRDM16* gene (chromosome 1p36), LVNC9 is brought about by mutation in the *TPM1* gene (chromosome 15q22). Mutation in the *MYBPC32* gene (chromosome 11p11) is implicated in LYNC10. There is also an X-linked form of LVNC, Barth syndrome, caused

by mutation in the *TAZ* gene on chromosome Xq28 that encodes tafazzin (TAZ), a mitochondrial protein.

TABLE 39.2 Genetic Variants of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

ARVC Variant	Chromosome Locus/Gene	Gene Product and Function
ARVC1	14q24.3/*TGF* B3	Encodes for transforming growth factor–β-3 involved in emb
ARVC2	1q43/*RYR2*	Encodes ryanodine receptor 2 involved in Ca^{2+} release into
ARVC3	14q12-q22/*Unknown*	In 1996, discovered in a study of three small families
ARVC4	2q32.1-q32.3/*TTN*	Encodes for Titin, an essential component of sacromeres an
ARVC5	3p25.1/*TMEM43*	*TMEM43* may have an important role in maintaining nucl keeping Emerin in inner nuclear membrane
ARVC6	10p14-p12/*Unknown*	
ARVC7	2q35/*DES*	Encodes the protein Desmin. Important role in maintaining s muscles
ARVC8	6p24.3/*DSP*	Encodes Desmoplakin, a constituent protein of desmosome
ARVC9	12p11.21/*PKP2*	Encodes for plakophilin 2 and is one of several proteins that in the myocardium,
ARVC10	18q12.1/*DSG2*	Encodes for desmogleins involved in desmosome cell adhes
ARVC11	18q12.1/*DSC2*	Encodes for desmocollin 2, a major component of desmoso
ARVC12	17q21.2/*JUP*	Encodes plakoglobin found primarily in cells of the heart an and desmosomes
ARVC13	10q21.3/*CTNNA3*	Encodes a protein from the vinculin/α-catenin family. Has a

D. From Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), {date}. World Wide Web URL: https://omim.org/

E. Arrhythmogenic disorders

1. Brugada syndrome. Disorders of the conduction system of the heart lead to significant clinical manifestations, most notably ventricular arrhythmias and sudden cardiac death. Two entities, long QT syndrome (LQTS) and Brugada syndrome, have been well described, and their respective genetic abnormalities have been characterized. Brugada syndrome was initially described by Josep and Pedro Brugada in 1992. Clinically, ventricular arrhythmias and sudden cardiac death occur, particularly in middle-aged men. Characteristic electrocardiographic features can help make the diagnosis, and, in some cases, certain drugs, including sodium channel blockers and tricyclic antidepressants, can unmask the abnormality on a surface electrocardiogram. Brugada syndrome is typically inherited in an ***autosomal dominant*** pattern with incomplete penetrance. It appears that the penetrance is age and sex

dependent. However, a de novo mutation can occur in approximately 1% of cases. Mutations in more than 15 genes have been identified as causing Brugada syndrome: *SCN5A, SCN1B, SCN2B, SCN3B, SCN10A, RNGRF, GPD1-L, HCN4, KCNE3, GPD1L, HCN4, KCNE3, KCND3, KCNJ8, KCNE5, CACNA1C, CACNB2, CACNA2D1, TRPM4, SLMAP,* and the *PKP2* gene. The *SCN5A* gene with approximately 300 known mutations is the gene most commonly associated with Brugada syndrome and accounts for approximately of 25% of cases. It has been mapped to chromosome 3p22.2 and is a voltage-gated sodium channel gene. *SCN1B* (chromosome 19q13.12), *SCN2B (*chromosome 11q23.3) *SCN3B (*chromosome 11q24.1), and *SCN10A* (chromosome 3p22.2) are also voltage-gated sodium channel genes. The *RANGRF* gene on chromosome 17p13 encodes a protein involved in the function of the Nav1.5 cardiac sodium channel. *GPD1-L,* an NAD-dependent glycerol-3-phosphate dehydrogenase gene, is associated with chromosome 3p22.3. *HCN4*, on chromosome 15q24, is a hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 gene. *KCNE3* (chromosome 11q13.4), *KCND3* (chromosome 1p13.2), *KCNJ8* (chromosome 12p12.1) are voltage-gated potassium channel genes also. *KCNE5* (chromosome Xq22.3) is an X-linked potassium voltage-gated channel gene. *CACNA1C (chromosome 12p13.33)* and *CACNB2* (chromosome 10p12.33-10p12.31) are two subunits of the L-type voltage-dependent calcium channels, whereas *CACNA2D1* gene (chromosome 7q21.11) and *TRPM4* gene (chromosome 19q13.33) are other calcium voltage–gated genes. The *SLMAP* gene (chromosome 3p14.3) is implicated in encoding an element of a conserved striatin-interacting phosphatase and kinase complex. *PKP2* gene (chromosome 12p11.21) encodes plakophilin *2.*In addition, some modifier genes have also been identified. Genetic testing in Brugada syndrome is used to confirm a clinical diagnosis. A negative result does not necessarily exclude the diagnosis. It may reflect that the individual does not have the condition, but it may also mean that the individual either has a mutation in a gene not part of the testing panel or has a mutation in a Brugada-associated gene not included in the panel or the mutation is yet undiscovered. Approximately only one-third of clinically diagnosed cases are found to have a genetic cause despite the large number of genes associated with Brugada syndrome.

2. **Long QT syndrome.** LQTS encompasses a range of disorders characterized clinically by **syncope and sudden cardiac death, with electrocardiographic abnormalities in the QT interval and in the T-wave morphology**. LQTS is usually inherited in an ***autosomal dominant pattern***. Recessive inheritance, seen in Jervell and Lange-Nielsen types 1 and 2, is rare. De novo mutations are uncommon. There are approximately 15 different types of LQTS based on the type of gene involved. Of these known genes *KCNQ1* (LQT1), *KCNH2*(LQT2) and *SCN5A* (LQT3) are the most frequently identified and account for approximately 75% of cases. Each of the remaining 12 genes account for less than 1% of cases. Approximately 20% of clinically diagnosed LQT is not linked to a variant in a known gene. The various forms of LQTS are often distinguishable by clinical features and genetic abnormalities. One such distinguishing feature is that those with LQT1 are typically at higher risk during periods of exercise, whereas those with the LQT3 variant are at higher risk during sleep. The *KCNQ1* gene encodes the catecholamine-sensitive portion of the potassium channel responsible for conducting the delayed rectifier current (I_{Ks}) in the LQT1 variant, whereas the *SCN5A* gene is affected in the LQT3 variant. The underlying defect involving the sodium channel results in a prolonged depolarization current, whereas defects involving the

potassium channel result in a longer QT duration secondary to inability to reestablish repolarization within the myocyte. The autosomal recessive phenotypes (Jervell and Lange-Nielsen types 1 and 2) are associated with bilateral sensorineural hearing loss.

Hundreds of mutations are involved in LQTS. However, most of the prognostic information available is based on the gene involved and not the specific mutation. Having the genotypic information can help in prognosis and in determining response to therapy. The rates of ventricular arrhythmias and sudden cardiac death vary based on the gene involved, as does the response to therapy. This information may be particularly helpful in trying to decide between medical therapy, implantable cardioverter–defibrillator implantation, or both. Table 39.3 lists the variants of LQTS and the genes involved.

3. **Atrial fibrillation.** AF is the most common of the arrhythmic disorders. The majority of adult-onset familial AF is inherited in an ***autosomal dominant*** pattern. In 2003, the first genetic mutation for AF was identified as an S140G mutation in *KCNQ1*. This mutation is responsible for a gain of function in the IKs channel complex. Mutations implicated in gain-of-function effects as well as loss-of-function effects on IKs have been reported. The majority of the mutations linked to AF have been found in the potassium ion channel genes (*KCNQ1, KCNE1, KCNE2, KCNE3* and *KCNE5, KCNJ2*, and *KCNH2*). The connexin 40 gene (*GJA5*) has also been implicated. Mutations in SCN5A encoding four regulatory β-subunits can cause AF also. Germline and somatic mutations have also been associated with AF.

The first GWAS study, in 2006, identified that the SNPs associated with AF were on chromosome 4q25. In that study SNP, rs2200733, was the most significant identified in European, Asian, and African populations. The 4q25 variants are near the *PITX2* gene, which is involved in left–right symmetry of the heart in development. It has not yet been proven how the variants at 4q25 exert their effect. SNPS associated with AF have been identified on at least 10 different chromosomes. Owing to the relatively small number of mutations identified for familial AF coupled with the genetic complexity, it is quite possible that there are many more mutations for familial AF that are still unknown.

TABLE 39.3 Genetic Variants Associated with Long QT Syndrome

LQT Variant	Gene	Chromosome Locus	Mode of Inheritance	Protein
LQT1	*KCNQ1*	11p15.5	Autosomal dominant	Catecholamine-sensitive
LQT2	*KCNH2*	7q35-36	Autosomal dominant	α-Subunit of I_{Kr} potassium
LQT3	*SCN5A*	3p21-24	Autosomal dominant	Cardiac sodium channel
LQT4	*ANK2*	4q25-27	Autosomal dominant	Ankyrin protein
LQT5	*KCNE1*	21q22.12	Autosomal dominant	β-Subunit of I_{Ks} potassium

TABLE 39.3 Genetic Variants Associated with Long QT Syndrome

LQT6	*KCNE2*	21q22.11	Autosomal dominant	β-Subunit of I_{Ks} potassium
LQT7	*KCNJ2*	17q23	Autosomal dominant	Subunit of I_{Kr} potassium c
LQT8	*CACNA1C*	12p13.3	Autosomal dominant	Subunit of the L-type volt
LQT9	*CAV3*	3p25	Autosomal dominant	Encodes caveolin-3, four cells *CAV3* gene mutations ma
LQT10	*SCN4B*	11q22.3	Autosomal dominant	β-voltage–gated sodium c
LQT11	*AKAP9*	7q21-22	Autosomal dominant	Encodes the A-kinase an
LQT12	*SNTA1*	20q11.2	Autosomal dominant	Syntrophin α-1 peripher dystrophin, and dystrop
LQT13	*KCNJ5*	11q24.3	Autosomal dominant	G protein–activated inwa
LQT14	*CALM1*	14q32.11	Autosomal dominant	Calmodulin 1, a calcium b
LQT15	*CALM2*	2p21	Autosomal dominant	Calmodulin 2, a calcium b
Jervell and Lange-Nielsen type 1	*KCNQ1*	11p15.5-15.4	Autosomal recessive	Subunit I_K channel
Jervell and Lange-Nielsen type 2	*KCNE1*	21q22.12	Autosomal recessive	β-Subunit of I_{Ks} potassium

F. Valvular heart disease

1. Mitral valve prolapse. Nonsyndromic MVP (see Chapter 16) is a common disorder that appears to have a strong genetic component, and the familial form is inherited in an ***autosomal dominant pattern*** with variable penetrance dependent on sex and age. Presentation of MVP may vary even within members of the same family. In addition, it occurs in an idiopathic form, and it is also associated with other valvular syndromes such as bicuspid aortic valve (BAV) and connective tissue diseases, which typically affect cardiovascular function such as Marfan syndrome (syndromic MVP), osteogenesis imperfecta, and Ehlers–Danlos syndrome. Prolapse of the mitral valve occurs primarily because of abnormalities in the connective tissue matrix of the valve itself. Myxomatous degeneration of the valve tissue leads to redundant tissue and weakening of both the valve and the subvalvular apparatus. Clinically, this manifests as displacement of the mitral valve leaflets into the left

atrium during systole and may progress to mitral regurgitation and eventual congestive heart failure with occasional rupture of the chordae. Although surgical repair and replacement have improved the long-term prognosis of this disorder, understanding the genetic basis of this disease may allow the earlier diagnosis and development of therapies to prevent progression.

Three chromosomal locations have been identified with MVP inherited in an autosomal dominant manner. These are *MMVP1*(chromosome 16p12.1-11.2), *MMVP2* (chromosome 11p15.4), and *MMVP3* (chromosome 13q31.1-32.1). X-linked myxomatous valvular dystrophy (XMVD) has been mapped to chromosome Xq28, and the P637Q mutation in the filamin A gene (*FLNA*) has been identified as a cause of XMVD. Additional mutations in the *FLNA* gene have been linked to X-linked MVP/XMVD. In 2015, the *DCHS1* gene at the chromosomal location for MMVP2 was discovered. This gene is a member of the cadherin superfamily and encodes calcium-dependent cell–cell adhesion molecules. A loss-of –function mutation (R2513H) in this gene is implicated in MVP. Additional mutations in this gene have been identified and their links to MVP are being investigated. In 2015, three loci, 2q35, 17p13, and 22q12, associated with MVP were identified.

2. **Aortic valve disease.** Aortic valve disease (see Chapter 15) can be divided into two different types based on clinical characteristics: **BAV and calcific trileaflet aortic valvular disease**. Calcific aortic valvular disease is typically a disease of the elderly. It was thought to be affected by those risk factors predisposing toward CAD but more recently is recognized as a separate condition from atherosclerosis. BAV is believed to be a congenital abnormality with an ***autosomal dominant*** mode of transmission with reduced penetrance. The prevalence of BAV in first-degree relatives of affected individuals has been reported as being as high as 9%. BAV is present in 0.2% to 2% of the population and is typically discovered earlier on in life and is frequently associated with disease of the aorta. What BAV and calcific aortic valvular disease have in common is the eventual progression to calcification of the aortic valve itself. Mutations in the *NOTCH1* gene located on chromosome 9 at q34.3 have been implicated in BAV development. NOTCH1 is a transmembrane protein with transcriptional regulatory activity that is vital not only for aortic valve development but also for calcification. It is thought that mutations in this gene may allow the normally repressed transcription factor Runx2 to facilitate the development of valvular endothelial cells into osteoblast-like cells and promote valvular calcification. Mutations in the *ACTA2* gene on chromosome 10q23.3, which codes for actin, have also been linked to BAV. Mutations in ubiquitin fusion degradation 1-like gene, located at 22q11.21, have also been implicated in BAV. This gene codes for a signaling protein that is prevalent during embryonic formation of cardiac outflow tracts. Another gene implicated in BAV is the *GATA5* gene on chromosome 20q13.33 encoding for a protein that is a transcription factor containing two GATA-type zinc fingers. This protein is necessary for cardiovascular development. Recent studies have identified associations between loss-of-function mutations of the *GATA5* gene and BAV. In 2014, Qu et al. reported that a loss-of-function mutation in the *NXK2-5* gene, location 5q35.1, was associated with BAV in a Chinese family. The *NXK2-5* gene encodes a homeobox-containing transcription factor that is involved in cardiac embryological development. Mutations in this gene are known to cause atrial septal defect, and tetralogy of Fallot. Three additional loci associated with BAV have been identified on the long arms of chromosomes 5, 13, and 18, but no specific genes have been discovered. Interestingly, in 2014, Researchers using a targeted next-generation sequencing approach identified variants in 26 genes not

previously implicated with BAV in humans. It is evident that many different genes are implicated in BAV and calcific aortic valvular disease

TABLE 39.4 Cardiovascular Manifestations of Systemic Metabolic Disease

Metabolic Disorder	Gene/Protein Defect	Effect upon Cardiovascu
Fabry disease	*GLA* gene mutations cause α-galactosidase deficiency causes an accumulation of globotriaosylceramide	LV hypertrophy, RV, hype heart disease, mitral hypertrophy of papillary dilatation, atrial enlarg function may be ir arrhythmias, and corona
Hereditary hemochromatosis(classified by Type)	*HFE* gene mutations cause defect in MHC class I-like protein (Type 1) *HJV* gene mutations cause defect in hemojuvelin (Type 2) *HAMP* gene mutations cause defect in hepcidin (Type 2) *TFR2* gene mutations cause defect in transferrin receptor-2 (Type 3) *SLC40A1* gene mutations cause defect in ferroportin (Type 4)	Abnormal proteins inv absorption and storage iron deposition in the hea cardiomyopathy, cardi failure, and arrhythmia
Niemann–Pick disease (classified by Types A, B, and C)	*SMPD1* gene mutations cause defect in sphingomyelinase (Types A and B) *NPC1* or *NCP2* gene mutations cause defect in proteins implicated in lipid transport (Type C)	Accumulation of sphingom tissue leading to cardion and B) Serum triglycerides and often elevated, HDL-ch (Type B) Abnormal accumulation lysosomes, and cell dysf of lack of lipids within leads to tissue and orga C)
Mucopolysaccharidosis type I (MPS I) Classified into severe (Hurler syndrome) and attenuated (Hurler–Scheie syndrome; Scheie syndrome) types	Mutations in *IDUA* gene cause deficiency in α-l-iduronidase	Biventricular enlargemer fibrosis, and valvular dise Severe MPS I results in failure with first 10 years

TABLE 39.4 Cardiovascular Manifestations of Systemic Metabolic Disease

Mucopolysaccharidosis type II (MPS II) Hunter syndrome Classified into severe and mild types	Mutations in the *IDS* gene cause deficiency in iduronate-2-sulfatase	Accumulation of glyc within lysosomes lead involvement including v that can lead to ventricu and heart failure. Cardia cause of morbidity
Danon disease	Mutations in the *LAMP2* gene cause deficiency in lysosome-associated protein-2	Cardiac involvement inclu arrhythmia, left VH, CHF dilated cardiomyop preexcitation (Wolff–P syndrome usually)
Gaucher disease (cardiovascular type) Autosomal recessive	Mutations in *GBA* gene cause deficiency of β-glucocerebrosidase	Accumulation of glucocere to cardiomyopathy, also aorta and aortic and mitr
Pompe disease Classified by type: classic infantile-onset, nonclassic infantile-onset, and late-onset.	Mutations in *GBA* gene cause deficiency in acid α-glucosidase	Accumulation of glyc biventricular concentri cardiomyopathy, arrhy failure
Primary carnitine deficiency	Mutations in *SLC22A5* gene result in absent or dysfunctional OCTN2 protein resulting in carnitine deficiency.	Accumulation of fatty acids cardiomegaly, hypertro cardiomyopathy, heart sudden death

G. CHF, congestive heart failure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; MHC, major histocompatibility complex; RV, right ventricular; VH, ventricular hypertrophy.

TABLE 39.5 Common Chromosomal Abnormalities and Associated Cardiovascular Disease

Syndrome	Chromosomal Abnormality	Associated Cardiovascular Abnormality
Down syndrome	Trisomy 21	Endocardial cushion defect, VSD, PDA, and tet

TABLE 39.5 Common Chromosomal Abnormalities and Associated Cardiovascular Disease

Turner syndrome	45X	Coarctation of the aorta, bicuspid AV, and anom
Patau syndrome	Trisomy 13	Dextrocardia, VSD, ASD, endocardial cushion d Fallot, coarctation of the aorta, and PDA
Edward syndrome	Trisomy 18	VSD, ASD, endocardial cushion defect, coarct tetralogy of Fallot, pulmonary valve stenosis,
Fragile X syndrome	*FMR1* gene (X chromosome) with trinucleotide repeats	Mitral valve prolapse, aortic root dilation

H. ASD, atrial septal defect; AV, aortic valve; PDA, patent ductus arteriosus; PV, pulmonary vein; SVC, superior vena cava; VSD, ventricular septal defect.

I. Inborn errors of metabolism. Cardiovascular disease is often a manifestation of genetic abnormalities in separate pathways, which produce secondary effects upon the cardiovascular system. Many of these genetic mishaps occur in multiple pathways essential to metabolism, and their resultant phenotypes often impose upon the cardiovascular system. Table 39.4 lists some examples of metabolic abnormalities and the associated cardiac manifestations.

J. Chromosomal abnormalities and cardiovascular disease. Chromosomal abnormalities that occur at the time of development can have serious implications with regard to the proper growth and development of a child. Although neuropsychiatric development is often delayed, the cardiovascular system is also affected in many of these disorders and often survival may be limited owing to the severity of congenital cardiac defects. Table 39.5 lists common syndromes associated with chromosomal structural abnormalities and the associated cardiovascular findings.

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CHAPTER 38

Cardiac Tumors

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I. INTRODUCTION. Cardiac neoplasms are **rare** in comparison with other forms of heart disease. Although secondary tumors of the heart are by definition malignant, primary tumors may be either benign or malignant. **Primary cardiac tumors are rare, occurring approximately 30 times less frequently than cardiac metastases**. In a large series of more than 12,000 autopsies, primary cardiac tumors occurred with an incidence less than 0.1%. Most of these primary tumors (approximately 75%) are benign, with cardiac myxoma being the most common. Cardiac sarcomas, followed by lymphomas, are the most common primary malignant tumors.

II. CLINICAL PRESENTATION. Patients may present with nonspecific constitutional symptoms or with cardiovascular symptoms from tumor interference with valvular structures (regurgitation, stenosis), myocardium (decreased contractility, arrhythmias), and/or pericardium (pericardial effusion) or from tumor embolization. However, the majority of cardiac tumors are found incidentally on echocardiography performed for other indications.

A. Constitutional symptoms. Many tumors, especially myxomas, are associated with a wide variety of systemic manifestations. Fever, chills, malaise, cachexia, and weight loss are not uncommon. Associated laboratory abnormalities, including leukocytosis, thrombocytosis or thrombocytopenia, hypergammaglobulinemia, as well as elevated erythrocyte sedimentation rate and C-reactive protein levels are frequently present as well. These findings are likely attributable to the constitutive production of **inflammatory cytokines** by the tumor or due to release from tumor necrosis. Myxoma cell production of **interleukin-6** and elevation of **antimyocardial antibodies** have been documented, with levels of these serum markers normalizing after tumor resection.

B. Embolic phenomena. Tumor embolization may account for the initial presenting symptoms, via either direct embolization of tumor fragments or thromboemboli released from the tumor surface. The type of emboli is dependent on tumor **location** as well as the presence of intracardiac shunts. **Right-sided** tumors, and left-sided tumors with left-to-right shunts, result in pulmonary emboli and if untreated may result in cor pulmonale. It may be difficult to clinically differentiate pulmonary tumor emboli from those because of venous thromboembolic disease. Chest radiography is usually not helpful. However, noninvasive imaging often has two unique characteristics that help differentiate tumor emboli from venous thromboemboli. First, tumor emboli may result in completely unilateral defects.

Second, defects caused by tumor emboli generally do not resolve with time or with anticoagulation. **Left-sided** tumor emboli may result in visceral infarction, limb ischemia, myocardial infarction, or transient ischemic attack/stroke. In addition, multiple vascular aneurysms may develop. Of the benign primary cardiac tumors, embolization is most frequently noted with cardiac myxomas and even more so if the tumor has a villous surface. The brain is the most common site for systemic embolization in primary cardiac neoplasms, involving both hemispheres in approximately 40% of cases. Embolic findings in a young person, in sinus rhythm and without valvular disease or endocarditis, should raise suspicion for the presence of an embolic source related to an intracardiac tumor.

C. Direct cardiac invasion/mass effect. Signs and symptoms are governed by tumor location and size. Intramyocardial tumors, which are most often found in the left ventricular free wall and intraventricular septum, generally remain asymptomatic when the tumor size is small but can result in arrhythmias, conduction abnormalities, and sudden cardiac death if they become larger. Impaired ventricular performance may mimic restrictive or hypertrophic cardiomyopathy. Rarely, ventricular rupture has been the initial presentation. Tumors of the left atrium, especially if mobile, may prolapse into the mitral valve, resulting in obstruction of atrioventricular (AV) blood flow. This results in signs and symptoms similar to mitral stenosis, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, and fatigue. Importantly, **syncope and sudden death** may also occur.

III. PHYSICAL EXAMINATION.

Physical examination may show signs of pulmonary venous congestion. A fourth heart sound (S_4) may be present, as may a widely split, **loud first heart sound** (S_1). The loud S_1 may be heard with left atrial tumors and is caused by late closure of the mitral valve, when the left ventricular–left atrial pressure crossover occurs at a higher pressure. Although this finding is also seen with mitral stenosis and preexcitation, the absence of a diastolic rumble or a short PR on an electrocardiogram should raise the possibility of left atrial tumor. Left atrial tumor may cause a holosystolic murmur at the apex radiating to the axilla (if tumor causes mitral incompetence) as well as a diastolic murmur (if the tumor obstructs mitral flow simulating mitral stenosis). The pathognomonic **tumor plop** manifests as an early diastolic sound, after an opening snap but before a third heart sound (S_3). Tumors of the **right atrium** often result in systemic venous congestion. Once significant pulmonary hypertension occurs, **systemic hypoxia, clubbing, and polycythemia** may develop as a result of right-to-left shunting. Right atrial tumors and intracavitary **right ventricular** tumors may present as right heart failure. A diastolic rumble that varies with inspiration may be noted and is due to tricuspid valve obstruction. The **P_2** is delayed and may have varying intensities. Jugular venous pressure waveform examination may demonstrate **prominent** a-**waves and Kussmauls sign**. Recurrent pulmonary emboli can potentiate pulmonary hypertension. **Left ventricular** tumors, when not intramural, typically result in signs and symptoms of pulmonary venous congestion or low-output states. Upon examination, findings may mimic aortic stenosis, subvalvular stenosis, or hypertrophic cardiomyopathy.

IV. DIAGNOSIS.

Because no clinical sign or symptom is specific, more advanced diagnostic methodology is universally required.

A. Electrocardiography (ECG). In isolation, ECG provides little added clue to the diagnosis. However, changes in rhythm or voltage or development of new AV block on

serial tracings may be the first sign of either extension of a primary cardiac tumor or development of secondary cardiac involvement.

B. Radiography. Chest radiography may be helpful in identifying epicardial tumors. Cardiomegaly, mediastinal widening, or cardiac silhouette irregularities may suggest the diagnosis. Calcifications are seen occasionally. Pulmonary congestion or oligemia may be noted in patients with large left or right intracavitary tumors, respectively.

C. Echocardiography. Transthoracic echocardiography (TTE) is usually the primary diagnostic tool in most patients with a sensitivity ranging from 55% to 93% (based on the TTE machine properties, mass location and size). If a tumor is strongly suspected or a mass is noted by TTE, transesophageal echocardiography (TEE) should be considered. TEE provides improved sensitivity (approximately 97%) and specificity, particularly with atrial masses, and allows for superior visualization of anatomic details, such as contour, cysts, calcification, and presence of a stalk. Three-dimensional echocardiography is also increasingly helpful in evaluation because of its ability to visualize complex cardiac masses.

D. Radionuclide imaging. Positron emission tomography scanning may be useful in metastatic disease to look for cardiac involvement.

E. Computerized tomography (CT). CT, especially multislice CT with contrast, is often used in the diagnosis and evaluation of cardiac masses. It can define tumor extension, assess tumor calcification, and evaluate the adjacent extracardiac structures (lungs, mediastinum, and great vessels).

F. Cardiac magnetic resonance (CMR). Like CT, CMR has an important role in the evaluation of cardiac tumors. Specifically, it characterizes size, shape, and surface features, as well as evaluating tissue composition—giving information regarding the type of tumor that is present. Magnetic resonance imaging (MRI) has the highest soft tissue contrast of the imaging modalities, and it is particularly helpful in distinguishing thrombus from tumor. It is also the most sensitive imaging modality for detecting the extent of tumor infiltration.

G. Angiography. Cardiac catheterization is **not necessary in most cases**. However, in the following scenarios, the risk and cost of angiography may be worthwhile: clarifying inadequate noninvasive imaging, defining blood supply for suspected malignant tumors (see Fig. 38.1), and evaluating coexistent valvular or coronary artery disease that could alter surgical approach. The major additional risk of angiography is embolization of tumor or thrombus. A transseptal approach is relatively contraindicated in cases of suspected left atrial myxoma, given the high frequency of involvement of the fossa ovalis and the accompanying risk of embolization.

H. Endomyocardial biopsy (EMB). Limited data exist on the utility of EMB in the management of cardiac tumors. Generally, diagnosis is made from noninvasive imaging; however, EMB can be considered if imaging is equivocal or if a tissue sample is required prior to treatment decisions (i.e., chemotherapy).

FIGURE 38.1 Coronary angiogram showing collateral blood flow supplying a suspicious mass. It turned out to be a malignant sarcoma in the right atrium.

V.PRIMAR CARDIAC MALIGNANCIES

A. Benign neoplasms. A description of specific benign cardiac tumors is given in subsequent text. Relative proportions are given in Table 38.1.

1. **Myxomas (Fig. 38.2).** They are the most common among the primary benign cardiac tumors in adults, accounting for approximately 50% of them. Most myxomas are sporadic (90%) and present typically as a lobular left atrial mass attached to the **interatrial septum (often in the region of the fossa ovalis)** via a pedicle. It is important to note that **tumors located on the posterior wall of the left atrium are usually not benign**. Less frequently, myxomas may be found in the right atrium, either ventricle, or arising from the AV valves. **Atrial myxomas are rarely inherited as part of the Carney complex** which consists of both cardiac and noncardiac myxomas, spotty pigmentation (i.e., pigmented nevi), and endocrine overactivity (pituitary, adrenocortical, and endocrine testicular tumors). Patients with the Carney complex typically present in the third decade, often have bilateral tumors, and have high recurrence rates following resection. If a myxoma syndrome is suspected, **screening echocardiography is recommended** for all first-degree relatives, particularly if the index patient is young, has multiple tumors, or has typical noncardiac features of the genetic syndrome.

   Pathologically, cardiac myxomas may be either smooth, round, or gelatinous, or friable and irregular in appearance. They sometimes contain a hemorrhagic core and frequently attach via a sessile or pedunculated base. The typical diameter at presentation is 4 to 8 cm and the typical mass is 15 to 180 g. **Histologically**, myxomas have characteristic patterns of "lipidic" cells within glycosaminoglycan-rich myxoid stroma. **Ultrastructurally**, myxoma cells resemble embryonic mesenchymal cells. **Immunohistochemically**, they demonstrate variable activity for endothelial cell markers, with reliable positivity to vimentin, indicating a mesenchymal derivation. Myxomas also produce vascular endothelial growth factor, likely contributing to angiogenesis and tumor growth.

2. **Papillary fibroelastomas.** They are the second most common primary cardiac tumors in adults and, grossly, these benign tumors resemble sea anemones, with frondlike arms protruding off a central stalk. They are avascular and typically pedunculated. The majority are located on the **ventricular surface of the aortic valve**, at the mid-portion of the valve, whereas the atrial side of the mitral valve is the second most common location (see Fig. 38.3). Rarely, they may present on the endocardial surfaces. Although these tumors are not associated with valvular dysfunction, in approximately 30% of cases, thrombus, with subsequent emboli, develops. Surgical resection is generally recommended for patients with a symptomatic presentation with embolization or in an asymptomatic patient with large, mobile tumors (1 cm or greater in diameter). Anticoagulation may be considered if recurrent embolization occurs in a nonsurgical candidate. Fibroelastomas may be differentiated from Lambl excrescences, which are also commonly found on the aortic valve, by their location on the mid-portion of the valve as opposed to the closure lines in case of Lambl excrescences.

TABLE 38.1 Relative Proportion of Benign and Malignant Tumors in Adults by Tumor Type

Benign Tumor	% of Group	Malignant Tumor
Myxoma	46	Angiosarcoma
Lipoma	21	Rhabdomyosarcoma
Papillary fibroelastoma	16	Mesothelioma

TABLE 38.1 Relative Proportion of Benign and Malignant Tumors in Adults by Tumor Type

Rhabdomyoma	2	Fibrosarcoma
Fibroma	3	Lymphosarcoma
Hemangioma	5	Osteosarcoma
Teratoma	1	Thymoma
AVN mesothelioma	3	Neurogenic sarcoma
Granular cell tumor	1	Leiomyosarcoma
Neurofibroma	1	Liposarcoma
Lymphangioma	1	Synovial sarcoma

3. AVN, atrioventricular nodal.

4. **Rhabdomyomas.** Rhabdomyomas, the most common benign tumor in **children** and **infants**, are frequently located within one of the ventricles. These tumors are nearly always **multiple**, and the majority of patients have at least one intracavitary, obstructing lesion. The most common presentation for this type of cardiac tumor in adults is arrhythmia; however, it may be clinically silent if the tumors are small. There is a clear association with **tuberous sclerosis**: 80% of rhabdomyoma patients have the disease and 60% of tuberous sclerosis patients have rhabdomyomas. In some cases, rhabdomyomas may regress spontaneously during childhood.

5. **Fibromas.** Generally, fibromas are found in **pediatric** populations as well; these benign connective tissue tumors are almost universally **intramural**. They are usually firm, circumscribed but unencapsulated, and may grow to **several centimeters**. They have preponderance for the left ventricle and, unlike rhabdomyomas, do not spontaneously regress. The **Gorlin syndrome** includes cardiac fibromas, multiple basal cell carcinomas, jaw cysts, and skeletal abnormalities.

6. **Lipomas.** These benign tumors occur at **all ages,** with men and women affected equally. Tumors range in size depending on their location. Seventy-five percent of tumors are found in the subendocardium, whereas the remainder are subepicardial, intramuscular, or valvular. Many tumors are **clinically silent** and identified only at autopsy. Subendocardial tumors may result in symptoms related to cavity obstruction, whereas subpericardial tumors can lead to compression of the heart and/or development of pericardial effusion. Intramyocardial tumors may result in arrhythmias or conduction disturbances and possibly sudden death. Valvular lipomas can lead to valvular insufficiency and heart failure. Lesions are generally **well encapsulated** with a center of predominantly benign fatty cells. Without pathologic confirmation, lipomas can be confused with lipomatous hypertrophy of the interatrial septum. Both MRI and CT are useful in diagnosing cardiac lipomas based on the characteristic features of fatty tissue with these techniques.

FIGURE 38.2 **A** and **B**: Large, mobile protruding left atrial tumor arising from the atrial septum seen on transesophageal echocardiography. Pathology was consistent with atrial myxoma.

7. **Hemangiomas/lymphangiomas.** These tumors are **very rare** and consist of benign collections of endothelial cells. Usually they are located within the intraventricular septum or AV node and as such may present as heart block, sudden cardiac death, or hemopericardium.

FIGURE 38.3 **A** and **B**: Mobile mass on the atrial surface of the mitral valve on parasternal long-axis view of mitral valve on transthoracic echocardiography. Pathology was consistent with mitral valve fibroelastoma.

B. Malignant neoplasms. Histologically, **primary malignant tumors are virtually always sarcomas**. Suggestive **characteristics** include rapid growth, mediastinal invasion, hemorrhagic pericardial effusion, precordial pain, and pulmonary vein extension. Primary malignant neoplasms make up approximately 25% of all primary cardiac tumors. Cardiac sarcomas are the most common primary malignancies of the heart.

1. **Angiosarcomas.** Almost always found within the right atrium, angiosarcomas often take the form of broad-based, lobular masses. Hemorrhagic pericardial effusions are not uncommon. Histologically, these tumors have ill-defined vascular channels lined with atypical endothelial cells. The blood flow through the tumor may produce a continuous precordial murmur. Despite resection and/or adjuvant therapy, clinical deterioration is rapid.
2. **Rhabdomyosarcoma.** These sarcomas a**re more common in children and may affect any cardiac chamber.** Tumors are generally infiltrative, but on occasion they may develop polypoid extensions, which can cause them to be mistaken for myxomas. Prognosis is poor.
3. **Mesothelioma.** The typical location of primary cardiac mesothelioma is the **pericardium**. Generally very diffuse, these tumors lead to symptoms consistent with pericarditis or hemorrhagic effusion. They may occasionally infiltrate the **AV node**, leading to conduction disturbances, sudden cardiac death, or tamponade. Much like cardiac sarcomas, these tumors carry a very poor prognosis.
4. **Other.** Fibrosarcomas, lymphosarcomas, liposarcomas, and other undifferentiated sarcomas represent the remainder of primary cardiac malignancies. These tumors are very rare and are generally infiltrative, involving multiple cardiac chambers. A clinical syndrome mimicking hypertrophic cardiomyopathy has been observed.

VI. SECONDARY CARDIAC MALIGNANCIES. As mentioned previously, most malignancies of the heart are secondary and, by definition, **metastatic**. The overwhelming majority of metastatic cardiac tumors occur in the **pericardium** and are usually **carcinomas**, as opposed to sarcomas. Because of increased prevalence, **the most commonly found metastatic tumor to the heart is lung cancer**. The typical presentation is of pericardial effusion or tamponade or pulmonary vein obstruction from direct extension. After metastatic lung cancer, breast cancer, lymphoma, leukemia, and renal cell carcinoma are the most common offenders. The tumor with **the greatest propensity to metastasize to the heart is melanoma**, followed by germ cell tumors and leukemia (Table 38.2). A new complaint referable to the heart in a patient with known extracardiac malignancy should prompt a thorough investigation to rule out cardiac malignancy. Unfortunately, prompt diagnosis usually does not favorably alter the prognosis.

VII. DIFFERENTIAL DIAGNOSIS. Establishing the correct diagnosis is imperative. A thorough differential diagnosis of **nonmalignant conditions** must be considered and ruled out. Possibilities include pericardial cysts, teratomas, lipomatous hypertrophy of the interatrial septum, thrombus, and sarcoid. Unfortunately, the final diagnosis in many cases must still be made pathologically.

VIII. THERAPY AND PROGNOSIS. The primary therapy for benign tumors remains **operative resection**, given the associated risk of lethal obstruction, arrhythmia, or embolization. Most surgeons perform excision with extracorporeal circulatory support in order to directly visualize the tumor, as well as a careful search for metasynchronous tumors. In higher risk patients, more extensive resection is recommended. The femoral or azygous vein is usually cannulated, as opposed to the right atrium, to avoid potential tumor fragment embolization. Mitral valve repair or replacement is usually unnecessary in the absence of associated bacterial endocarditis. An analysis reviewing 106 operations for sporadic atrial myxomas noted only one perioperative death. Survival at 25 years is no different when compared with age- and sex-matched controls. There are limited data regarding the use of a minimally invasive or robotic approach to cardiac tumor resection. Small series suggest that parasternal or partial sternotomy access does not compromise the safety or efficacy while allowing for shortened hospitalization and better cosmetic results. Long-term follow-up is not yet available for this approach.

TABLE 38.2 Metastatic Tumors to the Heart by Absolute Number and Greatest Propensity

Primary Tumor	Absolute Number	Primary Tumor	Nur
Lung	180	Melanoma	46
Breast	70	Germ cell	38
Lymphoma	67	Leukemia	33
Leukemia	66	Lymphoma	17
Esophagus	37	Lung	17
Uterus	36	Sarcoma	15
Melanoma	32	Esophagus	13
Gastric	28	Kidney	11
Sarcoma	24	Breast	10
Oral	22	Oral	9
Colon	22	Thyroid	9

IX. Regardless of the type of surgical resection or whether the tumor is sporadic, annual **follow-up noninvasive imaging is recommended** in all patients after resection. Recurrence rates of 12% to 22% have been quoted in patients with family histories, syndromes, and multiple tumors at original presentation versus 1% for patients with sporadic, isolated myxomas. Primary malignant tumors generally portend dismal prognoses. They are rarely cured by surgery because of the large amount of cardiac tissue

involved. Adjuvant therapy (i.e., chemotherapy and radiation) after resection does not affect the prognosis, although it may slow progression in individual cases. **Palliative resection** is advocated for obstructive symptoms. **Cardiac transplantation** has been performed for patients with both benign and malignant tumors, but thus far, series have been too small to reliably predict outcomes.

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CHAPTER 40

Heart Disease in Women

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I. INTRODUCTION. Cardiovascular disease (CVD) is the leading cause of death of women in the United States and most developed countries, accounting for 1 in every 4 female deaths. Despite aggressive campaigns by the American Heart Association (AHA) and other organizations, only 54% of the women surveyed in 2009 listed coronary heart disease (CHD) as a leading cause of death for women, and only 13% of the women surveyed identified CHD as a risk for them personally. Minority women are even less aware of their cardiovascular (CV) risk, which is higher than for age-matched white women.

Gender-related differences exist in the presentation and outcome of CVD. In a national registry of over 300,000 patients (40% women) admitted with acute myocardial infarction (MI) between 1994 and 1998, female patients were found to be older compared with males (approximately 72 years vs. 66 years, respectively). Women also had higher in-hospital mortality compared with men (17% vs. 12%). Risk of death is particularly high in younger women, more than twice that of men in the under-50 age group, and also in women who presented with ST-elevation myocardial infarction (STEMI). These differences highlight the need to better understand and treat CVD in women. This chapter summarizes current understanding of the gender-specific features of CVD and concludes with a discussion of pregnancy and CVD.

II. GENDER DIFFERENCES IN PATHOPHYSIOLOGY. There appear to be gender-based differences in the atherosclerotic process of men versus women. **Women, in general, have more diffuse atherosclerosis with less plaque volume and luminal obstruction than males**. The underlying mechanism of thrombosis also appears to differ, with thrombosis in women resulting from superficial erosion of intact atheroma versus frank plaque rupture in males. Vasoreactivity, thrombosis, and inflammation are influenced by a variety of hormones, present in varying quantities in men and women. Women have smaller coronary arteries than men and, interestingly, women taking androgens have much larger coronary arteries than their age-matched controls. It is well established that estrogen confers protection from coronary artery disease (CAD) in premenopausal women. The exact mechanisms by which this occurs are not fully understood; however, it is likely multifactorial, with estrogen signaling involved in regulation of vasomotor tone, inhibition of smooth muscle cell proliferation, and

maintenance of favorable metabolic conditions, including regulation of obesity, hypertension (HTN), and lipid profile. Animal studies suggest estrogen decreases oxidative stress via upregulation of the production of prostacyclin PGI_2, a molecule known to retard the progression of atherosclerosis. Additionally, women have higher levels of fibrinogen and factor VII, which may contribute to sex-related differences in endothelial function and hemostasis. There exists a clinical syndrome of typical angina pectoris with transient abnormal electrocardiogram (ECG) and/or ischemic stress testing, associated with normal or nonobstructive epicardial coronary disease on left heart catheterization (LHC). This clinical scenario is more common in women than men and is putatively caused by microvascular coronary dysfunction (MCD). In MCD, the microvasculature fails to appropriately vasodilate in response to increased myocardial oxygen requirements, perhaps because of hormonal signaling. The relationship between MCD and clinical outcomes is unknown. There is no known treatment or risk factor modification for microvascular dysfunction.

Stress cardiomyopathy, also known as Takotsubo cardiomyopathy or "broken heart syndrome" is another CVD **affecting predominantly postmenopausal women.** Stress cardiomyopathy is diagnosed when patients, often in the setting of severe emotional distress or physical trauma, present with chest pain, anterior ST-elevations, abnormal cardiac biomarkers, and characteristic appearance of an akinetic, ballooning apex on echocardiography or left ventricular (LV) ventriculogram. Diagnosis is a process of exclusion, including angiography which often reveals normal coronary vessels. The etiology of stress cardiomyopathy is not fully elucidated, but is believed to result from catecholamine toxicity with excessive sympathetic stimulation of the basal segment of the heart. Microvascular dysfunction and/or coronary vasospasm may also contribute to the pathophysiology of stress-induced cardiomyopathy. The prognosis of stress cardiomyopathy is very good, with the majority of patients recovering full ventricular function within weeks to months.

III. GENDER DIFFERENCES IN RISK FACTORS

A. Diabetes mellitus. Diabetes affects more women than men after the age of 60. In the female patient, diabetes increases the rate of CAD by three to seven times. Comparatively, men with diabetes have only a two- to threefold increased risk of CAD. Type 2 diabetes is associated with other components of the metabolic syndrome, all of which increase risk for CAD. Diabetes is also associated with the development of heart failure, with or without preserved ejection fraction (EF).

B. Hypertension. Women over the age of 65 have higher rates of HTN than males, with more than 73% of women aged 65 to 74 years diagnosed with HTN. A woman's risk of developing HTN increases if she is 20 lb or more overweight, has a family history of HTN, or is postmenopausal. Women with HTN have a higher risk of both CAD and congestive heart failure than men with HTN. This risk for CVD related to HTN rises steeply with age, although most studies show that treatment attenuates this risk.

C. Hyperlipidemia. Lipid fractions in women are affected by their menopausal status. Premenopausal women have lower low-density-lipoprotein cholesterol (LDL-C) levels and higher high-density-lipoprotein cholesterol (HDL-C) levels than age-matched men. As women age, LDL-C increases, HDL-C decreases, and triglycerides increase. Total

cholesterol and LDL-C are less predictive in women, unlike HDL-C, which is inversely associated with the risk.

D. Cigarette smoking. This is the single most preventable risk factor. Smoking leads to more CVD deaths than any other risk factor, likely owing to its effects of increasing inflammation, thrombosis, and oxidation of LDL-C. Smoking also has an antiestrogen effect, inducing unfavorable changes in lipid levels. There is a sixfold to ninefold increased risk of MI in female smokers compared with age-matched nonsmokers; in fact, the risk from smoking is equivalent to the risk of weighing about 42 kg more than a nonsmoking woman. However, with smoking cessation, risk is cut in half after 1 year without smoking and eventually declines back to baseline nonsmoker's risk.

E. Obesity and metabolic syndrome. More than 30% of American women are obese, and this number continues to climb. In women, obesity and body fat distribution (i.e., abdominal location) are independent risk factors for CAD. As shown by an examination of a cohort of 115,195 women from the Nurses' Health Study, risk of death from CVD increased with increasing body mass index (BMI).

F. Estrogen/menopause. Postmenopausal women have more CVD risk factors, such as obesity, HTN, and hyperlipidemia, likely owing to the precipitous decline in estrogen levels. The predominant source of estrogen changes from estradiol in the premenopausal state to the much weaker hormone estrone (produced by the conversion of androgens in peripheral adipose tissue) during menopause. Animal studies have shown that estrogen can have favorable CV effects, reducing cellular hypertrophy, enhancing vessel wall elasticity, and providing antioxidant and anti-inflammatory actions.

As part of the Women's Ischemia Syndrome Evaluation study results, endogenous estrogen deficiency in young women was shown to be a strong risk factor for CHD, with a 7.4-fold increased risk. Because of the protection from CAD afforded for premenopausal women, there was early enthusiasm for the use of hormone replacement therapy (HRT) to prevent CVD in postmenopausal women, sparked by data from observational studies. However, multiple randomized, placebo-controlled trials over recent years have shown evidence of increased risk for CVD with HRT, such that it is no longer recommended for primary or secondary prevention of CVD (see Section **VI.F**).

G. Physical inactivity. As women age, they become less physically active than their male counterparts. This contributes to weight gain and predisposes to the development of diabetes and HTN. In addition, with the cessation of estrogen production with menopause, there is increased abdominal fat deposition, further predisposing to CAD. There is a strong inverse association between the activity level and incidence of CV events (see Tables 40.1 and 40.2).

H. Novel risk factors. Traditional risk factors are known to underestimate CHD risk in women. For this and other reasons, research has been focused on identifying other novel biomarkers that can better define a woman's risk. Multiple biomarkers have been investigated (e.g., high-sensitivity C-reactive protein [hsCRP], brain natriuretic peptide, and fibrinogen), but the greatest promise appears to be with hsCRP. As part of the Women's Health Study, over 27,000 healthy American women had their CRP and LDL-C levels measured. The women were then followed for a mean of 8 years for the occurrence of the primary end point (MI, ischemic stroke, coronary revascularization, or death from CVD). Although minimally correlated with each other, both CRP and LDL-C levels had strong

linear relationships with CVD events, with CRP being the stronger predictor. Each biomarker tended to identify different high-risk groups, but better prognostic values were obtained when both were used together. Routine measurement of hsCRP is not currently recommended, but these data suggest hsCRP may add benefit to the risk assessment of women with intermediate CV risk.

IV.GENDER DIFFERENCES IN CLINICAL MANIFESTATIONS. CVD often manifests differently in women than men, potentially because of underlying differences in pathophysiology. This is particularly true for diabetic women. Women usually present at an older age and have more comorbidities than do men. As such, once the diagnosis of CAD is made, women are at higher risk for adverse outcomes.

A. Like men, women can present with typical symptoms of angina, such as substernal **chest pain** and **dyspnea on exertion** that is relieved by rest. These symptoms more often occur in older women, who present more similarly to men.

B. Women can also present with **atypical chest pain**; **shortness of breath**; **neck, shoulder, or arm pain**; **diaphoresis**; and **nausea/vomiting**.

C. Women are more likely to have subtle symptoms that require detailed history-taking to elicit, such as **chest "pressure or tightness," lightheadedness, palpitations, or fatigue**. Women most often have symptoms that occur at rest, wake them from sleep, or occur in times of psychological stress.

D. Women more often present acutely without preexisting prodromes of symptoms or with **sudden cardiac death**.

V.GENDER DIFFERENCES IN ASSESSMENT

A. **Exercise electrocardiography.** Guidelines suggest that women at low risk for CAD are not candidates for diagnostic testing, whereas women who are intermediate to high risk capable of performing 5 metabolic equivalents or greater should undergo an exercise ECG. As with men, an abnormality is identified if there is ≥1 mm of ST-segment depression or elevation. Generally, exercise ECG has lower sensitivity and specificity than other modalities, and this is even more prominent in women (sensitivity and specificity of 31% to 71% and 66% to 88%, respectively). This difference is not well understood, but it has been attributed to several factors, including lower ECG voltage and more frequent resting ST and T-wave changes. In general, women are more likely than men to have a false positive stress test; however, a negative exercise stress test has a negative predictive value of ~80%.

B. **Stress echocardiography (transthoracic echocardiography [TTE]).** Stress TTE tends to have higher specificity and lower sensitivity than stress perfusion imaging, as wall motion abnormalities occur later than perfusion abnormalities. However, stress TTE has the advantages of eliminating radiation exposure, decreasing cost, and providing the ability to assess LV function and cardiac structures. It has been shown to be a cost-effective strategy for determining CV risk in patients at intermediate risk.

C. **Stress myocardial perfusion scan.** Because of the limited sensitivity and specificity of exercise ECG in women, other modalities are frequently employed to assess the risk of CAD. The most frequently used test is the single-photon emission computed tomography (SPECT) scan, a radionuclide-based technique. Because alterations in myocardial perfusion generally occur earlier than electrocardiographic changes or wall motion abnormalities, this test is more sensitive than exercise ECG or echocardiography for estimating risk in either gender. For those individuals unable to exercise or attain target

heart rates, adenosine or dipyridamole can be used as a pharmacologic stress agent. To increase specificity, the higher energy isotopes (technetium 99m) are recommended in women to reduce the soft tissue attenuation artifacts (influenced by both breast tissue and obesity) that tend to occur anteriorly and laterally. Other limitations of SPECT can be critical in women. Because women have smaller hearts, the limitations in spatial resolution of SPECT can lead to small areas of hypoperfusion being missed.

D. Coronary angiography. Diagnostic coronary angiography is the gold standard for diagnosing CAD in both men and women. When evaluated by LHC, however, women more often have minimal to no obstructive CAD. For reasons not fully elucidated, women tend to experience vascular complications such as bleeding and renal failure related to diagnostic LHC more frequently than do men. The occurrence of a complication is thought to be related to older age at the time of presentation, smaller body size, smaller vessel size, and higher prevalence of diabetes. A radial approach to diagnostic and interventional coronary procedures leads to less bleeding complications than femoral catheterizations in both men and women and, when feasible, should be considered in women.

VI. GENDER DIFFERENCES IN THERAPIES.

Most CVD in women, as in men, can be prevented if risk factor modification occurs early and aggressively. Until recently, most of the clinical trial data, on which the guidelines for prevention and treatment of both genders are based, were derived from trials conducted largely in men. This information had been extrapolated to women because gender-specific trial data were lacking. Because of this uncertainty, more recent clinical trials have offered insights into gender-specific results, allowing for evidence-based guidelines for disease prevention and treatment in women. However, with only a few exceptions, the guidelines are the same for both men and women. The gender-specific results are highlighted here; for a full discussion, please see appropriate sections of previous chapters.

A. Aspirin. Aspirin (ASA) is the principal antiplatelet agent in patients with CAD. Its benefit in secondary prevention, as well as in acute coronary syndrome (ACS), STEMI, and after revascularization (coronary artery bypass grafting or percutaneous coronary intervention [PCI]), is well known and discussed elsewhere. However, there are very few gender-specific data in these instances, so most recommendations are extrapolated from trials conducted largely in men.

The role of ASA in primary prevention of CAD in women is better defined. Early data suggested that ASA may be protective as primary prevention for future CVD events in women, as it is in men. However, as part of the Women's Health Study, 39,876 healthy women older than age 45 were randomized to either ASA 100 mg on alternate days or placebo, and they were followed for the incidence of CV events (nonfatal MI, nonfatal stroke, or CV death) over 10 years. **Despite a 24% reduction in ischemic stroke, ASA had no benefit over placebo in reducing MI or CV death**. However, ASA did appear protective as primary prevention in those women aged 65 years or older, because it significantly decreased the risk of both MI and stroke in this age group. In 2016, the United States Preventive Services Task Force reported that low-dose ASA (≤100 mg/day) for primary prevention in both men and women showed the most significant positive benefit when initiated between age 40 and 69, with harm potentially exceeding benefit in people starting ASA after the age of 70. Harm may also outweigh benefits in men and women during the first 10 to 20 years of ASA use. Notably, there is an increased risk of bleeding

for women taking daily ASA, highlighting the need for an individualized approach to the use of ASA as primary prevention in older women.

B. Thienopyridines. Thienopyridines, the most common of which is clopidogrel, have proven beneficial, when given with ASA, to reduce the rate of stent thrombosis after PCI. Clopidogrel has also shown benefit in secondary prevention of CAD, ACS, and STEMI (discussed in detail elsewhere). Few of the clinical trials using clopidogrel have given gender-specific data, but there are some data available for specific settings.

In the substudy of the Clopidogrel in Unstable angina to prevent Recurrent Events trial, in which the patients received PCI, 2,658 patients with non–ST-segment elevation ACS undergoing PCI were randomly assigned to ASA plus clopidogrel or placebo for 9 months. Of the study population, 30.2% were women. Clopidogrel plus ASA long-term therapy improved outcomes in those patients who received PCI. This was more significant in men, but a definite trend toward benefit in women was evident as well. Similar results were seen for women in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, where 29% of the 2,116 patients were women. The CREDO trial showed benefit of post-PCI therapy with ASA and clopidogrel out to 1 year of therapy, again with a trend toward benefit in women. CREDO trial also revealed, by subgroup analysis, equally beneficial effects of a loading dose of clopidogrel in men and women.

C. Statins. The primary prevention efficacy of statins in women is unclear because of underrepresentation of women in clinical trials; however, multiple studies suggest that women achieve equal, if not greater clinical benefit from statins than men. This is potentially due to underlying differences in atherogenesis between the sexes. The Cholesterol Treatment Trialists' collaboration performed a meta-analysis of 27 statin trials where approximately one quarter of the patients were female. This meta-analysis showed that for equivalent reductions in LDL-C, men and women have similar relative risk reductions in vascular events. Furthermore, a post hoc subgroup analysis of the PROVE IT-TIMI 22 suggested that women may actually have greater risk reduction than men with lesser degrees of LDL-C reduction. In the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin, multivariable analysis showed greater decreases in plaque volume for women compared to men, across both rosuvastatin and atorvastatin treatment groups.

D. Hormone replacement therapy. Despite beneficial evidence from previous observational studies which demonstrated decreased rates of CVD in postmenopausal women, data from randomized control trials have presented conflicting results In 2002, the Heart and Estrogen/progestin Replacement Study (HERS) reported an association between oral HRT and increased rates of coronary disease and stroke. In this study of secondary prevention, 2,763 postmenopausal women with CAD were randomized to either 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate or placebo daily. After an average 4-year follow-up, there was no significant difference in the primary outcome of nonfatal MI or CHD death between the groups. Of interest, however, was the fact that the greatest numbers of CV events were noted within the first year in the HRT group. Not surprisingly, the HRT group had a greater incidence of venous thromboembolism (VTE) and gallbladder disease.

Because of the high number of CV events in the first year, the investigators thought that the beneficial effects of HRT might be observed after time, because it appeared that HRT

became more protective by 4 to 5 years of follow-up in the HERS population. With this in mind, the HERS II study followed 2,321 of the original HERS patients, the majority of whom stayed on their original treatment in an open-label format, for an average of 6.8 years. After the longer follow-up, there was still no difference in nonfatal MI or CHD death between the groups; however, there was an increased rate of stroke. These studies received significant publicity and led to a decrease in oral HRT prescriptions. These studies received criticism for enrolling patients with a mean age in the mid-60s, 10 years later than the average age of menopause. Subgroup analysis subsequently suggested that women started on HRT prior to age 60 may have a trend to decreased CV events.

To date, there have been nine primary prevention trials of HRT, which in a meta-analysis showed a significant association between oral HRT and increased incidence of stroke, pulmonary embolism, and VTE, but no significant association with all-cause mortality, death by CV cause, nonfatal MI, angina, or revascularization. A meta-analysis of the 10 secondary prevention trials published to date again showed a significant association between oral HRT and rates of VTE, but no association with all-cause mortality, death by CV cause, MI, angina, or revascularization. A subgroup analysis of these trials demonstrated an association with lower rates of all-cause mortality and CHD if oral HRT is started within 10 years of menopause or before 60 years of age.

Based on the 2011 American Heart Association Guideline for the Prevention of Cardiovascular Disease in Women, **HRT should not be recommended for the primary or secondary prevention of CVD**.

TABLE 40.1 Risk Classification of Cardiovascular Disease in Women

High Risk	At Risk	Optimal Risk
• Known CAD	• Subclinical atherosclerosis (e.g., coronary calcification, carotid plaque, or thickened intima media)	• Fasting blood glu
• Cerebrovascular disease	• Cigarette smoking	• Nonsmoker
• Peripheral arterial disease	• Poor diet	• Healthy (Dietary [DASH]-like) die
• End-stage renal or chronic kidney disease	• Physical inactivity	• Physical activity min/wk modera intensity, or com
• Diabetes	• Obesity (especially abdominal location)	• BMI < 25 kg/m^2
• 10-y Framingham global risk >10%	• Dyslipidemia (total cholesterol > 200 mg/dL, HDL-C < 50 mg/dL, or treated for dyslipidemia)	• Total cholesterol
	• HTN (SBP > 120 mm Hg, DBP > 80 mm Hg, treated HTN, or history of pregnancy-induced HTN)	• BP < 120/< 80 m
	• Family history of premature CAD (<55 y in men,	

TABLE 40.1 Risk Classification of Cardiovascular Disease in Women

	<65 y in women) • Metabolic syndrome or history of preeclampsia or gestational diabetes • Poor exercise capacity on exercise treadmill test and/or abnormal heart rate recovery after stopping exercise • Family history of premature CVD occurring in first-degree relatives in men <55 y of age or in women <65 y of age • Autoimmune diseases (e.g., SLE or RA)

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density-lipoprotein cholesterol; HTN, hypertension; RA, rheumatoid arthritis; SBP, systolic blood pressure; SLE, systemic lupus erythematosus.

Adapted from ACC/AHA guidelines 2011 update. Adapted from Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol*. 2011;57(12):1404–1423. Copyright © 2011 American Heart Association, Inc. With permission.

E. Lifestyle modification. The good news for women is that initiating lifestyle modifications can reduce CV risk by reducing the risk of developing diabetes. As part of the Diabetes Prevention Program Research Group, 3,234 patients (68% women) with impaired glucose tolerance were randomized to placebo, metformin (850 mg twice daily), or lifestyle modification (goal 7% weight loss and at least 150 minutes of physical activity per week). After almost 3 years of follow-up, the lifestyle modification group had a 58% reduction in the incidence of diabetes compared with 31% in the group with metformin. This translates to a decreased risk of CVD.

VII. EVIDENCE-BASED GUIDELINES FOR HEART DISEASE PREVENTION IN WOMEN.

The American College of Cardiology (ACC)/AHA guidelines emphasize the importance of recognizing the wide-ranging spectrum of CV disease in women. In general, a woman aged 20 years or older is first classified as at high risk, at risk, or at optimal risk based on the criteria in Table 40.1. Several factors should be evaluated, such as medical history, lifestyle, family history of premature CAD, Framingham risk score, and other genetic conditions, before decision regarding the aggressiveness of preventive therapy is finalized.

The guidelines are grouped into three main areas: lifestyle interventions, major risk factor interventions, and preventive drug interventions. Table 40.2 lists the class I and class IIa recommendations for primary or secondary prevention of CVD in women. These guidelines are suggested as a starting point, with therapy tailored to the needs of each individual patient.

TABLE 40.2 Evidence-Based Guidelines for Prevention of Heart Disease in Women

Lifestyle Interventions	Major Risk Factor Interventions
Class I Recommendations	
Smoking cessation (B)	Maintain optimal BP (<120/80 mm Hg) with lifestyle modification (B)
Exercise: 150 min/wk of moderate intensity exercise (e.g., brisk walking), 75 min/wk of vigorous intensity exercise (e.g., running), or combination (B)	Pharmacotherapy for BP ≥ 140/90 mm Hg (≥130/80 mm Hg in CKD or diabetes). Thiazide should be initial agent unless compelling indications for β-blockers and/or ACE inhibitor/ARB exist (e.g., ACS/MI) (A)
Weight loss to BMI <25 kg/m^2 and waist circumference ≤35″ (B)	Control of lipids through lifestyle modification (LDL-C < 100 mg/dL, HDL-C > 50 mg/dL, triglycerides < 150 mg/dL, and non–HDL-C [total cholesterol—HDL-C] < 130 mg/dL) (B
CV rehabilitation in those with recent ACS or PCI, angina, and recent CVA, PAD, or CHF (B)	Pharmacotherapy of lipids in those with CAD (A), diabetes, or 10-y absolute risk >20% (B) to goal LDL-C <100 mg/dL
Diet counseling to promote intake of fruits and vegetables, whole grain and high-fiber foods, and fish at least two times per week. Limit consumption of saturated fat, cholesterol, alcohol, sodium, and *trans*-fatty acids (B)	Pharmacotherapy of lipids in those with LDL-C ≥130 mg/dL after lifestyle modification and presence of multiple risk factors (or if LDL-C ≥160 mg/dL in those with multiple risk factors, even if Framingham risk <10%) (B Pharmacotherapy of lipids in those with LDL-C ≥190 mg/dL regardless of other risk factors Maintain HbA1c <7% in diabetics (B)
Class IIa Recommendations	
	Goal LDL-C < 70 mg/dL is reasonable in the very high risk (known CAD ⩽ multiple major risk factors, severe and poorly controlled risk factors, or diabetes) (B)
Class IIb Recommendations	
ω-3 fatty acid in the form of fish or capsule (e.g., EPA 1,800 mg/d) may be considered in women with hypercholesterolemia or	Pharmacotherapy with niacin or fibrates when HDL-C is low or non–HDL-C is elevated in high-risk women (after LDL-C goal reached)

TABLE 40.2 Evidence-Based Guidelines for Prevention of Heart Disease in Women

hypertriglyceridemia for primary or secondary prevention	(B)

AAA, abdominal aortic aneurysm; ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; ASA, aspirin; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cerebrovascular; CVA, cerebrovascular accident; EPA, eicosapentaenoic acid; ESRD, end-stage renal disease; HbA1c, glycosylated hemoglobin; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

Adapted from ACC/AHA guidelines 2011 update. Adapted from Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol*. 2011;57(12):1404–1423. Copyright © 2011 American Heart Association, Inc. With permission.

In general, it is suggested that the initial evaluation begin with a complete history, specifically eliciting symptoms of CVD, as well as a complete physical examination, with particular attention to blood pressure, BMI, and waist size. Laboratory evaluation should follow, including fasting lipids and glucose levels. During the evaluation, assessment of Framingham risk should be performed, as well as depression screening in those women with known CVD. **All class I lifestyle interventions** should be employed in **all women**, regardless of risk level.

If the woman is at **high risk** (established CAD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes, chronic kidney disease, or Framingham risk > 20%), the **class I major risk factor and preventive drug interventions** should be initiated (see Table 40.2). Consideration should also be given to some of the class II recommendations, particularly the **LDL-C goal of <70 mg/dL**.

There are some interventions that should not be considered under any circumstances. Table 40.3 lists those therapies that are **contraindicated** based on the results of recent clinical trials.

VIII. HEART DISEASE AND PREGNANCY

A. Introduction. Maternal cardiac disease is a major risk factor for nonobstetric mortality and morbidity in pregnant women. Substantial progress in the management of congenital heart disease has occurred over recent decades, so the majority of females born with heart defects now survive into their reproductive years. Advances in obstetrics have also enabled pregnancy in older mothers in whom HTN and acquired heart disease are more prevalent and can pose challenges for the pregnancy. Rheumatic heart disease is less common than in the past, but is still encountered, especially in immigrant populations in the United States, and may manifest clinically for the first time in pregnancy. Cardiac disease has significant bearing on both maternal and fetal outcomes, and it is therefore essential that cardiologists and internists have a working knowledge of the impact of pregnancy on various cardiac diseases on pregnancy and can tailor management appropriately. In most

cases, the presence of maternal heart disease does not preclude successful pregnancy, although thorough discussion and planning regarding risks and management strategies should begin prior to conception whenever possible.

TABLE 40.3 Class III Interventions (Ineffective, Possibly Harmful in Cardiovascular Disease Pre

Hormone replacement therapy or selective estrogen receptor modulators
Antioxidant vitamin supplementation (vitamin E, vitamin C, and β-carotene)
Folic acid with or without vitamin B_6 or B_{12} (folic acid supplementation should be used in the childb defects)
ASA in healthy women < 65 y

B. ASA, aspirin.

C. Adapted from ACC/AHA guidelines 2011 update. Adapted from Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol*. 2011;57(12):1404–1423. Copyright © 2011 American Heart Association, Inc. With permission.

D. Normal physiologic changes during pregnancy. A series of cardiocirculatory changes occur in pregnancy and peripartum. These changes **usually begin during the early first trimester** (5 to 8 weeks), peak in the late second trimester, and tend to plateau thereafter until the postpartum period. This second trimester peak in hemodynamic adaptations tends to correlate with the onset of clinical manifestations of cardiac complications during pregnancy.

1. The ***increase* in blood volume** during pregnancy is attributed to estrogen-mediated stimulation of the renin–aldosterone system, leading to salt and water retention. **The plasma volume expansion varies from 20% to 100% and averages around 50%**. The relatively greater increase in plasma volume as compared with red blood cell mass leads to the physiologic anemia of pregnancy, which usually manifests around 30 weeks.

2. Cardiac output, stroke volume, and heart rate. Table 40.4 summarizes the changes in heart rate, stroke volume, and cardiac output. **The cardiac output is estimated to increase by approximately 30% to 50% above baseline**. The increase is attributed to higher preload as a result of increased blood volume, decreased systemic vascular resistance, and an increase in maternal heart rate by 10 to 15 beats/min. During the third trimester, stroke volume and cardiac output are dependent on body position and increase in the lateral position (particularly left lateral) and decline in the supine position because of compression of the inferior vena cava by the gravid uterus.

TABLE 40.4 Normal Hemodynamic Changes during Pregnancy and Postpartum Period

Changes during Different Phases of Pregnancy				
Hemodynamic Parameter	**First Trimester**	**Second Trimester**	**Third Trimester**	**Labor and Deliv**
Heart rate	↑5%–10%	↑10%–15%	↑15%–20%	↑20%–30%
Stroke volume	↑5%–30%	↑30%–40%	↓20%–30%	↑300–500 mL wi

TABLE 40.4 Normal Hemodynamic Changes during Pregnancy and Postpartum Period

Cardiac output	↑5%–30%	↑30%–40%	↑>40%	↑50%
Systolic BP	↔ to ↓	↓	↔ to ↑	↑
Diastolic BP	↔ to ↓	↓	↓ to ↔	↑
Systemic vascular resistance	↓10%–30%	↓30%–40%	↓30%–40%	↑

BP, blood pressure.

3. **Blood pressure and systemic vascular resistance.** The decline in systemic vascular resistance causes blood pressure to begin to fall in the first trimester and reach a nadir of about 10 mm Hg below baseline by the end of the second trimester. The addition of low-resistance vessels in the uteroplacental bed also contributes to the decrease in afterload.

4. The pulse pressure widens due to the greater fall in diastolic blood pressure than in systolic pressure. As many as 11% of women develop the **uterocaval syndrome** of pregnancy, with a significant and symptomatic drop in blood pressure when lying supine because of vena caval compression. **Weakening of the vascular walls** of the medium and large muscular arteries occurs because of estrogen-mediated decreased collagen deposition and the effects of circulating elastase and relaxin. This makes pregnant women more susceptible to aortic dissection, especially in individuals with abnormally weak aortic tissue such as in Marfan syndrome.

5. **A hypercoagulable state** with decreased protein S, increased stasis, and venous HTN is also observed.

6. **Hemodynamic changes during labor and delivery.** Each uterine contraction displaces 300 to 500 mL of blood into maternal circulation (autotransfusion). Cardiac output increases approximately 75% during contractions because of an increase in stroke volume and heart rate. Blood pressure and oxygen consumption also rise. The magnitude of these changes is influenced by the mode of delivery and the method of anesthesia.

7. **Hemodynamic changes postpartum.** Despite blood loss during delivery (averaging 300 to 400 mL for vaginal delivery and 500 to 800 mL for cesarean section), there is a **temporary increase in effective venous return because of autotransfusion and relief of caval compression**. This may lead to an increase in stroke volume and cardiac output, resulting in augmentation in renal blood flow and a brisk diuresis. In women with preexisting cardiac disease, these rapid hemodynamic shifts may cause profound clinical deterioration. The hemodynamic changes associated with pregnancy usually persist for a few weeks postpartum and it may take up to 12 to 24 weeks for the parameters to return to their prepregnancy baseline.

8. **Cardiovascular evaluation in pregnancy**

1. **History.** Fatigue, dyspnea, ankle swelling, and reduced exertional capacity are common in normal pregnancy and can mimic cardiac disease. Chest pain, orthopnea, or paroxysmal nocturnal dyspnea may represent cardiac pathology.

2. **Physical examination.** Table 40.5 highlights the important cardiac findings in normal pregnancy. Signs of jugular venous distention, displaced point of maximal

impulse, and peripheral edema are common in normal pregnancy. Normal auscultatory findings in pregnancy include exaggerated physiologic splitting of S_2, a physiologic S_3, a physiologic systolic murmur in the pulmonic area, and the continuous murmurs of "mammary soufflé" or a cervical venous hum. Examination findings that are not physiologic include an S_4, a loud systolic murmur, a purely diastolic murmur, and fixed splitting of S_2 or pulmonary crackles.

3. **Noninvasive testing** with echocardiography is considered safe in pregnancy, and findings are as given in Table 40.5. Chest radiography should be performed only when absolutely necessary and with shielding of the pelvic area with protective lead. Magnetic resonance imaging is sometimes used for the diagnosis of cardiac disorders; its safety profile in pregnancy is unknown, and it should be avoided if possible.
4. **Invasive testing** with pulmonary artery catheterization (without fluoroscopy) can be utilized during pregnancy, labor, delivery, and the postpartum period for invasive monitoring and can be very useful for patients with hemodynamic complications. Cardiac catheterization during pregnancy is rarely needed, except in the setting of acute MI or to permit balloon valvuloplasty. Fluoroscopy and cine time should be minimized and direct radiation to the fetus avoided. Vascular access from the arm rather than the leg is preferred whenever feasible.

TABLE 40.5 Findings in Normal Pregnancy

Symptoms
Fatigue
Dyspnea
Palpitations
Reduced exercise tolerance
Orthopnea
Lower extremity edema
Physical examination
Hyperventilation
Lower extremity edema
Distended neck veins with prominent *a*- and *v*-waves and brisk *x* and *y* descents
Increased heart rate and wide pulse pressure
Upward and leftward deviation of point of maximal impulse
"Flow" murmurs (pulmonic and aortic)
Mammary soufflé (left sternal border, continuous murmur)
Increased first heart sound and exaggerated splitting of second heart sound

TABLE 40.5 Findings in Normal Pregnancy
Third heart sound
Electrocardiographic findings
Sinus tachycardia
Leftward axis deviation
Increased R/S ratio in leads V_1 and V_2
Repolarization changes
Echocardiographic findings
Increased LV diastolic dimension
Increased LV wall thickness
Mild increase in contractility
Moderate increase in size of right atrium, right ventricle, and left atrium
Functional pulmonary, tricuspid, and mitral regurgitation
Small pericardial effusion

F. LV, left ventricular.

G. **Risk assessment and general principles of management.** One of the most important steps in managing a woman with heart disease considering pregnancy is to establish the level of maternal and fetal risk. This involves a multidisciplinary approach, with preconception counseling, contraception advice, and discussion of potential maternal and fetal acute and long-term morbidity and mortality. Baseline functional class, severity of cardiac disease, LV function, and pulmonary pressures should guide the risk assessment. Table 40.6 delineates a stepwise approach for management of women with preexisting cardiac disease, and Table 40.7 lists high-risk predictors. **Maternal New York Heart Association (NYHA) class II symptoms or higher, LVEF <40%, or left-sided obstruction** are factors known to be predictive of neonatal complications, including premature birth, intrauterine growth restriction, respiratory distress syndrome, and death. **In certain conditions such as cyanotic congenital heart disease, Eisenmenger syndrome, or severe pulmonary HTN, pregnancy should be strongly discouraged, as patients with these conditions do not tolerate the hemodynamic changes of pregnancy**. Formal risk prediction scores include Cardiac Disease in Pregnancy, which is composed of four clinical features (prior arrhythmia or cardiac event, NYHA functional class >II or cyanosis, left heart obstruction, systemic LV dysfunction with LVEF <40%) with maternal cardiac event rates of 5%, 27%, and 75% for 0, 1, and >1 of the features, respectively, and the more recent ZAHARA predictors derived from a large population of congenital heart disease patients.

TABLE 40.6 Basic Management Principles for Pregnant Women with Valvular Heart Disease

TABLE 40.6 Basic Management Principles for Pregnant Women with Valvular Heart Disease

Risk Assessment
Preconception
Thorough history of cardiac symptoms and arrhythmias
Baseline exercise tolerance and functional class
Baseline ECG and echocardiography with ventricular function and pulmonary pressures
Detailed discussion with the patient about the potential risks to self and fetus
During Pregnancy
Follow-up evaluation at least once per trimester
Close monitoring of new symptoms or change in functional class
Serial echocardiography for development of any new symptoms or signs
Treatment
Preconception
Effective and safe contraception until pregnancy is desired
Consider valve repair or replacement, correction of anomaly prior to conception if pregnancy poses status
Adjust medications to prevent adverse fetal side effects
During pregnancy
Minimize medication use to only those absolutely required and discontinue or replace medications co
If symptoms worsen and if indicated, consider correction of anomaly or valve repair or replacement
Labor and delivery
Invasive monitoring as needed
Cesarean section for obstetric indication
Monitor for decompensated heart failure and pulmonary edema and treat accordingly
Postpartum
Adjust and optimize medications
Consider correction of anomaly or valve repair or replacement if indicated
Treat postpartum anemia
Counseling and contraception for future pregnancies

H. ECG, electrocardiogram.

I. Adapted from Stout KK, Otto CM. Pregnancy in women with valvular heart disease. *Heart*. 2007;93(5):552–558, with permission from BMJ Publishing Group Ltd.

J. Management of the pregnant patient with heart disease is a team effort involving the patient, her primary care physician, high-risk obstetric team, and cardiologist. **Prophylactic intervention for cardiac lesions that significantly increase the risk of pregnancy should be performed *before* pregnancy when appropriate and feasible.** Most patients with relatively low-risk cardiac conditions are successfully managed throughout pregnancy, labor, and delivery with conservative medical measures designed to optimize intravascular volume and systemic loading conditions. As with all pregnancies, medications should be used judiciously and only when absolutely required. Drugs that are contraindicated in pregnancy should be discontinued before conception if pregnancy is contemplated. Specific conditions and their management in pregnancy are described later. The list, although extensive, is not complete, as a detailed description of every condition is beyond the scope of this chapter.

TABLE 40.7 Risk Predictors of Adverse Maternal and Fetal Outcomes

Prior cardiac events or medication
Prior arrhythmia
NYHA class II or higher, or cyanosis
EF < 40%
Pulmonary HTN (pulmonary artery systolic pressure > 50% systemic pressure)
Severe AS (valve area < 1.5 cm^2, Doppler jet velocity > 4 m/s)
Symptomatic or severe MS
Severe aortic or mitral regurgitation with NYHA class III or IV symptoms
Hypertrophic obstructive cardiomyopathy
Maternal anticoagulation

K. AS, aortic stenosis; EF, ejection fraction; HTN, hypertension; MS, mitral stenosis; NYHA, New York Heart Association.

L. **Pregnancy in women with congenital heart disease**. In general, patients with noncyanotic congenital heart disease have better outcomes with pregnancy compared with patients with cyanotic disease. Where applicable, patients should be made aware of the potential inheritability of the congenital disease.

1. ***Antibiotics.*** The 2007 AHA endocarditis guidelines recommend against the use of prophylactic antibiotics for vaginal delivery for any patient with congenital heart disease, unless she has incompletely repaired disease, completely repaired disease using prosthetic materials within the past 6 months, or unrepaired cyanotic congenital heart disease. The 2008 ACC/AHA guidelines on the management of adults with congenital heart disease suggest it is reasonable to consider antibiotics at the time of membrane rupture prior to vaginal delivery for patients with prosthetic cardiac material or unrepaired/palliated cyanotic defects.

2. *Specific conditions and pregnancy*

a. Atrial septal defect (ASD) and patent foramen ovale (PFO). Isolated ASD or PFO is usually well tolerated in pregnancy and considered low risk in general. Paradoxical pulmonary embolism during pregnancy has been reported. Ideally, an ASD with a significant shunt (>1.5:1) should be corrected prior to pregnancy. Secundum ASD that is repaired prior to pregnancy is not associated with an increased risk of complications.

b. Ventricular septal defect (VSD). Isolated VSD without pulmonary HTN is usually well tolerated during pregnancy, and correction of VSD prior to pregnancy and before development of pulmonary HTN eliminates the risk. In pregnant patients with VSD and pulmonary HTN, a drop in blood pressure during or after delivery can result in transient shunt reversal. This may be prevented by close monitoring of blood pressure, volume replacement, and the use of vasopressors, if necessary. VSD is commonly inheritable.

c. Patent ductus arteriosus without pulmonary HTN usually has a favorable outcome. In patients with pulmonary HTN, the management principles are similar to those with VSD.

d. Coarctation of aorta (COA). Coarctation, although usually associated with favorable outcomes, has been associated with severe HTN, congestive heart failure, or aortic dissection during pregnancy. There is an association with congenitally bicuspid aortic valves (AVs). It is also associated with circle of Willis aneurysms, and cerebral hemorrhage from rupture of an aneurysm during pregnancy is possible. Limiting physical activity and controlling blood pressure may prevent complications such as cerebral hemorrhage and dissection. β-Blockers are usually the antihypertensive drugs of choice, although care should be taken not to lower the blood pressure excessively because this may compromise uteroplacental circulation. COA with evidence of systemic HTN, heart failure, or a peak gradient >20 mm Hg should be corrected prior to pregnancy, although this does not alleviate the risk for dissection. Correction of COA during pregnancy is indicated in patients with severe uncontrollable HTN or heart failure and may be performed percutaneously.

e. Congenital aortic stenosis (AS). A congenitally bicuspid AV is one of the most common causes of AS. These patients should be screened for other cardiac malformations including COA. The details of management are described later in Section VIII.F.2.

f. Pulmonic stenosis. Isolated pulmonic stenosis is usually well tolerated in pregnancy. It should be corrected prior to pregnancy if severe (peak gradient > 60 mm Hg). Percutaneous balloon valvotomy during pregnancy may be required in patients with severe right ventricular failure.

g. Ebstein anomaly. Noncyanotic Ebstein anomaly is usually well tolerated. Cyanotic patients are at very high risk for maternal heart failure and fetal prematurity or death. During labor and delivery, care should be taken to prevent a drop in blood pressure, and close hemodynamic monitoring is required along with rest, oxygen, and blood gas monitoring. It is sometimes associated with Wolff–Parkinson–White syndrome, and pregnancy may precipitate supraventricular arrhythmias.

h. Tetralogy of Fallot (TOF). Women with TOF who have undergone successful repair during childhood with little or no residual outflow tract gradient, no pulmonary HTN, and preserved ventricular function usually tolerate pregnancy well. In women with uncorrected or only partially corrected TOF, increased blood volume during pregnancy with

increased venous return and decreased systemic vascular resistance may result in right to left shunt and cyanosis. A similar process may also occur with a fall in blood pressure during labor and delivery. **The outcome of pregnancy is very poor for both mother and fetus once cyanosis occurs**. It is also associated with high rates of premature labor, spontaneous abortion, and fetal growth restriction. The risk of a cardiac defect in the neonate ranges from 3% to 17%; genetic counseling and screening for the 22q11 deletion should be offered to women with TOF. Patients with residual lesions after partial correction such as pulmonic regurgitation, right ventricular outflow obstruction, and right ventricular dysfunction are at risk for heart failure and arrhythmia during pregnancy. Poor prognostic signs include maternal hematocrit above 60%, arterial oxygen saturation below 80%, right ventricular HTN, and syncopal episodes.

i. **Eisenmenger syndrome. Pregnancy in women with Eisenmenger syndrome is associated with a very high maternal mortality in the range of 30% to 50%, with a 50% risk of fetal loss if the mother survives**. Maternal death occurs mostly between the first few days to first few weeks following delivery because of rapid hemodynamic deterioration. Therefore, patients with Eisenmenger syndrome should be strongly discouraged against pregnancy. Early therapeutic abortion may be considered given the danger to the mother. If pregnancy is continued, close monitoring is necessary. Restricted physical activity, continuous oxygen use for at least the third trimester, and consideration of pulmonary vasodilators are recommended. Because of increased incidence of thromboembolism, anticoagulant therapy is recommended, starting from the third trimester until 4 weeks postpartum. An attempt to shorten the second stage of labor by the use of forceps or vacuum should be made; cesarean delivery is associated with significantly higher mortality.

M. **Valvular heart disease and pregnancy. Lesions generally associated with high maternal and/or fetal risks include symptomatic mitral stenosis (MS), severe AS (with or without symptoms), mitral regurgitation (MR)or aortic regurgitation with NYHA class III and IV symptoms, valvular disease with severe pulmonary HTN or LV dysfunction, mechanical prosthetic valve requiring anticoagulation, Marfan syndrome, and hypertrophic cardiomyopathy (HCM)**. Lesions generally associated with low maternal or fetal risk include asymptomatic AS with normal ventricular function, mitral valve prolapse, mild MS, and MR or aortic regurgitation associated with NYHA functional class I or II symptoms.

1. **Mitral stenosis.** MS is one of the most common rheumatic valvular lesions seen in pregnancy and is poorly tolerated. The physiologic changes in pregnancy with increased blood volume and heart rate can lead to an increased pressure gradient across the valve and decreased filling time, respectively. This leads to increases in left atrial pressure and ensuing symptoms of pulmonary edema with dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Occurrence of atrial fibrillation with a rapid ventricular rate often causes further clinical deterioration. Patients with moderate to severe MS are more susceptible to these hemodynamic disturbances. The rapid increase in venous return during labor and delivery may cause significant decompensation and requires close monitoring.

   Management depends upon the severity of stenosis, symptoms, and time of diagnosis. **If MS is diagnosed prior to pregnancy, patients with severe MS (valve area < 1 cm^2) or moderate symptomatic stenosis should be offered percutaneous mitral balloon valvuloplasty (PMBV) or valve repair if PMBV is not feasible, before pregnancy**. In patients with

moderate asymptomatic stenosis, careful assessment of symptoms and exercise tolerance testing can help guide the decision for prepregnancy intervention. In patients with mild MS (valve area > 1.5 cm^2), pregnancy is usually tolerated with a favorable outcome. **Optimal management of an already pregnant patient with MS is aimed at reducing heart rate and left atrial pressure**. β-Blockers are the drug of choice, and selective β1-adrenergic drugs are preferred over nonselective β-blockers to avoid β2-adrenergic–mediated uterine relaxation. In patients with atrial fibrillation, digoxin may also be used for ventricular rate control. Electrical cardioversion can be performed safely during pregnancy if the hemodynamic status warrants restoration of sinus rhythm. Left atrial pressure may be controlled by salt restriction and very judicious use of diuretics (excessive use can lead to reduced uteroplacental perfusion). In patients with symptoms and signs of clinical deterioration despite optimal medical therapy, PMBV may be necessary during pregnancy. This should be avoided in the first trimester if possible and proper abdominal and pelvic shielding must be used. Echocardiographic guidance by an experienced operator can limit radiation exposure. In cases with severe MS refractory to medical therapy and not amenable to PMBV, mitral valve repair or replacement may be considered. Cardiopulmonary bypass during pregnancy carries a risk of fetal demise and should be performed with normothermic perfusion and high flow volumes with the mother in the lateral decubitus position to maximize placental perfusion.

Most patients with MS can safely undergo vaginal delivery. Patients with symptomatic moderate and severe MS should have hemodynamic monitoring and optimization guided by pulmonary artery catheterization during labor and delivery and in the immediate postpartum period (12 to 24 hours) when relief of uterocaval obstruction can cause increased venous return and pulmonary edema. Epidural anesthesia is usually better tolerated than general anesthesia, and cesarean section is generally performed for obstetric indications only.

2. **Mitral regurgitation.** The most common cause of MR during pregnancy is either rheumatic heart disease or mitral valve prolapse. MR is usually well tolerated in pregnancy because the fall in systemic vascular resistance leads to decreased LV afterload. Symptomatic decompensation may occur due to atrial fibrillation or HTN. Asymptomatic patients are managed conservatively without any therapy, whereas patients with decompensated heart failure are treated with diuretics and digoxin. In the peripartum period, increased venous return and systemic vascular resistance sometimes lead to decompensation requiring diuretics and afterload reduction. Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are contraindicated during pregnancy because of their teratogenic effect. Hydralazine may be used in patients with MR and HTN for afterload reduction. Acute MR because of ruptured chordae is rare in pregnancy and is usually not well tolerated. It may require intra-aortic balloon pump placement and emergent surgery.

3. **Aortic stenosis.** The most common etiology for AS in childbearing age is a congenitally bicuspid valve. Rheumatic AS is less common, but may occur in conjunction with MS. Mild-to-moderate AS with preserved LV function is usually well tolerated during pregnancy. **Severe AS (i.e., AV area < 1.0 cm^2 and mean gradient > 40 mm Hg) significantly increases the risk during pregnancy and may lead to significant hemodynamic deterioration, heart failure, and premature delivery**. Patients with severe AS should therefore be counseled against pregnancy or undergo surgery prior to conception. Symptoms such as chest pain, syncope, or dyspnea usually present late in the second trimester

or early in the third trimester. Patients with bicuspid AV and aortic root dilation, especially those with COA, are at increased risk for spontaneous aortic dissection.

When severe symptomatic AS is diagnosed during pregnancy, PABV should be performed before labor and delivery. Although PABV may reduce the risk of decompensation in patients with severe AS, it has limited durability and only suffices as a temporizing measure until the patient can safely undergo AV replacement. Aortic insufficiency (AI) that occurs as a postprocedural complication of PABV is usually well tolerated during labor and delivery.

Close invasive hemodynamic monitoring, as in patients with MS, may be required. Spinal anesthesia and epidural anesthesia are discouraged during labor and delivery because of their vasodilatory effects.

4. **Aortic regurgitation/aortic insufficiency.** AI is generally well tolerated in pregnancy because of the combination of reduced systemic vascular resistance and shortened diastole with the rise in heart rate. In a young woman, AI may be due to a congenitally bicuspid valve, an infective endocarditis, an autoimmune disorder (e.g., rheumatoid arthritis), or a dilated aortic annulus. Marfan syndrome should always be excluded because of its implications regarding aortic root stability. In symptomatic patients with decompensated heart failure, diuretics, digoxin, and hydralazine may be used for afterload reduction.

5. **Hypertrophic cardiomyopathy.** Most asymptomatic patients with HCM have a favorable outcome during pregnancy. The overall morbidity and mortality with HCM and pregnancy is, however, still higher than that in the general population. Symptoms such as chest pain, palpitations, worsening dyspnea, and syncope may occur and are more common in women who were symptomatic prior to pregnancy. Various arrhythmias, including supraventricular tachycardias, atrial fibrillation with hemodynamic deterioration and fetal distress, and ventricular fibrillation, have also been reported. There is an increased risk of fetal prematurity. Women should receive genetic counseling before conception whenever possible; the risk of inheriting the disease may approach 50% in certain familial forms of HCM.

Basic tenets of management in the pregnant HCM patient include maintenance of adequate intravascular volume to maintain appropriate LV end diastolic volume, as well as avoidance of tachycardia, both of which decrease LV outflow tract gradients. Blood loss, volume depletion, and vasodilators should be avoided. β-Blockers are usually the drug of choice for symptomatic patients. Patients with a history of syncope, life-threatening arrhythmias, or a family history of sudden cardiac death should be considered for prophylactic implantable defibrillators prior to pregnancy because of the potential arrhythmogenic effect of pregnancy.

Vaginal delivery is considered safe, but tocolytics with β-adrenergic properties and prostaglandins should be avoided. Epidural anesthesia is used with caution because of the peripheral vasodilatory effect, and excessive blood loss should be promptly repleted with fluids or blood transfusion. The brisk diuresis immediately postpartum may lead to a rapid decrease in intravascular volume and, therefore, a symptomatic increase in outflow tract gradient. This can be avoided by gentle intravenous (IV) hydration decreasing over 24 to 48 hours postpartum.

6. **Prosthetic heart valves.** The selection of an appropriate prosthetic valve in a woman of childbearing age is controversial. **Where possible, the patient's own valve should be conserved or repaired. When valve replacement is necessary, bioprosthetic and homograft valves are safer for mother and child, although their use is associated**

with an increased risk of degeneration in younger people, which may also be accelerated by pregnancy. In pregnant patients with well-functioning bioprosthetic valves, the management is similar to that of patients with native valves. Patients should be made aware of the possibility of valve degeneration and should be monitored for signs and symptoms of this.

Pregnancy should be discouraged in patients with mechanical heart valves, because mechanical valves, and their anticoagulation requirement, confer increased maternal mortality, morbidity, and fetal loss. In pregnant patients with mechanical heart valves, management of anticoagulation is challenging. Pregnancy is a thrombogenic state, and thrombosis has been reported in up to 10% to 15% of patients with mechanical prosthetic valves during pregnancy. The incidence is particularly high in patients with older generation valves (Björk-Shiley and Starr-Edwards) in the mitral position, but complications and deaths have also been reported in newer generation valves in the aortic position. The management of anticoagulation during pregnancy is discussed in detail in a separate section of this chapter.

N. Other cardiovascular diseases and pregnancy

1. **Hypertensive disorders in pregnancy.** Hypertensive disorders complicate 8% to 10% of pregnancies and are a major cause of maternal and perinatal morbidity and mortality. Hypertensive disorders can be broadly classified into chronic HTN, gestational HTN, and the preeclampsia–eclampsia spectrum.

a. **Chronic HTN** is defined as blood pressure of 140/90 mm Hg or greater before pregnancy, before 20 weeks of gestation, or persisting beyond postpartum day 42. It is associated with increased maternal and fetal morbidity and elevates the risk of preeclampsia development. Blood pressure treatment is aimed at minimizing maternal end-organ damage (such as LV hypertrophy, renal failure, or intracerebral hemorrhage), balanced against concerns that excessive pressure lowering may negatively impact fetal growth. The threshold for initiating drug therapy is controversial, and differing recommendations are offered by the various international society guidelines.

b. **Gestational HTN** is defined as HTN induced by pregnancy and diagnosed after 20 weeks of gestation and usually resolving within 42 days postpartum. Gestational HTN may portend the development of future primary HTN and CVD, but is otherwise usually associated with good maternal and fetal outcomes.

c. **Preeclampsia** occurs in 2% to 5% of all pregnancies, 10% of first pregnancies, and 20% to 25% of women with chronic HTN. It can be diagnosed with a systolic blood pressure above 140 or diastolic blood pressure of 90 and proteinuria exceeding 300 mg per 24-hour urine collection (or >30 mg/mmol in a spot urine sample), or an increase in proteinuria or loss of blood pressure control in a woman with chronic HTN. Symptoms supporting a diagnosis of preeclampsia include headache, blurred vision, abdominal pain, and shortness of breath. Onset is usually in the third trimester with rapid resolution after delivery, although postpartum cases are reported. **Eclampsia** is the development of grand mal seizures in a woman with preeclampsia. When preeclampsia is accompanied by poor prognostic features such as severe HTN, **HELLP syndrome** (hemolysis, elevated liver enzymes, low platelets), placental abruption, cerebral hemorrhage, pulmonary edema, or renal failure, the fetus must be delivered immediately, usually with rapid normalization of blood pressure. Table 40.8 lists different drug therapies used to treat HTN in pregnancy. IV labetalol is the drug of choice for acute hypertensive urgency or emergency in pregnancy. Hydralazine may also be used as a vasodilator. Sodium nitroprusside is usually avoided, especially in later stages of pregnancy, because of

concern for fetal cyanide toxicity if used for more than 4 hours and should be used only as a last resort in cases where emergent control of blood pressure is required. **Methyldopa, labetalol, and nifedipine are the most commonly used oral antihypertensive agents during pregnancy, although there is a paucity of evidence for optimal blood pressure targets or drug choices**. It is generally agreed that **systolic blood pressures of 150 to 160 mm Hg and/or diastolic blood pressures of 100 mm Hg and above should be treated**.

TABLE 40.8 Drug Therapy for Hypertension in Pregnancy

Drug	Mechanism of Action	Dosing	Comments
Drugs for Hypertensive Urgency and Emergencies			
Labetalol	α–β-Adrenergic blocker	20–80 mg IV q10–20 min (up to 300 mg)	Well tolerated; avoid in patient potential bronchoconstrictive eff
Hydralazine	Vasodilator	5–10 mg IV q15–30 min	Efficacious and safe during pregna
Sodium nitroprusside	Arterial-veno dilator	0.5–5.0 μg/kg/min	Concern for fetal thiocyanate toxic
Drugs for Long-Term Treatment of Hypertension			
Methyldopa	Central α_2-agonists	250 mg tid up to 4 g/d	May not be as effective in control up to 7 y of age
Labetalol	α–β-Adrenergic blocker	200–2,400 mg/d in two to three divided doses	Well tolerated; avoid in patient potential bronchoconstrictive eff
Nifedipine	Calcium channel blocker	Once daily sustained release dosing up to 120 mg/d	Short-acting nifedipine may preci be avoided; hypotension also p

2. HTN, hypertension.

3. Adapted from Elkayam U. Pregnancy and cardiovascular disease. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005:1965–1982. Copyright © 2005 Elsevier. With permission.

4. **Aortic dissection.** Aortic dissection during pregnancy has been reported in women with Marfan syndrome, systemic HTN, COA, Turner syndrome, and cocaine use. It occurs most commonly in the third trimester and the peripartum period. Transesophageal echocardiography is the key diagnostic tool, and a β-blocker is the preferred medication for management during pregnancy.

5. **Coronary artery disease. MI during pregnancy is rare**, occurring in 1 in 16,129 deliveries in the United States between 2000 and 2002. The possibility of MI should always be entertained in a pregnant or immediately postpartum woman, especially if her symptoms and ECG are suspicious for coronary ischemia. **Most MIs occur during the third trimester in older women who have had multiple prior pregnancies. *Coronary spasm, in situ coronary thrombosis, and coronary dissection are more frequently the underlying precipitants of MI*** than classic obstructive atherosclerosis. Acute MI may be the initial clinical manifestation of an underlying hypercoagulable state, such as the antiphospholipid antibody

syndrome. The diagnosis and management of acute MI in the pregnant patient should follow the guidelines established for the general population.

Medical therapy for acute MI must be modified in the pregnant patient. Thrombolytic agents increase the risk of maternal hemorrhage substantially (8%). Low-dose ASA, β-blockers, and nitrates are considered relatively safe. Short-term heparin administration has not been associated with increased maternal or fetal adverse effects. ACE-Is, ARBs, and statins are contraindicated during pregnancy; there is no established safety data for clopidogrel, ticagrelor, or glycoprotein IIb/IIIa inhibitors. Coronary angiography should be performed only when emergent angioplasty or coronary artery bypass grafting is anticipated.

6. **Arrhythmias.** Premature atrial complexes and premature ventricular complexes are the most frequent rhythm disturbances of pregnancy and are not associated with adverse maternal or fetal outcomes. No antiarrhythmic drug therapy is warranted.

a. **Atrial fibrillation and atrial flutter** are rare during pregnancy. Current ACC/AHA guidelines for management are detailed in Table 40.9. Rate control may be achieved with digoxin and β-blockers. Direct current cardioversion may be performed safely during any stage of pregnancy. Anticoagulation is recommended for chronic atrial fibrillation in the setting of underlying structural heart disease.

TABLE 40.9 ACC/AHA Guidelines for Management of Atrial Fibrillation in Pregnancy

Class I (Benefits >>> Risk) Procedure/Treatment Should Be Performed/Administered
Digoxin, a β-blocker, or a nondihydropyridine calcium channel antagonist is recommended to control th pregnant patients with AF
Direct current cardioversion is recommended in pregnant patients who become hemodynamically unstable
Protection against thromboembolism is recommended throughout pregnancy for all patients with AF (exce low thromboembolic risk). Therapy (anticoagulant or ASA) should be chosen according to the stage of p

b. ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; ASA, aspirin.

c. **Atrioventricular nodal reentrant tachycardia** is the most common supraventricular arrhythmia in pregnant and nonpregnant women. It can lead to hemodynamic deterioration in women with underlying heart disease owing to rapid rates. Adenosine may be administered safely to the pregnant patient for both diagnostic and therapeutic purposes.

d. **Ventricular tachycardia (VT)** is rare during pregnancy. It may, however, be the presenting manifestation of peripartum cardiomyopathy (PPCM). VT has also been associated with thyrotoxicosis and hyperemesis gravidarum. Most antiarrhythmic medications used to treat VT are safe during pregnancy, **except for amiodarone**, which should be used with extreme caution and only for arrhythmias not responding to other medications, because it may lead to **neonatal hypothyroidism**.

7. **Peripartum cardiomyopathy.** This is defined as the development of idiopathic LV systolic dysfunction in the last month of pregnancy or within 5 months of delivery, in the absence of any identifiable or preexisting cause of heart failure. The incidence of PPCM in the United States is estimated to be 1 in 3,000 to 4,000 live births and is **more common in women older than 30 years**. The following risk factors for PPCM have been

proposed: **multiparity, history of preeclampsia, eclampsia, or postpartum HTN, African descent, low socioeconomic status, or tocolytic therapy with β-agonists**. Symptoms include fatigue, dyspnea on exertion, orthopnea, nonspecific chest pain, peripheral edema, and abdominal discomfort and distention. PPCM has long been considered an idiopathic disease; however, recent studies suggest vascular dysfunction, hormonal insults, and underlying genetics may contribute to its pathogenesis. Standard management of pregnant patients presenting with decompensated heart failure includes oxygen, diuretics, digoxin, and vasodilators. ACE-Is and ARBs are absolutely contraindicated in pregnancy but should be commenced postpartum.

The prognosis after development of PPCM is variable. **Approximately 70% of women completely recover normal heart size and function, usually within 6 months of delivery**. The remainder either experience stable LV dysfunction or continue to experience clinical deterioration. Patients with severe cardiac dysfunction and decompensation should be evaluated for cardiac transplantation or mechanical support after pregnancy. Estimated maternal mortality ranges from 10% to 20%. Women with PPCM and **persistent LV dysfunction or whose LVEF was below 25% at initial presentation** are at **very high risk for complications, including death, in a subsequent gestation.**

8. **Primary pulmonary hypertension.** This is associated with **very high maternal mortality (30% to 40%) and poor fetal outcomes**. Worsening of symptoms occurs in the second and third trimesters, and death is usually from right ventricular failure or arrhythmias. Pregnancy should be strongly discouraged in patients with this diagnosis, and early therapeutic abortion should be considered for those who become pregnant. Anticoagulation throughout gestation, or at least during the third trimester, is recommended. Close hemodynamic monitoring during labor, delivery, and the early postpartum period is advised, and oxygen plus pulmonary vasodilators may be used.
9. **Pregnancy after cardiac transplantation. Pregnancy after cardiac transplantation is considered high risk for the mother and fetus**. Maternal morbidity is increased from HTN, preeclampsia, renal failure, premature rupture of membranes, and infection. Fetal growth restriction and preterm labor are also a concern, along with potential adverse fetal effects of immunosuppressive medications. One study examined the outcomes of 47 pregnancies in 35 transplant recipients. There was no increase in maternal mortality in this study, but increased maternal morbidity, premature deliveries, and fetal growth restriction were observed.

O. Medication considerations in pregnancy

1. **Cardiovascular drugs.** The most commonly used CV drug classes and their potential adverse effects during pregnancy are shown in Table 40.10.
2. **Anticoagulation during pregnancy.** Conditions requiring anticoagulation during pregnancy include mechanical prosthetic heart valves, chronic atrial fibrillation, acute VTE, Eisenmenger syndrome, antiphospholipid antibody syndrome, and inherited deficiencies predisposing to thromboembolism (e.g., prothrombin gene mutation and factor V Leiden deficiency).

The three most common agents considered for use during pregnancy are **unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and warfarin**. The Ninth Edition of the American College of Chest Physician's evidence-based clinical practice guidelines on antithrombotic therapy and prevention of thrombosis recommend LMWH for the prevention

and treatment of venothromboembolism in pregnant women. Avoidance of warfarin, oral direct thrombin and anti-Xa inhibitors (1C) is advised. For women with mechanical heart valves, warfarin is recommended in the first trimester if the daily dose is <5 mg and for all patients in the second and third trimesters. For women with mechanical valves and daily dose of warfarin >5 mg, LMWH twice daily with anti-Xa levels for monitoring or a continuous infusion of UFH with a partial thromboplastin time (PTT) ≥ twice the control is recommended during the first trimester. The ACC/AHA guidelines for selection of anticoagulation regimen in pregnant patients with mechanical prosthetic valves, updated in 2014, are presented in Table 40.11. Ultimately, the choice of anticoagulation regimens depends on the preferences of the patient and physician after consideration of the **maternal and fetal risks associated with the use of each drug**.

a. **Warfarin.** Warfarin freely crosses the placental barrier and can adversely affect fetal development. It has been associated with a high incidence of spontaneous abortion, prematurity, still birth, and fetal bleeding. **The incidence of warfarin embryopathy (fetal bone and cartilage formation abnormalities) has been estimated at 4% to 10%; the risk is highest when warfarin is administered during the 6th through the 12th week of gestation**. The risks are dose dependent, and women maintained on a daily dose of <5 mg daily have the lowest risks. When administered during the second and third trimesters, warfarin has been associated with fetal central nervous system abnormalities, such as optic atrophy, microencephaly, intellectual disability, spasticity, and hypotonia. Warfarin's anticoagulant effects are more potent in the fetus than in the mother because of lower fetal levels of the vitamin K–dependent clotting factors and can cause neonatal intracranial hemorrhage or a retroplacental hematoma. Warfarin is considered safe during breastfeeding. Women taking warfarin prior to pregnancy should be counseled regarding the risks and benefits of warfarin.

b. **Unfractionated heparin.** UFH does not cross the placenta and, unlike warfarin, does not have the teratogenic effects and is, therefore, considered safer. **It is, however, associated with maternal osteoporosis, hemorrhage, thrombocytopenia, or thrombosis (heparin-induced thrombocytopenia with thrombosis [HITT] syndrome), and a high incidence of thromboembolic events with older generation mechanical valves**. UFH may be administered parenterally or subcutaneously throughout pregnancy. Subcutaneous (SC) heparin use in patients with mechanical valve carries a 33% risk of valve thrombosis, compared to <4% when warfarin is used throughout pregnancy. The appropriate dose of UFH is based on an activated PTT (aPTT) of at least two times the control level. High doses of UFH are often required to achieve the goal aPTT because of the hypercoagulable state associated with pregnancy.

TABLE 40.10 Cardiovascular Drugs and Pregnancy

Drug	Indication	FDA Category	Potential Maternal or Fet
Adenosine	Arrhythmia	C	Limited data on use
Amiodarone	Arrhythmia	D	Hyper/hypothyroidism, cor effects
ACE-I/ARB	HTN	D	Contraindicated, IUGR, fetal death

TABLE 40.10 Cardiovascular Drugs and Pregnancy

ASA	CAD	C in the first and second trimesters D in third trimester	IUGR, bleeding in mother a
β-Blockers	Arrhythmia, HTN, MI, HOCM, hyperthyroidism, Marfan syndrome, MS	C/D	Fetal bradycardia, hypo category D and should b concerns)
Calcium channel blockers	HTN	C	Maternal hypotension ca potential tocolytic effects
Digoxin	Arrhythmia, heart failure	C	Possible low birth weig considered safe
Dofetilide	Atrial fibrillation	C	Possibly teratogenic in ani
Diuretics (thiazides)	HTN	B	Hypovolemia and reduced
Flecainide	Arrhythmia	C	Fetal death; limited data
Hydralazine	HTN, heart failure	C	Possible hypospadias, neonatal lupus-like synd
Lidocaine	Arrhythmia	B	Neonatal CNS depression
Methyldopa	HTN	B	Longest safety record, av depression
Nitrates	HTN	B/C (product specific)	Maternal hypotension caus
Procainamide	Arrhythmia	C	No adverse effects reporte
Propafenone	Arrhythmia	C	Limited data
Quinidine	Arrhythmia	C	Neonatal thrombocytopeni
Sodium nitroprusside	HTN, aortic dissection	C	Fetal thiocyanate toxicity, b
Sotalol	Arrhythmia	B	Fetal bradycardia; IUGR

c. FDA category: A, controlled studies show no risk; B, no evidence of risk in humans; C, risk cannot be ruled out; D, positive evidence of risk

d. ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ASA, aspirin; CAD, coronary artery disease; CNS, central nervous system; FDA, Food and Drug Administration; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension; MS, mitral stenosis; IUGR, intrauterine growth restriction; MI, myocardial infarction.

TABLE 40.11 ACC/AHA Guidelines for Selection of Anticoagulation Regimen in Pregnant Patient Valves

Class I (Benefits >>> Risk): Procedure/Treatment Should Be Performed/Administered
All pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulati monitoring
In women with mechanical prosthetic valves, warfarin is the recommended anticoagulant in the se trimesters
Pregnant women with mechanical valves should receive their care at a tertiary care center with a dedicate
Women requiring long-term warfarin therapy who are attempting to become pregnant should receiv counseling from a cardiologist knowledgeable in management of valvular heart disease
In pregnant women with mechanical valves who require less than 5 mg of warfarin a day to achieve a warfarin may be continued during the first trimester if a full discussion of risks and benefits occurs
In pregnant patients with mechanical prosthetic valves who receive dose-adjusted UFH, the aPTT should the control
In pregnant patients with mechanical prosthetic valves, the mother should be hospitalized prior to plann initiation of continuous IV UFH and discontinuation of warfarin
In patients with mechanical or bioprosthetic valves, it is reasonable to give low-dose ASA (75–100 mg/ and third trimesters of pregnancy in addition to anticoagulation with warfarin or heparin
Class IIa (Benefits >> Risk): It Is Reasonable to Perform Procedure/Administer Treatment
In patients with mechanical prosthetic valves, it is reasonable to avoid warfarin between weeks 6 and owing to the high risk of fetal defects
In patients with mechanical prosthetic valves, it is reasonable to resume UFH 4–6 h after delivery and be in the absence of significant bleeding
Class III (Risk ≥ Benefits): Procedure/Treatment Should Not Be Performed/Administered
LMWH should not be administered to pregnant patients with mechanical prosthetic valves unless ar monitored 4–6 h after administration

e. Level of evidence: A, multiple population risk strata evaluated; B, limited population risk strata evaluated; C, very limited population risk strata evaluated.

f. aPTT, activated partial thromboplastin time; ASA, aspirin; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

g. Adapted from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(22):e57–e185.

h. Low-molecular-weight heparin. The use of LMWH during pregnancy remains controversial, because it has not been adequately studied. Its advantages over UFH include a more predictable anticoagulant response and lower incidences of HITT and osteoporosis. It does not cross the placenta, and it may be safer to the fetus even though data in this regard are limited. A twice-daily dosing schedule should be used. **During pregnancy, the volume of distribution for LMWH changes, and it is essential to monitor anti-Xa levels.** The 4-hour-postdose target anti-Xa level varies between 0.7 to 1.2 and 1.0 to 1.2 U/mL depending on the guidelines followed; the manufacturer's specific target range should also be consulted. Although LMWH is the drug of choice for prophylaxis and treatment of deep venous thrombosis in pregnancy, the safety and efficacy of LMWH in pregnant patients with mechanical valves remain controversial.

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CHAPTER 41

The Athlete's Heart

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I. INTRODUCTION. An athlete can be defined as one who participates in sport, either individually or with a team, which requires regular and often intense training. The competitive athlete, by definition, competes against others and places a high premium on excellence. **The terms "athlete's heart," "athlete's heart syndrome," or "exercise-induced cardiac remodeling" refer to the structural, functional, and electrical adaptations that occur with prolonged and intense exercise training.**

Morganroth initially put forward the concept of sport-specific cardiac remodeling in the 1970s. Divergent cardiac adaptation for dynamic and static sports became known as the **Morganroth** hypothesis.

A. Dynamic training. The metabolic requirement of working muscles increases during dynamic exercise (e.g., running). To meet demand, the cardiovascular system responds through two principal mechanisms: increased cardiac output (CO) and reduced peripheral vascular resistance (PVR). CO is determined by heart rate and stroke volume and, in athletes, can increase up to sixfold during vigorous exercise, compared to during resting conditions. The increase in preload and CO during endurance exercise creates a volume overload (isotonic) stress on the heart. In addition, exercise-induced reduction in PVR, through recruitment and dilation of peripheral vascular beds (mainly in working skeletal muscle), also contributes to increased CO.

The augmentation of CO during dynamic exercise is mainly driven by a rise in heart rate mediated by an autonomic nervous system (i.e., parasympathetic withdrawal and sympathetic augmentation). The maximal heart rate is largely determined by age and does not increase further with conditioning.

Stroke volume is mainly determined by the end-diastolic volume (i.e., chamber size) and, to a lesser degree, by the end-systolic volume (regulated by a sympathetically mediated augmentation of cardiac contractility). End-diastolic volume increases in trained athletes, which augments CO during exercise. Therefore, characteristic findings in the highly trained endurance athlete include resting bradycardia and a balanced increase in left ventricular (LV) dimensions and wall thickness (eccentric hypertrophy).

B. Static training. Conversely, the sustained contraction of peripheral muscle beds during static, or strength training (e.g., weight lifting) acts to compress peripheral blood vessels and causes a marked increase in PVR. This response is further augmented by an exercise-induced surge in sympathetic tone and catecholamine release. During intense

strength exercise, the left ventricle may transiently have to work against a peripheral systolic blood pressure of up to 400 mm Hg. The increase in PVR is accompanied by only a limited increase in CO and, therefore, strength exercise mainly creates a pressure overload (isometric) stress on the heart. According to the Morganroth hypothesis, strength training will result in an increase in LV wall thickness that is not matched by an increase in LV chamber dimension (concentric hypertrophy). However, this theory was recently challenged by a meta-analysis performed by Utomi and coworkers, which failed to show a pattern of concentric hypertrophy in strength athletes, possibly because athletes participating in "pure" pressure overload sports (e.g., weight lifting) often have a training regimen that also includes volume overload exercise, as part of their conditioning. An increase in such "cross training" since the 1970s, when Morganroth first put forward the evidence of concentric hypertrophy in strength athletes, may explain why we see this phenomenon less frequently today.

FIGURE 41.1 Classification of sports. This classification is based on peak static and dynamic components achieved during competition. It should be noted, however, that higher values might be reached during training. The increasing dynamic component is defined in terms of the estimated percent of maximal oxygen uptake (Max O_2) achieved. The increasing static component is related to the estimated percent of maximal voluntary contraction (MVC) reached. The lowest total cardiovascular demands (cardiac output and blood pressure) are IA, while the highest are IIIC. [a] danger of body collision; [b] increased risk if syncope occurs. (Reprinted from Mitchell JH, Haskell W, Snell P, et al. Task Force 8: classification of sports. *J Am Coll Cardiol.* 2005;45(8):1364–1367. Copyright © 2005 American College of Cardiology Foundation. With permission.)

Importantly, many sports (e.g., rowing and cycling) have overlapping physiology, exposing the heart to both volume and pressure overload stress. Nevertheless, sports are often classified according to the type(s) of stress placed on the cardiovascular system. For example, the 36th Bethesda Conference divide sports into nine categories based on these principles (Fig. 41.1). **Knowledge of the expected cardiac changes according to the demands of their sports is important when evaluating the cardiovascular system of athletes.** Furthermore, the degree of cardiac adaptation also varies according to age, gender, ethnicity, and genetic factors. Below, exercise-induced structural cardiac remodeling of the ventricles, atria, and aorta is described.

II. STRUCTURAL CARDIAC ADAPTATIONS WITH REPETITIVE EXERCISE.

Structural cardiac remodeling (e.g., enlargement of cardiac chambers) can become evident as soon as 90 days after commencing on an intense exercise regimen. These adaptations improve both cardiac efficiency (e.g., lower heart rate for a given exercise intensity) and maximal exercise capacity (e.g., increase maximal CO).

A. The left ventricle.

Volume overload stress, when applied repetitively, typically produces dilation of the left ventricle, accompanied by a balanced increase in wall thickness (eccentric hypertrophy). In a large series of young healthy athletes (n = 1,309), representing 38 different sporting disciplines, LV end-diastolic diameter (LVEDD) ranged from 38 to 66 mm (mean 48 mm) in women and 43 to 70 mm (mean 55 mm) in men. More than 40% of male athletes had LVEDD exceeding 54 mm, and 14% had very pronounced dilation exceeding 60 mm. Furthermore, a recent meta-analysis reported a mean LVEDD of 55 mm

(95% CI: 54 to 56) and 52.4 mm (95% CI: 51.2 to 53.6) in endurance- and resistance-trained athletes, respectively. However, it is our experience that LVEDD can be significantly larger in highly trained endurance athletes. Indeed, one study evaluating 286 Tour de France cyclists reported that LVEDD exceeded 60 mm in more than 50% of the athletes.

Therefore, when considering that the upper normal limit of LV chamber size is usually defined as 58 mm for men, the **diagnostic challenge in differentiating athlete's heart from pathologic changes** (i.e., dilated cardiomyopathy) becomes evident. This challenge is compounded by an **occasionally observed low-normal or mildly reduced LV ejection fraction (EF) in highly trained endurance athletes**. For example, in the study mentioned above, 6% of the Tour de France cyclists had an LVEF of ≤52%. In a study of National Basketball Association players (a sport with a greater static component than cycling), on the other hand, an EF <50% was observed only in <1%. A meta-analysis of studies comparing endurance- and resistance-trained athletes reported a normal EF in both groups, with no significant difference between the two. Mean EF was 63% (95% CI: 61 to 64) in the endurance-trained athletes and 66% (95% CI: 62 to 70) in the resistance-trained athletes. Therefore, although an EF that appears low can occasionally be seen in extreme endurance athletes, this finding is not as common as often supposed. When faced with a diagnostic dilemma in an apparently **healthy athlete with LV dilation and reduced EF**, it can be useful to perform an **exercise test to demonstrate normal myocardial recruitment and supranormal exercise capacity**. In addition, the healthy endurance athlete with LV dilation will invariably have four-chamber dilation, normal diastolic function, and eccentric hypertrophy. Abnormal diastolic function or findings isolated to the left ventricle, on the other hand, suggest pathology (Table 41.1).

Endurance training tends to augment diastolic filling, which can be demonstrated by high E-wave and mitral annular tissue velocities. The improved early LV relaxation and filling allows for preservation of stroke volume during exercise at high heart rates. In fact, it has been reported that endurance exercise training can attenuate, or even reverse, the decline in diastolic function typically seen with ageing.

The normal distribution of LV septal wall thickness has been investigated in several large series of athletes. In one study of Caucasian elite athletes (n = 947), wall thickness exceeded 12 mm in only 1.7%. Several other series corroborate that a thickness >13 mm is relatively rare in athletes. However, many of these studies were performed primarily in Caucasian male adult athletic cohorts. It has become clear that a number of **factors have to be considered when assessing the athlete with increased wall thickness**, including the **sport type and training regimen, race, gender, and age** of the athlete. For example, black athletes generally develop more hypertrophy in response to exercise compared to white athletes. In one large study (n = 300), 18% of black athletes had a septal wall thickness >12 mm, compared to only 4% of white athletes. Furthermore, in this study, 3% of black athletes, but none of the white athletes, developed significant LV hypertrophy (LVH) (>15 mm). The mechanism behind the augmented LVH response in black athletes, which is present across sporting disciplines, is not clear, but has been attributed to a combination of genetic, endocrine, and hemodynamic factors.

Because of **phenotypic overlap with mild hypertrophic cardiomyopathy (HCM),** athletes with a septal wall thickness of 13 to 15 mm are often considered to be in a

diagnostic "gray zone." In such cases, other echocardiographic parameters are often useful to differentiate physiologic LVH from HCM. For example, in athletes, **septal wall thickness is typically accompanied by an increase in LV size (>55 mm)**. Importantly, LV chamber size appears to remain <50 mm even in HCM patients that participate in competitive sports against medical advice. An LV size >55 mm in HCM patients, on the other hand, is usually due to progressive myocardial fibrosis and thinning, accompanied by systolic dysfunction and heart failure symptoms. Such advanced HCM is typically not compatible with participation in competitive sports. Importantly, marked LVH is uncommon in very young athletes and should raise the suspicion for HCM, particularly if present before 16 years of age. **Furthermore, physiologic LVH is usually accompanied by normal parameters of diastolic function and is not asymmetric.** Myocardial deformation assessment using speckle tracking echocardiography is an emerging tool that may be a useful adjunct in differentiating HCM from athlete's heart. Typically, strain is normal in the athlete, while there is a reduction in strain at the site of greatest hypertrophy and fibrosis in HCM. Of note, in <10% of cases, HCM may be limited to the apical segments of the left ventricle, which may be difficult to appreciate on echocardiography. Therefore, when the suspicion for HCM remains high, despite initial reassuring echocardiographic findings, contrast-enhanced echocardiography or magnetic resonance imaging (MRI) can be used. Cardiac MRI is also useful to identify asymmetric areas of hypertrophy and to identify scar using delayed gadolinium enhancement. Furthermore, MRI, in conjunction with echo, can be used to identify abnormalities of the mitral valve apparatus, which is seen in up to 75% of patients with HCM. **If the diagnosis remains uncertain despite extensive imaging workup, detraining (i.e., exercise reduction or abstinence) may be used as a diagnostic tool.** Detraining may induce regression of physiologic cardiac changes, whereas HCM-induced hypertrophy typically does not regress after stopping athletic activity. In a seminal study of six Olympic athletes, septal wall thickness was reduced from 13.8 ± 0.9 mm to 10.5 ± 0.5 mm following 6 to 34 weeks of voluntary training reduction. Currently, genetic testing for HCM is not a reliable method to rule out the presence of disease, but can be useful as a rule-in test, if positive (Table 41.1).

TABLE 41.1 Summary of Cardiac Assessment to Differentiate Cardiac Pathology from Exercise

Exercise-Induced Cardiac Remodeling	HCM	DCM
12-Lead ECG		
Multiple training-induced features—see International Recommendations for ECG Interpretation in Athletes	LVH with TWI extending beyond V_2 (Caucasian) or V_4 (Black) athletes. ST-depression	Nonspecific ECG changes such as Q-waves, poor R-wave progression, ST-depression and TWI
Echocardiogram		
Balanced LV and RV dilation and symmetric hypertrophy. LVEDD >55 mm. Normal diastolic	Asymmetric wall thickening. LVEDD <45 mm. Abnormal diastolic function and strain	Typically isolated LV dilation with reduced LVEF Abnormal diastolic function

TABLE 41.1 Summary of Cardiac Assessment to Differentiate Cardiac Pathology from Exercise

function and strain pattern	pattern. Dynamic outflow obstruction	and strain
Magnetic Resonance Imaging		
Balanced LV and RV dilation and symmetric hypertrophy. No LGE	Asymmetric hypertrophy. Patchy mid-wall or RV insertion point LGE. Abnormal papillary muscle morphology and attachment	Mid- or subepicardial LGE Dilated LV with thinned myocardium
Exercise Stress Testing		
Normal/supranormal exercise capacity. LVEF normalizes with exercise in athletes with a borderline low resting LVEF	Exercise-induced LVOT gradient. Abnormal blood pressure response. Ventricular ectopy. Reduced functional capacity	Low-normal to abnormal exercise capacity. Reduced myocardial recruitment LVEF typically does not completely normalize with exercise
Additional Workup to Consider in Challenging Cases		
–	Holter monitoring. Detraining and genetic testing	–

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; RV, right ventricular; RVEF, right ventricular ejection fraction; TWI, T-wave inversion.

B. The right ventricle. Pressure overload–induced cardiac remodeling, seen in strength training, is usually limited to the left ventricle by virtue of mitral valve shielding. Endurance exercise–induced cardiac remodeling, on the other hand, affects all cardiac chambers including the right ventricle. The thin-walled right ventricle typically responds to volume overload stress by dilation, without concomitant hypertrophy. However, right ventricular (RV) response to exercise stress has been less well characterized than in the left ventricle, and "cutoff" values to define normal ranges are less well defined. In a recent study of 102 endurance athletes, RV chamber dilation exceeded the upper limit of normal in >50%. Importantly, the RV enlargement was accompanied by LV dilation in almost all cases. Isolated RV dilation, on the other hand, is rare in athletes and should raise the suspicion for a pathologic process (e.g., arrhythmogenic right ventricular cardiomyopathy [ARVC]). Furthermore, because exercise-induced RV dilation tends to be a global process, any significant regional changes (aneurysmal or saccular dilation, or regional akinesia) warrant further investigation (Table 41.1).

C. **The atria. Left atrial (LA) enlargement** (>40 mm anterior–posterior dimension by echocardiography) **is common in athletes as a result of increased preload.** One study of 1,777 athletes demonstrated that it was present in >20%, with a much higher prevalence in endurance-trained athletes. An upper limit of 45 mm in women and 50 mm in men has been suggested to differentiate athlete's heart from pathologic conditions. Recent studies have also shown a high prevalence of right atrial (RA) enlargement. Assessment of atrial function plays an important role in differentiating athlete's heart from pathology. The atria initially act as a "reservoir" during ventricular systole as the left atrium fills with blood, then a "conduit" as blood passively flows into the ventricle during early diastole, and finally as a "booster" during atrial contraction. These functions can be measured on echocardiography. The left atrium responds to exercise-induced increases in preload by augmenting reservoir and conduit functions although LA active emptying is lower in athletes. Similarly, speckle tracking echocardiography exhibits normal reservoir function and reduced active contribution of the atrium to ventricular filling at rest. Reduced reservoir function and unbalanced enlargement of the atria are features more consistent with pathology.

D. **The aorta. Volume and pressure overloads during endurance and strength exercise, respectively, place a significant hemodynamic stress on the aorta.** A recent meta-analysis showed that the aortic root diameter measured at the sinus of Valsalva and the aortic valve annulus was 3.2 and 1.6 mm greater in athletes (n = 5,580) compared to matched nonathletic controls (n = 727). However, there are conflicting data whether endurance- or strength-type exercise produces more aortic root dilation. Regardless, this small increase in aortic dimensions is considered clinically insignificant. **Marked aortic root dilation (>4 cm) is unusual in athletes and should raise the suspicion for an underlying pathologic process.**

III. ELECTROPHYSIOLOGIC CARDIAC ADAPTATIONS TO REPETITIVE EXERCISE.

Exercise-induced cardiac remodeling not only affects cardiac structure and mechanical function but can also induce profound cardiac electrophysiologic changes. As a result, an athlete's electrocardiogram (ECG) has the potential to raise alarm for an underlying cardiomyopathy, and false-positive findings have remained one of the major arguments against including the 12-lead ECG as part of the initial pre-participation screening of athletes in the United States. To better identify athletes who need further evaluation and to avoid false-positive test results, several ECG criteria have been proposed. The **Seattle Criteria**, published in 2012, reduced the false-positive rate from as high as 40% in criteria used in the early 2000s, to ~10%. The recently published **International Criteria for ECG** Interpretation in Athletes, further reduces the false-positive rate without affecting sensitivity, mainly by no longer categorizing isolated LA and RA enlargement, RV hypertrophy (RVH), and left and right axis deviation as abnormal. This is based on data showing that such ECG findings have a very low diagnostic yield in athletes. Normal and abnormal ECG findings in athletes according to the international criteria are shown in Figure 41.2. An additional category of "borderline" changes is now used; features seen in isolation are considered benign but if there is more than one borderline feature, further evaluation is recommended.

A. **Cardiac rate, rhythm, and conduction changes in athletes.** Extensive exercise may result in profound resting sinus bradycardia (occasionally as low as 30 beats/min),

sinus arrhythmia, ectopic atrial and junctional rhythm, first-degree atrioventricular (AV) block, and second-degree Mobitz type I AV block. These changes are attributed mainly to a shift in autonomic balance with repetitive exercise resulting in a heightened parasympathetic (vagal) tone and concomitant sympathetic withdrawal. Importantly, when physiologic, these changes disappear with exercise (a state of heightened sympathetic tone and vagal withdrawal). In the absence of symptoms, such changes are considered normal in athletes. In contrast, second-degree Mobitz type II AV block and third-degree AV block are extremely rare in athletes and are more suggestive of cardiac conduction disease.

Incomplete right bundle branch block (iRBBB) is seen in up to one-third of athletes and has been attributed to RV remodeling and dilation, which results in an increase in cardiac conduction time and is considered a normal variant. Complete RBBB, although seen in only 1% of athletes, is now considered to be a borderline ECG finding according to the new international recommendations. Complete left bundle branch block is not an athletic adaptation and should trigger further evaluation.

FIGURE 41.2 The international criteria for ECG interpretation in athletes. AV, atrioventricular; ECG, electrocardiogram; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; PVC, premature ventricular complex; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; SCD, sudden cardiac death. (Reprinted from permission from Sharma S, Drezner JA, Baggish A, et al. International recommendations for electrocardiographic interpretation in athletes. *J Am Coll Cardiol.* 2017;69(8):1057–1075. Copyright © 2017 Elsevier. With permission.)

Ventricular arrhythmias are not uncommon in athletes. In one study, 355 competitive athletes with frequent premature ventricular complexes (PVCs) on screening ECG and/or a history of palpitations were further evaluated using 24-hour Holter monitoring. Athletes were subsequently divided into three groups based on the total number of PVCs and/or presence of non-sustained ventricular tachycardia (NSVT): group A (n = 71; >2,000 PVCs /24 hour and/or ≥1 episode of NSVT/24 hour), group B (n = 153, ≥100 to <2,000 PVCs and no NSVT), and group C (<100 PVCs and no NSVT). Overall, 93% of athletes had no significant cardiac abnormalities after extensive further cardiac testing including echocardiogram, MRI, and exercise ECG. In 7% (n = 26) of athletes, a cardiac abnormality was identified (mitral valve prolapse with mild mitral regurgitation in 11, ARVC in 7, myocarditis in 4, and dilated cardiomyopathy in 4). The prevalence of cardiac abnormalities was 30%, 3%, and 0% in groups A through C, respectively, suggesting that the presence of >2,000 PVCs/24 hour and/or NSVT in an athlete should trigger further evaluation, keeping in mind that pathology will be identified less than a third of the time.

B. Voltage criteria for ventricular hypertrophy and atrial enlargement. Voltage criteria for LVH are common in athletes and present in up to 70% of male athletes. It is particularly common in adolescent athletes (attributed to the thinner chest wall) and black athletes (attributed to more pronounced underlying ventricular hypertrophy). Increased QRS voltage criteria, when present in isolation, do not warrant further investigation. However, in the presence of pathologic Q-waves, ST-depression, T-wave inversion (TWI), or symptoms, LVH on ECG warrants further investigation with an echocardiogram or other testing modalities as clinically indicated, primarily to rule out HCM (Fig. 41.3).

FIGURE 41.3 Summary of the changes associated with athlete's heart and the overlap between cardiomyopathy. ARVC, arrhythmogenic right ventricular cardiomyopathy; HCM, hypertrophic cardiomyopathy; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; PVC, premature ventricular complex; TWI, T-wave inversion. (Adapted from permission from Prakash K, Sharma S. The electrocardiogram in highly trained athletes. *Clin Sports Med*. 2015;34(3):419–431. Copyright © 2015 Elsevier. With permission.)

Voltage criteria for RVH are present in up to 12% of athletes. Most experts do not recommend further evaluation of this ECG finding in the absence of symptoms or other abnormalities, which is recognized in the new International Criteria for ECG Interpretation in Athletes (Fig. 41.2). Similarly, voltage criteria for RA and LA enlargement are also common in athletes. Any of these findings in isolation are considered normal adaptations to training; however, if there are more than one of these features or they are associated with other abnormalities, further testing is warranted.

C. **Repolarization changes.** Exercise-induced changes in autonomic tone and/or electrical remodeling may also produce repolarization changes in athletes, including the early repolarization pattern (ERP) and TWI. **ERP is present in up to 90% of athletes and is considered a normal variant in asymptomatic athletes.** Interestingly, ERP may develop before, and independent of, LVH.

TWI is one of the more challenging ECG changes to interpret in athletes, as they are also the hallmark of many cardiomyopathies, including ARVC and HCM. Importantly, the prevalence and morphology of TWI vary across demographic factors such as age, gender, and race. For example, **TWI is present in approximately 5% of white athletes and in up to 25% of black athletes.** Furthermore, in black athletes, TWI commonly extends to leads V_2 to V_4, without any evidence of underlying pathology (Fig. 41.4).

The international criteria only consider TWI to be abnormal if T-waves are >1 mm in depth in more than two leads, excluding V_1, III, and aVR (except in black athletes where V_2 to V_4 are also excluded). TWI should be considered abnormal if extending beyond V_2 in white athletes, beyond V_4 in black athletes, or if it is accompanied by Q-waves or ST-depression. In ambiguous cases, the ST-segment preceding TWI may offer important diagnostic clues. In patients with ARVC, precordial TWI is usually preceded by an isoelectric ST-segment, whereas the ST-segment in athletes with TWI is usually convex. In one study, T-waves normalized with submaximal exercise in healthy athletes, which may offer another diagnostic tool beyond echocardiography and MRI. As a last resort, detraining can be used because TWI typically normalizes in athletes after 6 weeks of exercise restriction. In one study, pathologic TWI was associated with cardiac disease in 44.5% of athletes when extensive investigation was performed using echocardiography, cardiac MRI, exercise testing, and 24-hour Holter monitoring. Echocardiography only identified about half of these abnormal cases, which has led many experts, including the authors of the International Recommendations for ECG Interpretation in Athletes, to advocate more extensive investigations in these athletes. However, it is unclear how broadly applicable these data are, and further race-, body habitus-, and sport-specific studies are needed.

FIGURE 41.4 The 12-lead electrocardiogram demonstrates convex ST-segment elevation in anterior leads (V_1 to V_4) followed by T-wave inversion. Note that the repolarization pattern has normalized in lead V_5.

Athletes have slightly longer QT-intervals compared to nonathletes, which has been primarily attributed to LVH. It has been reported that 6% of athletes have a corrected QTc exceeding the upper limit of normal (470 in men and 480 in women). However, it should be kept in mind that a prolonged QTc in isolation (i.e., in the absence of other long QT syndrome criteria) only has a positive predictive value of 7%. Further evaluation is therefore essential, and the diagnosis should not be made solely based on the ECG. Of note, QT-intervals are notoriously difficult to measure in athletes because of the common presence of sinus arrhythmia and U-waves. In sinus arrhythmia, an average QTc based on several beats should be used and care must be taken to exclude the U-wave. The shape of the T-wave should also be carefully investigated for notched or bifid morphologies, as they may be suggestive of a true ion-channel disorder.

IV. RISK OF EXCESSIVE EXERCISE. It is undisputed that habitual moderate and vigorous exercise promotes health. Paradoxically, for individuals with unrecognized cardiac disease there is an increased risk of an adverse cardiac event during strenuous exercise. Recognizing this causal relationship, pre-participation screening and eligibility/disqualification guidelines have been implemented in many parts of the world to reduce this risk. A more recent concern is whether, at the extremes of exercise, the cardiovascular benefits of exercise are offset by adverse effects on the cardiac structure and function of otherwise normal hearts. Some have suggested that the benefits of exercise exhibit an inverted J-shaped relationship to overall health, even in individuals without underlying cardiac disease. Proposed mechanisms are that repeated high-intensity exercise, without sufficient recovery time, results in inflammation, myocardial injury, and accelerated atherosclerosis, ultimately leading to fibrosis and adverse cardiac remodeling. **Several studies have shown that sinoatrial node disease, advanced heart block, and atrial fibrillation are more common in veteran athletes compared to sedentary peers.** It has been suggested that extreme endurance exercise may even accelerate coronary atherosclerosis. One study showed that veteran marathon runners have higher coronary artery calcium scores compared to age-matched sedentary controls. The study drew criticism over potential recruitment bias, because of a higher proportion of former smokers in the athlete group. However, more recent studies, including a study with master athletes having no coronary artery disease risk factors, also found a higher proportion of athletes with high coronary artery calcium scores, compared to age-matched sedentary controls. When taken together, the data appear to suggest that longstanding exercise promotes formation of calcified coronary artery plaques. The clinical significance of this, however, remains uncertain.

An evolving concept in sports cardiology is exercise-induced adverse remodeling of the right ventricle, that is, “exercise-induced ARVC.” During endurance exercise, the right ventricle is subjected to the same preload as the left ventricle. However, because the pulmonary vascular resistance (in contrast to the systemic vascular resistance) decreases only minimally with exertion, pulmonary artery pressures may exceed 80 mm Hg during vigorous exercise in some athletes, exerting a disproportionately large afterload stress on

the thin-walled right ventricle. The concept of exercise-induced RV insult is supported by studies showing a correlation between post-exertional right (but not left) ventricular dysfunction and cardiac biomarker (e.g., Troponin and B-type natriuretic peptide) release. Furthermore, malignant ventricular arrhythmias in veteran endurance athletes originate from the right ventricle in the majority of cases and have been associated with significantly reduced right ventricular EF. Finally, mice and rat models have demonstrated that excessive exercise can induce RV fibrosis and accelerate development of the ARVC phenotype in genetically predisposed animals. The concept of chronic exercise–induced cardiac damage is depicted in Figure 41.5.

FIGURE 41.5 Theoretical model of chronic exercise-induced cardiac arrhythmogenic remodeling. RV, right ventricular. (From Sharma S, Zaidi A. Exercise-induced arrhythmogenic right ventricular cardiomyopathy: fact or fallacy? *Eur Heart J*. 2012;33(8): 938–940. Reproduced by permission of Oxford University Press.)

However, it should be emphasized that these studies are generally small cross-sectional studies evaluating small subsets of lifelong extreme endurance athletes. Despite these concerns it should be emphasized that the risk of adverse cardiovascular events is significantly higher in those who lead a sedentary lifestyle compared to individuals who regularly participate in any level of exertion. Further, longitudinal studies of elite athletes including Olympians, Tour De France cyclists, and cross-country skiers have reported an increase in their life expectancy compared to the general population. Overall, the remarkable benefits of regular exercise are well defined and should be promoted for most individuals to improve cardiovascular health.

V. ELIGIBILITY AND DISQUALIFICATION FOR ATHLETES WITH CARDIAC DISEASE.

Eligibility and disqualification recommendations for athletes with cardiac abnormalities have been published by the American College of Cardiology/American Heart Association and the European Society of Cardiology. These guidelines are extensive and a complete overview of this topic is beyond the scope of this chapter; however, it is important to recognize that many of the recommendations are based on the assumption that exercise is a modifiable risk factor for sudden cardiac death (SCD). For most cardiac conditions, this assumption is largely unproven and based on expert opinion. As newer data have emerged, such recommendations have been modified. For example, athletes with ICDs were previously restricted from all competitive sports with the exception of IA (low static, low dynamic) sports; current guidelines suggest they may now participate in higher static and dynamic component sports after appropriate counseling if free from appropriate device therapies for a period of 3 months. This modification was based on the results of a registry of such athletes who continued to compete against medical advice and demonstrated no increased risk of SCD. Similarly, athletes with long QT syndrome were previously disqualified from most competitive sporting activities until objective data demonstrated a low risk of cardiac events in those who are asymptomatic and are taking appropriate treatment. Conversely, continued participation in competitive sports has been shown to accelerate progression of certain diseases, such as ARVC, along with increasing the risk of ventricular arrhythmias. Therefore, significant exercise restrictions should be recommended in athletes with ARVC. It is clear that these decisions are nuanced. Many sports cardiologists advocate

transitioning away from a strict paternalistic framework for decision making regarding eligibility to compete for athletes with cardiac disorders in favor of a shared decision-making model. This model incorporates appropriate counseling of the patient and other relevant stakeholders (such as family and team) regarding the risks and benefits and uncertainties of continued exercise in the context of the underlying cardiac disorder and encourages participation of all parties in reconciling this information with their personal preferences and beliefs.

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CHAPTER 42

Dyslipidemia

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I. INTRODUCTION. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the industrialized world. It is estimated that 30% of all deaths worldwide can be ascribed to cardiovascular causes, and this number is expected to rise further as the incidence of CVD in the developing world increases as a result of lifestyle changes.

A. Morbidity and mortality. CVD is the number one killer in the United States, accounting for 36% of all deaths. CVD is responsible for one death every 40 seconds and claims more lives each year than all forms of cancer combined. One of every seven deaths in the United States is caused by coronary heart disease (CHD). There are 15.5 million Americans with a history of myocardial infarction (MI) or angina pectoris. As many as 660,000 Americans have a new MI each year, and 326,200 are victims of sudden cardiac death. The average age at first MI is 65.1 years for men and 70.2 years for women. According to the Centers for Disease Control and Prevention, elimination of all forms of CVD would raise the overall life expectancy by 7 years.

B. Economic consequences of CVD. The economic burden of CVD and stroke in the United States was estimated to be $316.6 billion in 2011 to 2012 and is projected to increase to $918 billion by 2030. In 2010, CVD was the leading cause of hospitalization, contributing to >5.8 million patient discharges and 4.4 million emergency department visits.

C. Prevention of coronary artery disease (CAD). Table 42.1 shows important targets for secondary prevention among patients with known coronary or noncoronary vascular disease. The goals for primary prevention are similar, but the cost-effectiveness of medical intervention is not so favorable in all populations. The consequences of modest population-wide risk reduction (e.g., reduction in fat intake [currently 33% of total calories] and cholesterol levels) and lifesaving technologies (e.g., surgery, angioplasty, and coronary care units) have reduced the death rate and possibly contributed to reduced morbidity, but the burden of CVD remains a major challenge.

TABLE 42.1 Goals for Secondary Prevention among Patients with Known Vascular Disease

Risk Factor	Goal
Hypertension (mm Hg)	140/90

TABLE 42.1 Goals for Secondary Prevention among Patients with Known Vascular Disease

Dyslipidemia (mg/dL)	LDL < 100 (<70 in very high-risk patients) [or non-HDL <100 for very high-ris Society and Canadian Societies of Cardiology, National Lipid Association and No goal per the ACC/AHA 2013 guidelines. High-intensity statin therapy is reco Triglycerides < 100
Physical activity	30 min, three or four times per week
Body mass index	≤24.9 kg/m^2
Diabetes mellitus	Near-normal blood sugar (HbA1c < 6.5%)
Smoking	Complete cessation

II. HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

III. **HYPERLIPIDEMIA.** Dyslipidemia is an important **correctable predictive factor for CAD**. There is a strong, independent, continuous, and graded relation between total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) level and risk of CAD events. This relation has been clearly demonstrated in men and women in all age groups. More than one-half of US adults (105 million) have TC levels >200 mg/dL, and of these, 37 million have values >240 mg/dL. In general, a 1% increase in LDL-C level leads to a 2% to 3% increase in risk of CAD.

A. Physiology

1. **Lipoproteins** are large molecular compounds that are essential to the transport of cholesterol and triglycerides within the blood. They contain a lipid core composed of triglycerides and cholesterol esters surrounded by phospholipids and specialized proteins known as **apolipoproteins**. The **five major families of lipoproteins** are **chylomicrons and chylomicron remnants, very low density lipoproteins (VLDLs), intermediate-density lipoproteins, low-density lipoproteins (LDL), and high-density lipoproteins (HDLs)**.

2. **Apolipoproteins** are necessary for the structure and enzymatic processes of lipids. Apolipoprotein A1 (**apo A1**) is a major component of **HDL**, and apolipoprotein B (**apo B**) is the main apolipoprotein for the remaining **non-HDL** lipoproteins.

B. Lipid-lowering trials. Aggressive lipid-lowering drug treatment of persons at various risk levels reduces CAD morbidity and mortality rates and increases overall survival. Although the association between hyperlipidemia and CAD was established much earlier, the demonstration of a relationship between reduction in serum lipid levels and a reduction in all-cause mortality had to await the development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or "statins." Multiple randomized trials have provided overwhelming evidence of the benefit of statins in both primary and secondary prevention of cardiovascular events.

1. **Primary prevention trials**

a. The **West of Scotland Coronary Prevention Study (WOSCOPS) (1995)** demonstrated that treatment of men at relatively high risk with profoundly elevated cholesterol levels significantly reduced the risk of heart attack and death from heart disease. The double-blind study randomized 6,600 healthy men with a baseline mean LDL-C level of 193 mg/dL to pravastatin (40 mg/d) or to placebo, for an average of 5 years, and

demonstrated a 31% relative reduction in the incidence of nonfatal MI or CAD death. Follow-up of this population published in 2007 showed that the statin group continued to experience lower rates of cardiovascular death after a further 10 years, even though only one-third continued to take statins during the additional follow-up period.

b. The **Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (1998)** demonstrated benefit among patients with more typical risk profiles, including lower cholesterol values, than among those in the WOSCOPS. AFCAPS/TexCAPS patients had a baseline mean TC level of 220 mg/dL and LDL of 150 mg/dL. The study randomized 6,600 patients to lovastatin 20 to 40 mg daily or placebo and demonstrated a 36% relative risk reduction (RRR) for first acute major coronary events in the lovastatin group.

c. The **Heart Protection Study (HPS) (2002)** randomized 20,536 subjects with a mean LDL of 131 mg/dL in a 2 × 2 factorial design to daily simvastatin (40 mg) or placebo and to antioxidants or placebo (the antioxidant arm did not show any benefit or harm). The study focused on patients who were deemed high risk for CVD but not thought to merit treatment with statins based on the prevalent clinical practice at that time. Increased risk was defined as presence of or history of CAD, cerebrovascular disease, peripheral arterial disease, diabetes mellitus, or treated hypertension. Simvastatin therapy was associated with a 13% reduction in all-cause mortality, including an 18% reduction in coronary death rate. The beneficial impact of statin therapy was seen with respect to all cardiovascular end points, with significant reductions in risk of nonfatal MI, incidence of first stroke, and coronary and noncoronary revascularization. **Treating patients with LDL levels <100 mg/dL was also associated with a beneficial reduction in vascular events.** The benefit was maintained in patients receiving other cardioprotective medications, such as angiotensin-converting enzyme inhibitors, β-blockers, and aspirin. Although not strictly a primary prevention trial, the HPS provided evidence to support treatment of risk as endorsed by the National Cholesterol Education Program (NCEP) guidelines. However, the HPS results refuted the threshold LDL level (as proposed by NCEP III at that time) below which statins were not previously indicated.

d. **Pravastatin in Elderly Individuals at Risk of Vascular Disease (2002)** randomized 5,804 patients between the ages of 70 and 82 years with mean LDL of 147 mg/dL to placebo or pravastatin. These patients had preexisting coronary, cerebral, or peripheral vascular disease or had a history of smoking, hypertension, or diabetes. The study demonstrated a 15% reduction in the composite of coronary death, nonfatal MI, and stroke over a period of 3 years. The study demonstrated the efficacy of primary and secondary prevention in the elderly.

e. The **Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (2002)** randomized 10,355 hypertensive patients with one other coronary risk factor and a baseline mean LDL-C level of 148 mg/dL to pravastatin 20 to 40 mg/d or usual care. The study did not demonstrate a mortality difference in the two arms after a follow-up period of 4.8 years. This lack of observable difference in outcome might have resulted from the relatively modest LDL reduction (17% with pravastatin vs. 8% in usual care) or the fact that 26% of the patients in the "usual care" group were taking a statin at the end of the trial.

f. The **Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (2003)** randomized 10,305 patients with hypertension and at least three other cardiovascular risk factors and a baseline mean LDL-C level of 133 mg/dL to atorvastatin 10 mg/d or placebo. The study was stopped prematurely after a median follow-up of 3.3 years by

the safety monitoring committee because of a significantly higher incidence of the primary end point (nonfatal MI or fatal CHD) in the placebo group. The study demonstrated a 36% RRR for the primary end point in the atorvastatin group compared with the placebo group. Further analysis demonstrated that the benefit of statin therapy started after only 1 year of treatment. There was also a significant reduction (RRR of 27%) in the incidence of fatal and nonfatal stroke in the atorvastatin group. This study, like the HPS, provided further evidence of the benefit of statins in patients at high risk for CVD without regard for baseline TC or LDL levels.

g. The **Collaborative Atorvastatin Diabetes Study (CARDS) (2004)** randomized 2,838 diabetic patients with one additional cardiovascular risk factor, no history of CVD, and an average baseline LDL-C of only 117 mg/dL to atorvastatin 10 mg/d or placebo. This study was also terminated prematurely owing to an excess incidence of the primary end point (a composite of acute coronary events, coronary revascularization, or stroke) in the placebo group after a median follow-up of 3.9 years. Overall, the atorvastatin group had an RRR of 37% for the primary end point and 27% for all-cause mortality. The importance of this trial was its demonstration of the clinical benefit of statin use in diabetic patients regardless of baseline LDL-C level, making a compelling case for statin use in all diabetic patients with at least one additional cardiovascular risk factor. According to the NHANES III data, 82% of diabetic patients in the United States would meet the entry criteria for the CARDS trial.

h. The **Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (2005)** trial focused on the prevention of CHD in patients with type 2 diabetes using fenofibrates. The study randomized patients with type 2 diabetes diagnosed after 35 years of age with no clear indication for cholesterol-lowering therapy at baseline to fenofibrate (200 mg/d) or placebo. The study failed to show a difference in the primary composite end point of CHD or nonfatal MI between the two groups at 5-year follow-up. However, several secondary end points were lower in the fenofibrate group including nonfatal MI and coronary revascularization.

i. **Japan EPA Lipid Intervention Study (2007).** The goal of this trial was to evaluate treatment with the fish oil supplement eicosapentaenoic acid (EPA) in addition to statin therapy compared with statin therapy alone among patients with hypercholesterolemia (baseline LDL 187 mg/dL and median triglycerides 151 mg/dL). The study randomized patients in an open-label manner to treatment with EPA (1,800 mg/d) in addition to statin therapy (pravastatin 10 mg/d) or simvastatin (5 mg/d) or to statin therapy alone. At a mean follow-up of 4.6 years, there was a significant reduction in the primary end point of major adverse cardiovascular events in the EPA plus statin group (2.8% vs. 3.5%). This was driven primarily by a significant reduction in rates of unstable angina and a trend toward lower rates of nonfatal MI and revascularization. No difference was seen in sudden cardiac death or fatal MI.

j. The **Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (2008)** focused on patients with normal LDL-C levels but increased levels of high-sensitivity C-reactive protein (CRP). This was the first clinical trial to demonstrate that statin therapy may benefit patients with low-to-normal LDL levels and no known CVD. The study randomized 17,802 healthy subjects with an LDL-C <130 mg/dL and a CRP ≥2.0 mg/L to daily rosuvastatin of 20 mg or placebo. The trial was stopped early for a mortality benefit after a median follow-up of 1.9 years. The study demonstrated that after 1 year of therapy, there were lower levels of LDL-C (55 vs. 110 mg/dL) and lower levels of CRP (2.2 vs. 3.5 mg/L) in the rosuvastatin-treated group. There was also a lower incidence of the primary end point of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial

revascularization procedure, or confirmed death from cardiovascular cause (0.77 vs. 1.36 events per 100 person-life years) as well as the risk of all-cause mortality (1.00 vs. 1.25 deaths per 100 person-life years) in the rosuvastatin-treated group.

k. The **Action to Control Cardiovascular Risk in Diabetes Lipid Trial (ACCORD Lipid) (2010)** was designed to evaluate whether the addition of fenofibrate to statin therapy among patients with type 2 diabetes (baseline LDL 100 mg/dL and median triglycerides 164 mg/dL) would be effective in preventing cardiovascular events. The study randomized half of the patients within the initial ACCORD trial with type 2 diabetes and treated with a statin medication to fenofibrate (160 mg daily) or placebo. Although a significant reduction in median triglyceride level (164 to 122 mg/dL) was seen with the addition of fenofibrate to statin therapy, there was no reduction in the primary end point (first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) when compared with statin therapy alone. In a subgroup analysis, a trend toward benefit of fenofibrate was shown in the group of patients with diabetes that had a significant dyslipidemia (low HDL and high triglycerides). Additional subgroup analysis showed a trend toward harm in women (but not men) in the fenofibrate group that warrants further investigation in future studies.

2. **Secondary prevention trials**

a. The **Scandinavian Simvastatin Survival Study (4S) (1994)** was the first secondary prevention trial to demonstrate a clear reduction in total mortality. Simvastatin reduced total mortality among patients with CAD by 30%, largely because of a 42% reduction in deaths from CAD. The 4S treated 4,444 men and women with CAD and mean baseline LDL of 188 mg/dL, with a range of 130 to 266 mg/dL.

b. The randomized, controlled **Cholesterol and Recurrent Events Trial (1996)** was designed to evaluate the effects of treatment with pravastatin on 4,159 persons who had experienced acute MI 3 to 20 months before randomization and had moderately elevated TC levels (mean 209 mg/dL) and LDL levels (mean 139 mg/dL). The benefits of pravastatin therapy in preventing recurrent coronary events were similar in the subset analysis of age, sex, ejection fraction, hypertension, diabetes mellitus, and smoking.

c. The **Long-Term Intervention with Pravastatin in Ischemic Disease Study (LIPID) (1998)** was the first to examine the use of a statin for patients with a history of unstable angina. The LIPID study provided new data on noncoronary mortality (i.e., stroke) and on other groups, such as women and patients with diabetes, who previously had been underrepresented in clinical trials. LIPID demonstrated improved CAD outcomes among all patients, including those with unstable angina.

d. **The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) (1999)** was a multicenter study that randomized patients with known CHD and low HDL-C (≤40 mg/dL) and LDL-C (≤140 mg/dL) levels to gemfibrozil (1,200 mg/d) or placebo with a mean follow-up of 5.1 years. The study showed that gemfibrozil therapy was associated with a significant 22% reduction in the combined incidence of nonfatal MI and CHD death. This was the first lipid intervention trial to show that raising HDL-C concentrations in patients with CHD and low HDL-C and LDL-C levels will reduce the incidence of major coronary events.

e. **Myocardial Ischemia Reduction with Acute Cholesterol–Lowering Trial (2001).** This trial demonstrated cardiovascular benefits with initiation of early statin therapy following acute coronary syndrome (ACS). The trial randomized 3,086 adults with

unstable angina or non–Q-wave MI to high-dose atorvastatin (80 mg/d) or placebo between 24 and 96 hours after hospital admission. There was a reduction in the primary end point of nonfatal infarction, cardiac arrest with resuscitation, or recurrent symptomatic ischemia requiring hospitalization in the atorvastatin group (14.8% vs. 17.4%, RRR of 16%). The benefit was driven primarily by a 26% reduction in recurrent symptomatic ischemia. The trial did not show a mortality benefit (death, MI, or need for revascularization).

f. **Pravastatin or Atorvastatin Evaluation and Infection Therapy–TIMI 22 (PROVE-IT–TIMI-22) (2004).** This trial was designed to determine whether intensive lipid-lowering therapy in patients with ACS reduced major coronary events and mortality more than "standard" lipid lowering. A total of 4,162 patients who had been hospitalized for ACS within the preceding 10 days were randomized to atorvastatin 80 mg/d or pravastatin 40 mg/d. After 2 years of follow-up, the composite end point (all-cause mortality, MI, unstable angina, coronary revascularization, and stroke) was significantly reduced by 16% with atorvastatin compared with pravastatin. High-dose atorvastatin was well tolerated, with no cases of rhabdomyolysis. Of note, the LDL-C level attained on atorvastatin 80 mg/d was 33 mg/dL lower than on pravastatin with a mean of 62 mg/dL. These results suggested that the use of intensive lipid-lowering therapy to achieve very low LDL-C levels was of benefit in a group of patients at high risk for recurrent coronary events.

g. **A to Z trial: phase Z (2004)—early intensive vs. a delayed conservative simvastatin strategy in patients with acute coronary syndromes (2004).** This trial studied whether early initiation of high-dose statin therapy would lead to a reduction in long-term cardiac events compared with a more conservative, delayed low-dose statin strategy in high-risk patients with ACS. The trial enrolled a total of 4,497 patients with a recent ACS, TC level ≤250 mg/dL and median LDL level 111 mg/dL, and at least one additional risk factor who were randomized to either intensive statin therapy strategy (simvastatin 40 mg for 1 month, followed by 80 mg through 2 years) or a conservative strategy (placebo for 4 months followed by simvastatin 20 mg through 2 years). Although the study showed an early and sustained reduction in LDL in the aggressive strategy arm, it did not show a significant reduction in the primary composite end point of cardiovascular events (cardiovascular death, MI, readmission for ACS, and CVA) or death from any cause compared with a more conservative strategy. There were also more patients who developed creatine kinase (CK) concentrations more than 10 times the upper limit of normal in the aggressive strategy arm (9 vs. 1) and three patients who developed rhabdomyolysis while on simvastatin 80 mg.

h. The **Treating to New Targets (TNT) (2005)** trial sought to demonstrate the benefit of intensive lipid-lowering therapy in patients with stable coronary disease. The trial randomized 10,001 patients with clinically evident CHD and baseline LDL-C levels <130 mg/dL to atorvastatin 80 mg/d or atorvastatin 10 mg/d. After 4.9 years of follow-up, the group receiving atorvastatin 80 mg/d had a 22% RRR in the primary composite end point of death from CHD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke compared with the group receiving atorvastatin 10 mg/d. High-dose atorvastatin was remarkably safe, with a 1.2% incidence in elevation of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) more than three times the upper limit of normal, compared with a 0.2% incidence in the atorvastatin 10 mg group. Rates of myalgias and rhabdomyolysis were similar between the two groups. This study provided compelling evidence that the use of intensive statin

therapy to reduce LDL-C to levels below 100 mg/dL had marked clinical benefit in patients with stable CHD.

i. The **Incremental Decrease in End Points through Aggressive Lipid Lowering (2005)** trial randomized 8,888 patients with a prior history of acute MI and baseline LDL level of 122 mg/dL to atorvastatin 80 mg/d or simvastatin 20 mg/d. After 4.8 years of follow-up, there was a nonsignificant difference in the risk of the composite end point of coronary death, acute MI, or cardiac arrest. However, if either stroke or revascularization was added to the primary end point, the results favored the atorvastatin group, and the associated hazard ratios were similar to the results of PROVE-IT and TNT. Despite the published negative result of this trial, it provided complementary evidence for the benefit of intensive LDL lowering in patients at high risk for coronary events.

j. **The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (2015)** was a study that compared the effect of adding ezetimibe versus placebo to simvastatin in patients with a recent ACS. The study randomized 18,144 patients who had been hospitalized for ACS within the preceding 10 days and had LDL cholesterol levels of 50 to 100 mg/dL if they were receiving lipid-lowering therapy or 50 to 125 mg/dL if they were not to either ezetimibe (10 mg) and simvastatin (40 mg) versus placebo and simvastatin (40 mg). Over median follow-up of 6 years, the median LDL level was 53.7 mg/dL in the ezetimibe–simvastatin group versus 69.5 in the simvastatin monotherapy group. There was 6.4% RRR and 2% absolute risk reduction in the primary end point of cardiovascular death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke in the ezetimibe–simvastatin group. There were no increased side effects in the ezetimibe–simvastatin group. This trial was the first trial to highlight that more intensive LDL reduction with non-statin medications (ezetimibe) can reduce the risk of recurrent CVD in a secondary prevention population.

k. The **Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (2011)** was a study that compared treatment of extended-release niacin versus placebo among statin-treated patients with established heart and vascular disease and baseline LDL 71 mg/dL and HDL 35 mg/dL. The study randomized 3,414 patients with optimally treated LDL-C and low HDL-C with established vascular disease (documented by coronary angiography or by prior MI, or carotid angiography or prior ischemic stroke, or peripheral arterial disease) to extended-release niacin (1,500 to 2,000 mg/d) or placebo. There was no significant difference in the primary composite outcome of CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary/cerebral revascularization (16.4% in the extended-release niacin group vs. 16.2% in the placebo group). The study was terminated 18 months early after it was evident that the addition of extended-release niacin would not be beneficial. Furthermore, there was a small (numerical) excess in ischemic strokes and hospitalizations for ACS.

l. **The Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)** was a trial to assess the effects of adding extended-release niacin (2 g) in combination with laropiprant (40 mg) to effective statin-based LDL cholesterol–lowering treatment in 25,673 high-risk patients with prior vascular disease (baseline LDL 63 mg/dL and HDL 44 mg/dL). Laropiprant is an antagonist of the prostaglandin D2 receptor DP_1 that has been shown to improve adherence to niacin therapy by reducing flushing in up to two-thirds of patients. The niacin–lopiprant group had a lower LDL by 10

mg/dL and a higher HDL by 6 mg/dL; however, there were no significant differences in the incidence of major adverse vascular events between the treatment group and placebo. There was an increased incidence of worsening of diabetes control in the treatment group. This trial provided evidence that increasing HDL levels did not necessarily improve cardiovascular outcomes which was also later found in cholesterylester transfer protein (CETP) inhibitor trials.

m. **CETP inhibitor trials:** CETP is responsible for transfer of cholesterylesters from HDL to LDL and VLDL, thus leading to increased HDL levels and reduced LDL levels if inhibited. Several preclinical studies have shown a significant ability of this class of drugs to increase HDL levels by >50% and reduce LDL levels by >20% and there was tremendous excitement about its potential. However, randomized trials examining clinical outcomes showed either no effect or possibly harm of CETP inhibitors when added to a statin therapy background. In ILLUMINATE, torcetrapib was associated with an increased risk of cardiovascular events by 25% and mortality risk by 50% despite reducing LDL by 25% and increasing HDL by 72% thought to be due to an off target effect of increasing blood pressure. The DAL-OUTCOMES study (15,871 patients) and ACCELERATE study (12,000) were terminated because of lack of efficacy. These trials highlight the importance of approving new drugs based on large trials examining clinical outcomes rather than approving them based on their effect on surrogate markers. CETP inhibitors had consistent positive effects on LDL and HDL, yet showed harm or no effect on cardiovascular clinical outcomes. More recently, the HPS3/TIMI55-REVEAL trial (30,449 patients) showed that adding anacetrapib to high-intensity statin therapy (HIST) in patients with CVD resulted in a lower rate of coronary events but there was no effect on death. Many experts argue that the observed benefit in this trial was mainly related to the magnitude of LDL lowering. Given the inconsistent evidence for clinical benefit from this class of drugs, the exact role of CETP inhibitors in clinical practice needs to be better defined in future studies.

n. **Proprotein Convertase Subtilisin/Kexin type 9 inhibitors:** Proprotein convertase subtilisin/kexin type 9 (PCSK-9) is a protease that promotes the binding and degradation of LDL receptors intracellularly. As such, inhibition of PCSK-9 leads to increased LDL receptors on the cell membrane and therefore, increased uptake of LDL leading to a reduction in LDL serum levels. It only took a decade since genetic variants increasing PCSK-9 expression were identified and shown to be associated with life-long lower levels of LDL and cardiovascular events to development of monoclonal antibodies that inhibit PCSK-9. Phase II and III clinical trials have shown a promising effect of PCSK-9 inhibitors. In the OSLER and ODYSSEY LONG TERM trials, evolocumab and alirocumab, respectively, showed ~60% reduction in LDL levels on a background of statin therapy in high-risk cardiovascular patients. Furthermore, they were associated with ~50% reduction in cardiovascular events, although these trials were not designed as outcome trials and the event rate was low over a short period of follow-up. Based on these preliminary promising results, the US Food and Drug Administration (FDA) approved the use of evolocumab and alirocumab for treatment of patients with clinical atherosclerotic cardiovascular events and familial hypercholesterolemia as **adjuncts to maximally tolerated statin therapy if greater reductions in LDL levels are required**. The short-term results of some of the large clinical outcome trials are as follows. The FOURIER trial (27,564 patients) randomized patients with CVD on HIST to evolocumab vs. placebo. Evolocumab resulted in 60% reduction in LDL levels (median posttreatment LDL was 30 mg/dL) and was associated with a 15% decrease in CV events at 2

years. However, the annual cost of PCSK-9 inhibitors is very high at this time and there has been significant debate regarding their cost-effectiveness in clinical practice given the small absolute clinical benefit (NNT over 2 years is 74) and high cost to benefit ratio. Gathering more data will be necessary to determine the optimal cost for these drugs in comparison to the suggested benefit.

3. **Meta-analyses**

a. **CTT Collaborators (2005).** A large meta-analysis of 90,056 individuals from 14 randomized trials of statin drugs, this analysis demonstrated an impressive 12% reduction in all-cause mortality for each 1 mmol/L (39 mg/dL) reduction in LDL. There was a 19% reduction in coronary mortality and 21% reduction in MI, coronary revascularization, and stroke. Statin use showed benefit within the first year of use, but was greater in subsequent years. Statins were also remarkably safe, with no increase in cancer seen and a 5-year excess risk of rhabdomyolysis of 0.1%.

b. **Cannon—Intensive Statin Therapy (2006).** A meta-analysis of 27,548 patients from four trials that investigated intensive versus standard lipid-lowering therapy found a significant 16% odds ratio reduction in coronary death or MI in the group that received intensive therapy. There was a nonsignificant trend toward decreased cardiovascular mortality.

c. **Boekholdt—Very low levels of atherogenic lipoproteins from statin trials (*J Am Coll Cardiol*, 2014).** This meta-analysis of 38,153 patients from eight statin trials showed that there was significant interindividual variability in response to statins with more than 40% of patients on HIST not reaching LDL <70 mg/dL. Those who achieved very low levels of LDL <50 mg/dL had a lower risk of cardiovascular events than those who achieved moderately low levels.

C. **Management of lipids.** Despite overwhelming evidence supporting the treatment of dyslipidemia, a large number of patients remain untreated. The NCEP Adult Treatment Panel III has released guidelines for the treatment of hyperlipidemia in adults and these were based on LDL treatment targets. However, the ACC/AHA released new guidelines in 2013 that abandoned the use of treatment targets to guide therapy and instead recommended statin therapy to certain patient populations. This has been a source of extensive debate lately particularly in the setting of recent studies showing benefit of non-statin medications such as ezetemibe or PCSK-9 inhibitors. It is worth mentioning that the European Society of Cardiology, Canadian Society of Cardiology, National Lipid Association, and the International Atherosclerosis Society continue to recommend LDL and non-HDL treatment targets but here we will focus on the ACC/AHA guidelines.

1. **The new ACC/AHA 2013 cholesterol treatment guidelines:**

a. **TC, LDL-C, and HDL-C levels.** All adults 20 years or older and **without a history of CAD or other atherosclerotic disease**should have a fasting lipid panel (i.e., TC, LDL-C, HDL-C, and triglyceride levels) every 5 years. If a nonfasting lipid panel is obtained and the TC level is 200 mg/dL or the HDL-C is <40 mg/dL, a follow-up fasting lipid panel is recommended

b. **Heart healthy lifestyle habits are the foundation of atherosclerotic cardiovascular disease (ASCVD) prevention. In patients not taking statins, recalculate the estimated 10-year ASCVD risk using the new 2013 calculator every 4 to 6 years in patients aged 40 to 75 years without clinical ASCVD or diabetes and with LDL 70 to 189 mg/dL.**

c. **HIST is defined as that which lowers LDL levels by ≥50% whereas moderate intensity therapy lowers it by 30% to less than 50%.**

d. **Patient groups who are candidates for statin therapy:**

1. **1 Patients with clinical ASCVD:** Patients should receive HIST unless they are >75 years old or cannot tolerate HIST in case of which moderate intensity statin is recommended.
2. **2 Patients with LDL ≥190 mg/dL:** HIST is recommended unless patients cannot tolerate it.
3. **3 Patients with type 1 or 2 diabetes mellitus, age 40 to 75 and with LDL 70 to 189 mg/dL:** Moderate intensity statin is recommended unless the 10-year estimated ASCVD risk by the pooled cohort equation is ≥7.5% in case of which HIST is recommended.
4. **4 Patients without diabetes mellitus or ASCVD, age 40 to 75, with LDL 70 to 189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5%:** Moderate- to high-intensity statin is recommended.

e. **ASCVD prevention using statins may be less clear in other patient groups:** In selected individuals, use other factors to determine eligibility for statin therapy such as the presence of additional factors influencing ASCVD risk (e.g., family history of premature CAD), drug–drug interactions, and patient preference for initiating statin therapy.

f. **In selected individuals who do not meet criteria for statin therapy per the new guidelines, further risk stratification with other tools such as coronary artery calcium, high-sensitivity C-reactive protein levels, lifetime risk of ASCVD, or ankle-brachial index may be of value in certain situations.**

g. **Use of the new Pooled Cohort Equations is recommended to estimate 10-year ASCVD risk in both white and black men and women who do not have clinical ASCVD.** This equation replaces the Framingham Risk Score. There has been some criticism that the new equation overestimates the number of patients that may benefit from statin therapy leading to more widespread use of statins.

h. **Despite the well-proven concept that lower LDL is associated with lower ASCVD risk, the guidelines did not recommend using non-statin medications to reduce LDL beyond maximally tolerated statin therapy because of the lack of outcome data at that time.** However, recent data from the IMPROVE-IT trial examining adding ezetemibe to simvastatin in addition to PCSK-9 inhibitor trials have shown there may be incremental value to using these medications to lower LDL further after using maximally tolerated statin therapy.

2. **Types of therapy**

a. **Therapeutic Lifestyle Changes (TLCs)** encompass **increased physical activity, ideal weight maintenance, and a diet** that includes a reduced intake of saturated fat (<10% of total calories), reduced intake of added sugars (<10% of total calories), <2,300 mg of sodium per day, and cholesterol (<200 mg/d). Other TLCs are listed in Table 42.2. Intake of *trans*-fatty acids should be kept to a minimum. For most patients, it is essential to reduce saturated fat intake over total fat intake; for patients with metabolic syndrome, a fat intake of 30% to 35% may be optimal for reducing lipid and nonlipid risk factors. High-carbohydrate diets may worsen the lipid abnormalities in these patients. Dietary carbohydrates should be derived predominantly from foods rich in complex carbohydrates, such as whole grains, fruits, and vegetables. Daily intake of 5 to 10 g of viscous fiber reduces LDL levels by approximately 5% and the use of plant stanols and sterols (2 to 3 g/d) by another 6% to 15%. **TLCs can achieve an almost 30% reduction in LDL-C level in highly motivated individuals and should form the cornerstone of all preventive activity**. Benefits of LDL-C lowering may be evident within 6 to 12 months, although the individual response to a cholesterol-lowering diet

depends on many factors. Some of the response is genetically determined, and increased body mass index is associated with less response to dietary change. LDL-C should be measured 6 weeks after initiating optimal diet, and if the goals are not met, intensification of TLCs and use of plant sterols or stanols should be considered. Referral to a dietitian for education and dietary counseling is often invaluable at this stage. If, after 3 months of TLCs, adequate control is not achieved, drug therapy should be considered.

TABLE 42.2 Components of Therapeutic Lifestyle

Component	Recommendation	A
	Diet	
Saturated fat	<7% of total calories	8
Dietary cholesterol	<200 mg/d	3
Polyunsaturated fat	Up to 10% of total calories	
Monounsaturated fat	Up to 20% of total calories	
Total fat	25%–35% of total calories	
Carbohydrate	50%–60% of total calories	
Dietary fiber	20–30 g/d	
Total protein	15% of total calories	
	Therapeutic Options for LDL Lowering	
Plant stanols/sterols	2 g/d	6
Increased viscous soluble fiber	5–10 g/d (consumption of 10–25 g/d may have added benefit)	3
Physical activity	Enough moderate activity to expend at least 200 kcal/d	

o. LDL, low-density lipoprotein.

c. **Pharmacotherapy.** The high efficacy of statins in lowering LDL-C level and their demonstrated mortality benefits make them the agents of first choice for treatment of most forms of hyperlipidemia. Table 42.3 summarizes the most commonly used agents affecting lipoprotein metabolism.

1. **1 HMG-CoA reductase inhibitors. HMG-CoA reductase inhibitors are** the first-line therapy in the management of hypercholesterolemia. The category includes seven drugs: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin.

1. **(a) Effectiveness.** When dietary measures are inadequate, HMG-CoA reductase inhibitors effectively **lower TC and LDL-C levels in patients with mixed hyperlipidemias** (i.e., elevated cholesterol and triglyceride levels). HMG-CoA reductase inhibitors are **extremely effective in reducing LDL-C levels in most patients with primary hypercholesterolemia.** HMG-CoA reductase inhibitors decrease TC by 15% to 60% and LDL-C by 18% to 55% and increase HDL-C levels by 5% to 15%. Declines in apo B levels commensurate with reductions in LDL have been

demonstrated. Statins also reduce triglyceride levels by 7% to 30% but have minimal effects on apo A1, apo A2, and lipoprotein (a) [Lp(a)]. **All statin drugs at the starting dose and within one to two dose titrations are well tolerated, efficacious**, and reasonably equivalent with respect to safety profiles.

2. **(b) Adverse effects.** Statins are remarkably safe drugs, with a low incidence of side effects. However, they are contraindicated in pregnancy.

1. **i. Minor side effects.** The most common side effects are **mild gastrointestinal disturbances** (e.g., nausea, abdominal pain, diarrhea, constipation, and flatulence). Headache, fatigue, pruritus, and myalgias are other minor side effects, but none of these complaints usually warrant discontinuation of therapy.

2. **ii. Liver function test abnormalities.** Mild, transient elevations in liver enzymes have been reported with all HMG-CoA reductase inhibitors. Marked elevation of transaminases is rare, but clinicians should avoid or use caution before starting statins in patients with acute or chronic liver disease. In the HPS, only 0.5% of patients had to stop treatment because of elevated ALT levels. Even when taking the highest dose of atorvastatin (80 mg), patients in PROVE-IT and TNT had only a 3.3% and 1.1% incidence, respectively, of transaminase elevation more than three times the upper limit of normal. In general, for each doubling of a statin dose, there is a 0.6% increase in risk of elevation of transaminase levels. **Current recommendations state that therapy should be discontinued when greater than threefold elevation occurs.** Enzyme levels typically return to normal within 2 weeks. Lower doses of the same medication can be reinstituted or a different statin can be tried. **Monitoring of hepatic aminotransferase levels is recommended for those taking HMG-CoA reductase inhibitors, but the frequency of monitoring has been debated.** Current package inserts for most statins recommend obtaining a liver panel prior to initiation of statin therapy, prior to dose titration, and when "clinically indicated." More frequent monitoring is recommended for patients taking the highest dose of a statin. In recent clinical trials, the high-dose statin that appears to have the highest incidence of transaminase elevation is atorvastatin. A panel of hepatologists who examined the potential hepatotoxicity of statins made a recommendation to obtain a liver panel prior to initiating statins as a baseline measurement of hepatic transaminases and bilirubin. If the baseline measurements were within normal limits, the panel recommended follow-up measurement of transaminases only if there was symptomatic or physical evidence of liver disease. An ACC/AHA/NHLBI clinical advisory panel on the safety and use of statins recommends measurement of transaminases at baseline, 12 weeks after starting therapy, and then annually or more frequently if indicated. The most recent ACC guideline do not recommend repeat testing.

TABLE 42.3 Drugs Affecting Lipoprotein Metabolism

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraind
HMG-CoA reductase inhibitors (statins)	Lovastatin (20–80 mg) Pravastatin (20–40 mg) Simvastatin (20–80 mg) Fluvastatin (20–80 mg) Atorvastatin (10–80 mg) Rosuvastatin (10–40 mg)	LDL-C ↓ 18%–55% HDL-C ↑ 5%–15% TG ↓ 7%–30%	Gastrointestinal distress Myopathy Increased liver enzymes	Absolute: disease Relative: certain c
Bile acid	Cholestyramine (4–16 g)	LDL-C ↓ 15%–30%	Gastrointestinal	Absolute:

TABLE 42.3 Drugs Affecting Lipoprotein Metabolism

sequestrants	Colestipol (5–20 g) Colesevelam (2.6–3.8 g)	HDL-C ↑ 3%–5% TG—no change or increase	distress Constipation Decreased absorption of other drugs	TG > 40 Relative: T
Nicotinic acid	Immediate release (crystalline nicotinic acid [1.5–3 g]) Extended release (Niaspan; 1–2 g) Sustained release (1–2 g)	LDL-C ↓ 5%–25% HDL-C ↑ 15%–35% TG ↓ 20%–50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: Severe Relative: D Peptic u
PCSK-9 inhibitors	Evolocumab (140 mg subQ every 2 wk or 420 mg every month) Alirocumab (75 mg subQ every 2 wk)	LDL-C ↓ 60%	Flu-like symptoms Injection site reactions Diarrhea Muscle pain or spasm	Contraindi Absolute— hyperse inhibitor
Fibric acids	Gemfibrozil (600 mg bid) Fenofibrate (200 mg) Clofibrate (1,000 mg bid)	LDL-C ↓ 5%–20% (may be increased in patients with high TG) HDL-C ↑ 10%–20% TG ↓ 20%–50%	Dyspepsia Gallstones Myopathy	Absolute: Severe

[a]Cyclosporine, macrolide antibiotics, various
, and cytochrome P450 inhibitors (fibrates and niacin should be used with appropriate caution).

GI, gastrointestinal; HDL-C, high-density
sterol; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol; PCSK-9,
rtase subtilisin/kexin type 9; TG, triglyceride.

5. **iii. Myopathy**, a rare but potentially serious side effect of HMG-CoA reductase inhibitors, presents with muscle pain, stiffness, or aching and elevations in serum CK level to more than 10 times the upper limit of normal. **CK measurements are not needed unless symptoms occur.** Statin-naïve patients should be warned to report symptoms of muscle pain or stiffness immediately if they occur after starting the drug. The risk of myopathy may be increased in the elderly, those with a low body mass index, those with multisystem disease such as chronic renal failure, those in the perioperative period, and those on multiple medications. Simvastatin 80 mg has been associated with a slightly higher incidence of myopathy and rhabdomyolysis compared with other statins, especially when combined with gemfibrozil. This could be due to the decreased rate of plasma clearance of simvastatin in older versus younger patients. Death from statin-induced rhabdomyolysis is exceedingly rare, with an incidence of 1.5 deaths per 10 million prescriptions. Statin-associated myalgias (muscle symptoms without elevations in serum CK) occur with somewhat higher frequency, about 1.4% to 1.5% in published clinical trials but up to 5% to 10% in registries, and can appear at any time during statin therapy, even years after initiation of

treatment. Muscle symptoms usually resolve with discontinuation of the statin. There is recent evidence that statin inhibition of mitochondrial coenzyme Q10 may be responsible for statin-induced myalgias, and there are conflicting small studies regarding the benefit of CoQ10 supplementation on statin myalgias.

6. **iv. Drug interactions.** When statins are used in combination with certain pharmaceutical agents, such as erythromycin, gemfibrozil, azole antifungals, cimetidine, methotrexate, or cyclosporine, the risks of CK elevation and myositis increase. These drug combinations should be avoided or used judiciously with interval measurements of CK levels and liver function. Pravastatin and fluvastatin are safer in combination with other drugs because these two drugs do not use the cytochrome P450 3A4 microsomal pathways for metabolism. Verapamil and amiodarone are two commonly used cardiovascular agents that inhibit this pathway, and the concurrent use of simvastatin, atorvastatin, or lovastatin may, therefore, predispose to an increased risk of myositis. Recently, the FDA has recommended that simvastatin should not be prescribed at a dose of 80 mg, given the higher rate of myopathy at this dose unless patients have already safely taken this dose for >12 months. Patients requiring this dose to maintain lipid goals should be transferred to another statin drug capable of achieving that goal. Simvastatin dosage in combination with amiodarone, diltiazem, or verapamil should not exceed 10 mg daily and should not exceed 20 mg daily in combination with amlodipine or ranolazine.

2. **2 Bile acid sequestrants** lower LDL-C level by interfering with reabsorption of bile acids in the distal ileum, reducing the amount returned to the liver. They are safe and free of systemic side effects because they are not systemically absorbed; however, gastrointestinal side effects such as constipation are common, and compliance is poor as a result. The average LDL level decrease is approximately 15% to 30%, with a small rise seen in HDL level (3% to 5%). Triglycerides show no change or may rise; therefore, these agents should be avoided in patients with elevated triglycerides. Two small angiographic trials, the NHLBI Type II Coronary Interventional Study and the St. Thomas Atherosclerosis Regression Study, have demonstrated reduced progression of CAD on serial angiograms in men with hypercholesterolemia who were taking cholestyramine. These agents may be of particular benefit in patients with minor elevation in LDL-C, for young patients, for women considering pregnancy, and in combination with a statin in those with very high LDL-C levels. In a pregnant patient, additional supplementation of iron and folate may be necessary because resins used over the long term can interfere with their absorption.

3. **3 Nicotinic acid or niacin.** Niacin affects all lipid parameters favorably (i.e., LDL reduction of 5% to 25%, triglyceride reduction of 20% to 50%, and HDL elevation of 15% to 35%). It is one of the only agents that reduces Lp(a) significantly (up to 30%). Unfortunately, compliance is poor because of frequent side effects. Flushing and pruritus, gastrointestinal discomfort, glucose intolerance, and hyperuricemia often accompany the use of niacin. Hepatotoxicity is rare but is more commonly seen with the sustained-release preparation. It is often heralded by a dramatic reduction in lipid levels. There are limited data on long-term therapy with this agent. Niacin may be particularly useful for patients who do not have substantial elevations in their LDL-C levels, and low doses may be used to treat diabetic dyslipidemia. High doses should be avoided in patients with diabetes, and the drug should be avoided in those with a history of gout, peptic ulcer disease, or active hepatic disease. In the HPS2-Thrive trial, niacin and laropiprant on a background statin therapy did **not** reduce adverse cardiovascular events despite raising HDL concentrations.

4. **4 Fibrates are effective at lowering triglyceride levels** by 20% to 50% and raising HDL levels by 10% to 20%. The mechanism of action involves activation of the nuclear transcription factor peroxisome proliferator–activated receptor α, with resultant increases in hepatic synthesis of apo A1 and A2 (raising HDL) and increase in lipoprotein lipase–mediated lipolysis, thus lowering

triglyceride levels. LDL level reduction varies with the agent used and may range from 5% to 20% in patients who are not hypertriglyceridemic. Fenofibrate appears to lower LDL more effectively than gemfibrozil. Although a higher mortality rate was seen in the clofibrate arm of the World Health Organization (WHO) clofibrate study, such a finding was not seen in subsequent studies of gemfibrozil or fenofibrate. These agents have been demonstrated to impart a reduction in risk of CAD events and are of use in patients with elevated triglycerides. The VA-HIT (1999) found a reduction in fatal and nonfatal MI with gemfibrozil use in men with CAD who had low HDL levels (mean 32 mg/dL), but the FIELD trial (2005) did not find a significant reduction in the primary end point of CAD death or MI in diabetic patients. Although fibrates are often used in combination with statin therapy to treat mixed dyslipidemia, there are no studies demonstrating reduction in clinical events with this approach. This combination increases the risk of myopathy. For patients with very high triglyceride levels (>1,000 mg/dL), fibrate therapy reduces the risk of pancreatitis.

5. **5 Cholesterol absorption inhibitors** such as ezetimibe inhibit cholesterol absorption by the enterocyte. Ezetimibe reduces cholesterol absorption from the small bowel by 23% to 50% and reduces serum LDL level by 14% to 20% when used in combination with a statin. Reduction in clinical end points or surrogate end points has not been demonstrated for this group of drugs in all people. The Study of Heart and Renal Protection trial reported that cholesterol lowering with a combination of simvastatin and ezetimibe in patients with chronic kidney disease significantly reduced the risk of major atherosclerotic events by 17%, including significant reductions in the risk of nonhemorrhagic stroke and revascularizations, when compared with placebo. However, the ENHANCE study failed to demonstrate any additional benefit of the use of ezetimibe added to statin over statin alone in slowing progression of carotid intimal thickness in a cohort of patients with familial hyperlipidemia. IMPROVE-IT, a phase III trial comparing ezetimibe/simvastatin versus simvastatin in subjects with stabilized high-risk ACS, showed that the addition of ezetemibe led to lower LDL levels and lower rates of cardiovascular events.
6. **6 CETP inhibitors** such as torcetrapib, dalcetrapib, anacetrapib, and evacetrapib inhibit the process in which triglycerides from VLDL or LDL are exchanged for cholesteryl esters from HDL, resulting in higher HDL levels and reduction of LDL levels. Results from a torcetrapib study in 2004 demonstrated a significant increase in HDL (61%) and a decrease in LDL (17%) when receiving the drug in addition to atorvastatin and a 46% increase in HDL when receiving the drug alone. However, the phase 3 ILLUMINATE trial was terminated in 2006 after an increase of cardiovascular events and mortality was shown to be associated with the drug. As described above, several recent trials have concluded that CETP inhibitors fail to decrease cardiovascular events despite efficient lowering of LDL and raising of HDL levels raising suspicion about whether this class of drugs will continue to be investigated.
7. **7 Proprotein Convertase Subtilisin/Kexin type 9 inhibitors.** PCSK-9 is a protease that promotes the binding and degradation of LDL receptors intracellularly. As such, inhibition of PCSK-9 leads to increased LDL receptors on the cell membrane and therefore, increased uptake of LDL leading to a reduction in LDL serum levels. It only took a decade since genetic variants increasing PCSK-9 expression were identified and shown to be associated with life-long lower levels of LDL and cardiovascular events to development of monoclonal antibodies that inhibit PCSK-9. Phase II and III clinical trials have shown a promising effect of PCSK-9 inhibitors. In the OSLER and ODYSSEY LONG TERM trials, evolocumab and alirocumab, respectively, showed ·60% reduction in LDL levels on a background of statin therapy in high-risk cardiovascular patients. Furthermore, they were associated with ·50% reduction in cardiovascular events, although these trials were not designed as outcome trials and the event rate was low over a short period of follow-up. Based on

these preliminary promising results, the FDA approved the use of evolocumab and alirocumab for treatment of patients with clinical atherosclerotic cardiovascular events and familial hypercholesterolemia as adjuncts to maximally tolerated statin therapy if greater reductions in LDL levels are required. There are several large outcome trials currently underway.

1. **(a) Choice of an agent and combination therapy.** The use of statin therapy for treatment of hyperlipidemia should be guided by the expected change in LDL-C levels (Table 42.4). Most statins have a log-linear dose–response pattern, with each doubling of dose associated with a further 7% reduction in LDL-C levels. Adverse effects of statins are also dose dependent and rise with the use of higher doses.

TABLE 42.4 Average Reduction in Low-Density Lipoprotein Cholesterol Associated with the Starting Do

Agent	Average LDL-C Reduction (%)
Lovastatin (20 mg)	24
Pravastatin (20 mg)	24
Simvastatin (20 mg)	35
Fluvastatin (20 mg)	18
Atorvastatin (10 mg)	37
Rosuvastatin (10 mg)	47

LDL-C, low-density lipoprotein cholesterol.

1. **i. HMG-CoA reductase inhibitors and bile acid resins.** In isolated forms of LDL elevation, this combination exhibits highly complementary mechanisms of action. The combination of a statin with a bile acid sequestrant is ideal, owing to the lack of potentiation of side effects. The sequestrant provides little added toxicity, and the LDL-C lowering needed may not necessitate a full sequestrant dosage. Unfortunately, patient compliance with the combination is poor because of the common side effects of resins. Although the combination may reduce **LDL level by as much as 70% in some patients**, there appears to be a ceiling effect, with no LDL lowering occurring beyond the original level with an increase in dose of either agent.
2. **ii. Combining a statin with niacin** is attractive because it can favorably influence all lipid subfractions. The side effects of the combination are increased but not synergistic, and the risk of myopathy may be lower than previously believed. The main serious side effect of the combination is hepatotoxicity, which may be reduced by using extended-release niacin. In small studies using this combination, the risk of hepatotoxicity (i.e., persistent elevation of AST or ALT of more than three times the upper limit of normal) at niacin doses of 2 g/d was about 1%. The HPS2-Thrive showed no benefit in adding niacin + lopiprant to statins.
3. **iii.** The combination of a statin plus fibrate is highly effective for treating mixed hyperlipidemias. Although theoretically appealing, no reduction in clinical events has been demonstrated with this approach. The combination is associated with an increased risk of myopathy. Although earlier work suggested a higher incidence, later studies suggest this complication may be seen in approximately 1% of patients with the currently used agents.
4. **iv.** The combination of a statin plus ezetimibe has been studied in small trials and has proved to be highly safe and effective at lowering LDL-C levels. Given the small number of patients treated and short

follow-up periods, it is suggested that this combination should be reserved for the patients who fail maximal statin doses or are intolerant of statins.

5. **v.** The combination of statin and PCSK-9 inhibitors is extremely effective at lowering LDL-C levels by ~60% without many side effects. The FDA has approved this approach for patients with residual hypercholesterolemia and known ASCVD and patients with heterozygous or homozygous familial hypercholesterolemia. The approval was based on trials showing a significant decrease in LDL and a signal toward reduced CV events; however, trials designed to study the impact of this combination on cardiovascular events are still underway.

3. Therapy of specific lipid disorders

a. **Very high LDL levels** usually result from inherited disorders of lipoprotein metabolism and carry a high risk of premature atherosclerosis with its attendant morbidity and mortality. **Hypothyroidism** may be associated with markedly elevated LDL levels and should be ruled out in any patient presenting with elevated LDL level. In addition to treating hypothyroidism, most of these patients will need high-dose statin therapy in addition to dietary restrictions. The addition of a bile acid sequestrant with an additional third agent (i.e., niacin) is often warranted to achieve target levels. Ezetimibe is another agent that may prove useful in this group. Therapy should be initiated early, and family members should be screened for hyperlipidemia. Patients with homozygous familial hyperlipidemia are deficient in LDL receptors, and measures that reduce cholesterol absorption (e.g., diet, ileal exclusion, bile acid sequestrants, and ezetimibe) or act by LDL receptor upregulation (e.g., statins) are largely ineffective. These patients may be treated with PCSK-9 inhibitors and LDL apheresis and should be managed in tertiary care centers only. It is important to note that PCSK-9 inhibitors may not work in patients with homozygous familial hypercholesterolemia with mutations that lead to complete absence of production of LDL receptors.

b. **Elevated triglyceride levels** may be caused by many factors, and more than one cause may be active in a given patient. **Minor elevations in triglyceride levels (150 to 299 mg/dL)** are usually caused by obesity, sedentary lifestyle, smoking, excess alcohol intake, and high-carbohydrate diets. In other patients, secondary causes such as diabetes, renal failure, Cushing disease, nephrotic syndrome, or medications (e.g., protease inhibitors, corticosteroids, retinoids, β-blockers, and oral estrogens) may be responsible. Genetic causes may be pertinent to others. The therapy for this group of patients involves identification and treatment of secondary causes (if present), change in medications, and lifestyle changes. These patients benefit from total caloric restriction and switching from a very high-carbohydrate diet to a more balanced diet. Very high **triglyceride levels (≥500 mg/dL)** usually result from genetic defects of lipoprotein metabolism; in some patients, there is a combination of factors at play. These patients are at risk for acute pancreatitis (especially with triglyceride levels >1,000 mg/dL), and treatment is directed at prevention of this condition. This is achieved with a combination of dietary measures (using very low fat diets [<15% calories from fat] and substituting medium-chain fatty acids in patients with triglyceride levels >1,000 mg/dL), increasing physical activity, maintaining optimal weight, and initiating fibrates or niacin therapy. Fibrates are especially efficacious in this group. Statins are not especially effective agents for triglyceride reduction and should be considered only after the other two agents. Patients with an **intermediate rise in triglyceride levels (200 to 499 mg/dL)** are a more heterogeneous group, with a wide array of underlying pathogenetic mechanisms at play. This pattern is often a result of an intersection of poor lifestyle, secondary causes, and genetic factors. These patients often have

other markers of increased atherogenic risk, such as increased small LDL, low HDL, or elevated VLDL remnants. They need to be treated aggressively to bring the LDL level to the target; statins, with their ability to lower non–HDL-C, are the preferred agents. **After the LDL target has been achieved, the secondary goal is non–HDL-C (goal of 30 mg/dL higher than target LDL-C)**. These patients also need aggressive TLCs. High-dose statins often suffice to achieve the LDL-C and non–HDL-C goals, but for most patients, a second agent becomes necessary. The choices are niacin or fibrates in addition to a statin; these combinations carry an increased risk of hepatotoxicity or myopathy, and careful monitoring for these is essential. Refractory cases may benefit from fish oil supplements (>3 g/d), which, by reducing VLDL production, can lower the serum triglyceride concentration by as much as 50% or more; however, many currently available over-the-counter fish oil supplements contain <50% active ω-3 fatty acids. The commercial preparation Omacor, which has been available for many years in Europe and is now also available in the United States, contains 90% ω-3 fatty acids. The US FDA limited approval for Omacor to the treatment of severe hypertriglyceridemia (≥500 mg/dL) because of concerns that it appears to increase LDL-C levels. Weight loss by obese patients should be encouraged; it is associated with an improvement in the lipid profile and facilitates pharmacologic therapy if still necessary. The STRENGTH trial is currently underway to assess the impact of ω-3 fatty acid treatment on cardiovascular outcomes in patients with elevated triglyceride levels.

c. **Low HDL-C** levels often accompany minor or modest elevations in triglyceride levels. Low HDL level has been shown in epidemiologic studies to be an independent risk factor of CVD. However, despite a multitude of research on currently available therapies to raise HDL and recent investigation of several newer agents that raise HDL, there has been no conclusive evidence that raising serum HDL-C levels contributes to lower rates of CVD. In patients who have isolated low HDL levels without any elevation in triglyceride levels, the first goal is to identify and modify lifestyle factors (e.g., high-carbohydrate diet, sedentary lifestyle, obesity, and smoking) and medications (e.g., progestational agents and anabolic steroids). The next step encompasses calculation of 10-year risk and treating LDL-C with a statin when appropriate. The AFCAPS/TexCAPS study found a clear benefit for statin therapy in patients with low HDL-C levels.

d. **Diabetic dyslipidemia.** Patients with diabetes are at an increased risk for cardiovascular events and fare poorly after CAD manifests. Diabetes is associated with an increase in small LDL particles and is often associated with high triglyceride and low HDL levels. As such, it also leads to significant discordance between estimated LDL levels and levels of non-HDL or TC/HDL ratio, which are better predictors of risk in this patient population. Hyperglycemia is an independent risk factor for CAD. Primary prevention is important in this group and was demonstrated to be efficacious in the HPS trial. **All diabetic patients (with LDL 70 to 189 mg/dL) should be considered for statin therapy and TLCs.** Secondary goals include improved non–HDL-C levels and TC/HDL-C levels and treatment for elevated triglyceride levels. Blood sugar control and insulin therapy often facilitate the former, but fibrates or low-dose niacin may be necessary in some patients. Patients with diabetes also often have coexisting hypertension. Blood pressure control and smoking cessation are essential because both interventions are highly effective at reducing cardiovascular events in this population.

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SUGGESTED READING

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USEFUL INTERNET RESOURCES

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Baylor: http://www.lipidsonline.org/
https://my.clevelandclinic.org/health/diagnostics/17085-heart-risk-factor-calculators
Pooled Cohort Equation Calculator: http://tools.acc.org/ASCVD-Risk-Estimator/
ACC/AHA Cholesterol treatment guidelines
2013: https://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a
New LDL equation calculator from Johns Hopkins: http://www.ldlcalculator.com

CHAPTER 43

Nonlipid Cardiovascular Risk Factors

Donald Clark III

I. INTRODUCTION. Over 80% of patients with coronary heart disease have at least one conventional risk factor, including hyperlipidemia, hypertension (HTN), diabetes, and tobacco use. These must be addressed to reduce the incidence of cardiovascular events. This chapter describes the nonlipid cardiovascular risk factors (except diabetes, which is discussed in Chapter 44). Nontraditional biomarkers and risk factors are also discussed.

II. HYPERTENSION. HTN contributes to all cardiovascular comorbidities: coronary artery disease (CAD), myocardial infarctions (MIs), cerebrovascular accident (CVA), systolic heart failure, diastolic heart failure, and peripheral vascular disease (PVD). It is associated with increased total mortality among men and women of all ages and ethnic groups, regardless of CAD. It is defined as a blood pressure of ≥140/90 mm Hg **or** the need for antihypertensive medication. It is thought to be present in at least 30% of the US adult population. Evidence from the Framingham Heart Study suggests that this is underestimated, as normotensive 55-year-old persons have a 90% residual lifetime risk of developing HTN.

A. Etiology. HTN is a complex disease modified by environmental and genetic determinants.

1. Genetics. HTN does not follow the classic Mendelian rules of inheritance attributable to a single-gene locus.

a. However, Liddle syndrome (mutation of **chimeric 11-β-hydroxylase-aldosterone synthase gene**) and variants in the angiotensinogen locus are documented exceptions that cause primary HTN among whites.

2. Contributors to HTN include variations in sodium intake, alcohol intake, renal function, vascular function, the sympathetic nervous system, the renin–angiotensin system, hyperinsulinemia/insulin resistance, and prostaglandins.

B. HTN impact on cardiovascular risk and mortality

1. Positive relationship between systolic and diastolic blood pressures and cardiovascular risk has long been recognized.

a. The **Multiple Risk Factor Intervention Trial (MRFIT)**. Prospective study (11.6 years of average follow-up period) with more than 361,000 subjects demonstrated the relationship between blood pressure and CAD. Baseline blood pressure elevations increased risk for CAD. The relationship was stronger for systolic blood pressure than for diastolic blood pressure. Death rate for men with systolic blood pressures of 140 to 149

(2.4/1,000) and 150 to 159 mm Hg (3.1/1,000) was 40% higher compared with men with a baseline systolic blood pressure <120 mm Hg.

b. Death rate at follow-up can be lowered by 36% with primary prevention of HTN in the general population. In addition, rates of stroke and CAD fall with antihypertensive therapy.

c. Subjects with blood pressure <120/<80 mm Hg have the fewest cardiovascular events.

d. **Prehypertension.** This is defined as blood pressure within the high-normal range (120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic) and which may confer some increased risk for cardiovascular disease. Risk ratios of 2.5 for women and 1.6 for men have been reported in patients in the prehypertensive range. These patients should undertake lifestyle modifications (e.g., diet, exercise, and weight loss) to help prevent or delay the development of frank HTN in the future.

e. The gradual rise in blood pressure over a person's lifetime and the increased prevalence of **HTN among the elderly** are **not benign**. Epidemiologic studies of the elderly demonstrate a U-shaped relationship between blood pressure and mortality. After adjustment for deaths within the first 3 years of the follow-up period, there is a positive linear relationship between blood pressure, cardiovascular disease mortality, and all-cause mortality. Isolated systolic HTN increases as the population ages, which confers increased risk for morbidity and mortality.

1. 1 **Systolic Hypertension in the Elderly Program (SHEP)** showed that 8% of persons aged 60 to 69 years have isolated systolic HTN, defined as systolic blood pressure >160 mm Hg and diastolic blood pressure <90 mm Hg, as do 11% of those aged 70 to 79 years and 22% of those aged 80 years or older.

2. 2 The relationship between systolic and diastolic blood pressures and cardiovascular events is more pronounced among persons aged 65 years and older. The association is stronger and more consistent for systolic blood pressure than for diastolic blood pressure and is evident at levels considerably <140 mm Hg.

2. **Rate of cardiovascular events.** Elevations in diastolic or systolic blood pressure values translate into significant increases in cardiovascular events. Generally, the yearly percent risk of cardiovascular events is between 0.5% and 2.5% for hypertensive subjects aged 40 years or older. Beginning at 115/75 mm Hg, each increase in blood pressure of 20/10 mm Hg doubles the risk of cardiovascular disease.

3. **Systolic blood pressure is a greater predictor of risk.** Over the past few years, **greater emphasis has been placed on systolic blood pressure in characterizing cardiovascular risk**. Age-adjusted 10-year mortality in the MRFIT revealed systolic blood pressure to be a stronger predictor of events from CAD than diastolic blood pressure. High systolic blood pressure conferred a CAD risk regardless of diastolic blood pressure. According to the SHEP study, isolated systolic HTN, which accounts for 60% of cases of HTN among the elderly, is highly correlated with cardiovascular disease, and it is important that it is controlled.

C. **Clinical presentation.** Detection of HTN begins with proper **blood pressure measurements**, which should be obtained at each health-care encounter.

1. Data for evaluation are acquired through the medical history, physical examination, laboratory tests, and other diagnostic procedures. Evaluation of patients with documented HTN has the following three objectives:

a. To identify known causes of high blood pressure

b. To assess the presence or absence of end-organ damage and cardiovascular disease, the extent of the disease, and response to therapy

c. To identify other cardiovascular risk factors or concomitant disorders that may define prognosis and guide treatment

2. A **medical history** should focus on identifying important risk factors or symptoms of HTN.

3. Repeated **blood pressure measurements** determine whether initial elevations persist and necessitate prompt attention, or the blood pressure has returned to normal and the patient needs only periodic surveillance. Ambulatory blood pressure monitoring is clinically helpful and is most commonly used to evaluate patients with suspected "office" or "white-coat HTN." It is also helpful in the care of patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic HTN, and autonomic dysfunction.

a. **Office visits.** Clinicians should explain to patients the meaning of their blood pressure readings and advise them of the **need for periodic remeasurement**. Blood pressure is measured in a standardized manner with equipment that meets certification criteria.

1. 1 The patient sits in a chair with her or his back supported and the arms bared and supported at heart level.
2. 2 Patients should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurement.
3. 3 Measurement should begin after at least 5 minutes of rest.
4. 4 The appropriate cuff size must be used to ensure accurate measurement. The bladder within the cuff should encircle at least 80% of the arm. Many adults need a large adult cuff.
5. 5 Measurements are taken preferably with a mercury sphygmomanometer. Otherwise, a recently calibrated aneroid manometer or a validated electronic device can be used.
6. 6 The systolic blood pressure and diastolic blood pressure are recorded. The first appearance of sound is used to define systolic blood pressure. The disappearance of sound is used to define diastolic blood pressure.
7. 7 Two or more readings separated by 2 minutes should be averaged. If the first two readings differ by >5 mm Hg, additional readings should be obtained and averaged.

b. **Ambulatory blood pressure monitoring.** A variety of commercially available monitors that are reliable, convenient, easy to use, and accurate are available. These monitors are typically programmed to take readings every 15 to 30 minutes throughout the day and night while patients go about their normal daily activities. The readings can be downloaded for computer analysis.

1. 1 **Normal** ambulatory blood pressure values are **lower than clinical readings while patients are awake** (<135/<85 mm Hg) and are **even lower while patients are asleep** (<120/<75 mm Hg). The blood pressure often falls by 10% to 20% during the night. This change is more closely related to patterns of sleep and wakefulness than to the time of day.
2. 2 **Patients with HTN.** Ambulatory blood pressure correlates more closely than clinical blood pressure with a variety of measures of end-organ damage or left ventricular hypertrophy (LVH).

Prospective evidence suggests that among patients for whom an elevated clinic pressure is the only abnormality, ambulatory monitoring may help identify a group at relatively low risk for morbidity.

4. **Physical examination** should include the following components:

a. **Funduscopic examination** for hypertensive retinopathy (e.g., arteriolar narrowing, focal arteriolar constrictions, arteriovenous crossing changes, hemorrhages and exudates, and disk edema).

b. Examination of the **neck** for carotid bruits, distended veins, or an enlarged thyroid gland.

c. Examination of the **heart** for abnormalities based on rate and rhythm, increased size, precordial heave, clicks, murmurs, and S_3 and S_4.

d. Examination of the **lungs** for rales and bronchospasm.

e. Examination of the **abdomen** for bruits, enlarged kidneys, masses, and abnormal aortic pulsation. Abdominal bruits, particularly those that lateralize to the renal area and/or have a diastolic component, suggest renovascular disease. Abdominal or flank masses may indicate polycystic kidneys.

f. Examination of the **extremities** for diminished or absent peripheral arterial pulsations, bruits, hair loss, and edema. Delayed or absent femoral arterial pulses and decreased blood pressure in the lower extremities may indicate aortic coarctation.

g. **Neurologic assessment.**

h. **Other assessments.** Labile HTN or paroxysms of HTN accompanied by any or all of the following symptoms and signs—chest discomfort ("pressure"), headache ("pain"), palpitations, pallor, and diaphoresis ("perspiration")—may indicate the presence of a pheochromocytoma. Truncal obesity with purple striae suggests Cushing syndrome.

D. Laboratory evaluation

1. It is recommended that the clinician request routine laboratory tests before initiating therapy to determine the presence of end-organ damage and other risk factors. These include **urinalysis, complete blood cell count, blood chemistry, and 12-lead electrocardiogram (ECG)**.

2. Additional diagnostic procedures may be indicated to seek causes of HTN: poor response to drug therapy, well-controlled patients whose blood pressures begin to increase, and those with sudden onset of HTN. **Optional tests** include creatinine clearance; microalbuminuria, 24-hour urinary protein, blood calcium, uric acid, lipid panel, glycosylated hemoglobin, and thyroid-stimulating hormone levels; and limited echocardiography to determine the presence of LVH.

a. **Clues from laboratory tests** include unprovoked hypokalemia (i.e., primary aldosteronism), hypercalcemia (i.e., hyperparathyroidism), and elevated creatinine or abnormal urinalysis (i.e., renal parenchymal disease).

b. The **presence of LVH** as determined by ECG or echocardiography is an important risk factor for adverse cardiovascular events and an independent predictor of high risk for CAD, cardiovascular disease, and all-cause mortality. LVH, the consequence of chronic pressure or volume overload and obesity, seems to be a stronger predictor of MI and CAD death than the degree of HTN. LV mass, as assessed with echocardiography, is a powerful predictor of cardiovascular events, cardiovascular mortality, and all-cause mortality.

3. **More complete assessment** of cardiac anatomy and function with conventional echocardiography, examination of structural alterations in arteries by means of ultrasonography, measurement of ankle–arm index, and plasma renin activity and urinary sodium determinations may be useful in assessing **cardiovascular status** in select patients.

E. Risk stratification

1. **Classification of blood pressure** is given in Table 43.1. The criteria are limited to patients not taking antihypertensive medication and without acute illness. Classification is based on the average of two or more blood pressure readings. When systolic blood pressure and diastolic blood pressure fall into different categories, **the higher pressure should be selected** to classify the patient's blood pressure.
2. Risk for cardiovascular disease among patients with HTN is determined by the **blood pressure level** and by the **presence or absence of end-organ damage or other disease-modifying risk factors** (smoking, dyslipidemia, and diabetes). The presence or absence of these factors is determined during the routine evaluation of patients with HTN (e.g., history, physical examination, and laboratory tests).
3. **Therapy.** Antihypertensive treatment has proved **beneficial in the prevention and reduction of the progression of HTN, CVAs, congestive heart failure (CHF), renal insufficiency, and renal failure**. Antihypertensive treatment markedly reduces the prevalence of CAD events: CAD mortality (by 16%), the rate of fatal stroke (by 40%), and the incidence of heart failure (by 50%), with similar numbers of deaths prevented.

TABLE 43.1 Classification of Blood Pressure for Adults Aged 18 Years and Older

Category	Systolic Blood Pressure (mm Hg)		Diastolic Bloo
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

4. **Nonpharmacologic therapy**

a. **Weight reduction** reduces systolic and diastolic blood pressures. Most clinical trials have demonstrated that weight reduction is directly related to blood pressure reduction. A weight loss of approximately 10 lb (4.5 kg) may reduce both systolic and diastolic blood pressures by 2 to 3 mm Hg. Among patients with high-normal blood pressure, the need for medical therapy may be averted for one-half through weight reduction by means of physical activity and calorie restriction.

b. **Exercise** reduces blood pressure by means of decreasing resting heart rate and peripheral vascular resistance and by modifying serum norepinephrine and insulin levels. After an increase in physical activity, both systolic and diastolic blood pressures have been demonstrated to fall by 7 mm Hg with or without weight reduction. Moderate-intensity exercise is as effective as high-intensity exercise for reducing blood pressure.

c. **Diet.** A modest, independent benefit of **salt reduction** has been demonstrated. HTN is less common in societies that consume low-salt, high-potassium diets. Although the theory that excessive salt intake produces HTN has been difficult to prove in large

clinical trials, most data support the role of dietary salt excess for some persons. In general, low-salt diets, such as the Dietary Approaches to Stop Hypertension (DASH; 2,300- and 1,500-mg sodium diets), are recommended to most patients with HTN. Pooled estimates have suggested that **salt restriction is most important for older persons, those with higher baseline levels of blood pressure, and particularly those who are salt sensitive**. Salt restriction reduces the need for combination antihypertensive medications.

d. Tobacco and immoderate alcohol use (more than two daily drinks for men and more than one daily drink for women) increase blood pressure. **Cessation of smoking and excessive alcohol use** markedly reduces blood pressure and further reduces cardiovascular risk.

5. Medical therapy

a. Priority of therapy

1. **1** Therapy for most patients with **uncomplicated HTN** at stage 1 should **begin with the lowest dose** to prevent adverse effects. If blood pressure remains uncontrolled after 1 to 2 months, the next dose level may be prescribed. It may take months to adequately control HTN. Most antihypertensive agents may be taken once each day. To improve patient compliance, this regimen is used whenever possible.

2. **2** For patients at **higher risk**, those in risk group 2, or those at particularly high risk for CAD or CVA event, drug therapy to **achieve maximum beneficial reductions** in blood pressure should **proceed without delay.** If blood pressure is elevated by 20/10 mm Hg above the goal, guidelines recommend starting two agents simultaneously.

3. **3** There is **no debate regarding the need for aggressive blood pressure reduction** in patients with **diastolic blood pressures >115 mm Hg and systolic blood pressures >160 mm Hg**.

4. **4** In the setting of hypertensive emergency **(HTN with end-organ damage, often with neurologic symptoms)**, patients with a systolic blood pressure >200 mm Hg or a diastolic blood pressure >120 mm Hg may need **hospitalization** for therapy.

5. **5** Although some patients may respond to single therapy, **two or more drugs are often required**. The intervals between changes in regimen should not be prolonged, and the maximum dose of some drugs may be increased.

b. **Medication selection.** Special considerations include concomitant disease, demographic characteristics, quality of life, cost, and use of other drugs that may cause drug interactions.

1. **1 Concomitant diseases** (see Table 43.2). Antihypertensive medications may worsen some diseases and improve others. Agent selection involves consideration of coexisting disease, simplification of regimens, and reduction of cost. Special emphasis should be given to diabetes and chronic renal disease. Such patients should be aggressively treated to maintain a goal blood pressure of <130/80 mm Hg.

TABLE 43.2 Management of Hypertension in Specific Clinical Syndromes

Condition	Treatment
Acute coronary syndrome	β-Blockers or nitrates; CCB
Hypertension among African Americans	Diuretic or CCB
Arrhythmia Sinus bradycardia, SSS, or AV block	Diuretic, ACE inhibitor, or amlodipine

TABLE 43.2 Management of Hypertension in Specific Clinical Syndromes	
Atrial fibrillation or flutter and SVT	β-Blocker, diltiazem, verapamil, or clonidine
Benign prostatic hypertrophy	α-Blocker
COPD with bronchospasm or asthma	CCB or ACE inhibitor
Diabetes	ACE inhibitor
Advanced age (>65 y)	Diuretic, CCB, or ACE inhibitor at lower doses to avoid postu
Gout	Any *except* diuretics
Congestive heart failure Systolic	ACE inhibitor, diuretic, β-blockers
Diastolic	CCB, β-blockers, or aldosterone antagonist
HOCM	β-Blockers or verapamil
Liver dysfunction	Any *except* methyldopa and labetalol
Post–myocardial infarction	ACE inhibitor, β-blocker, or both
Osteoporosis	Thiazide diuretics
PVD	Vasodilator, ACE inhibitor, CCB, or α-blocker
Renal insufficiency (creatinine > 2 mg/dL)	Loop diuretics, ACE inhibitor, CCB, α-blocker, labetalol, or a
Diabetic nephropathy	ACE inhibitor
Smokers	α-Blockers, ACE inhibitors, or CCB
Isolated systolic hypertension	Diuretics, CCB, and ACE inhibitors

ACE, angiotensin-converting enzyme; AV, atrioventricular;
, calcium-channel blocker; COPD, chronic obstructive pulmonary disease; HOCM, hypertrophic obstructive
omyopathy; PVD, peripheral vascular disease; SSS, sick sinus syndrome; SVT, supraventricular tachycardia.

1. **(a) Reduction of long-term cardiovascular morbidity and mortality.** Diuretics and β-blockers were drug classes originally shown in randomized trials to reduce morbidity and mortality. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that angiotensin-converting enzyme (ACE) inhibitors reduced the risk of cardiovascular events in patients with vascular disease or diabetes plus one other cardiovascular risk factor. However, the fact that HOPE was a trial with placebo control rather than active control suggests that blood pressure lowering, and not drug class effect, may have been responsible for the improved outcomes. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study showed a preferential reduction in cardiovascular events with the angiotensin receptor blocker losartan compared with atenolol in hypertensive patients. This improvement was primarily driven by a reduction in the number of strokes in the losartan group.
2. **(b)** The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the incidence of cardiovascular events in hypertensive patients treated with a thiazide-type diuretic (chlorthalidone), calcium channel blocker (amlodipine), or ACE inhibitor (lisinopril) who

were followed over 5 years. A fourth arm of the trial consisting of treatment with the α-blocker doxazosin was stopped prematurely because of increased cardiovascular events, specifically a doubling in the risk of CHF in the doxazosin arm compared with the chlorthalidone arm. The results indicated no difference in the three remaining groups regarding the primary outcome of combined fatal coronary heart disease or nonfatal MI. Chlorthalidone was superior to amlodipine in preventing heart failure and superior to lisinopril in preventing stroke and combined cardiovascular disease. Given their clear efficacy, relatively low cost, and high tolerability, **thiazide diuretics are therefore considered initial agents of choice for most patients with HTN and core components of multidrug regimens.**

3. **2 Dosage.** For most patients, a **low dose of the initial drug** choice is initiated and then titrated to the desired effect. The optimal formulation provides 24-hour efficacy with a once-daily dose, with at least a 50% of the peak effect remaining at the end of 24 hours. Long-acting formulations increase adherence, reduce cost, provide consistent blood pressure control, and protect against early-morning sudden death. Diurnal blood pressure control is reported to improve when long-acting medication is taken at night rather than in the morning.
4. **3 Special populations.** Neither sex nor age usually affects responsiveness to various agents. In general, HTN among **African Americans** is more responsive to monotherapy with diuretics and calcium-channel blockers than with β-blockers or ACE inhibitors. However, if a β-blocker is needed for other therapeutic benefits, then differences in efficacy can usually be overcome with reduction of salt intake, higher doses of the drug, or addition of a diuretic.
5. **4 Drug interactions.** Some drug interactions may be beneficial. For example, diuretics acting on different sites in the nephron may increase natriuresis and diuresis. Diltiazem may reduce the amount of cyclosporine needed in transplant recipients. Other interactions may be harmful. Nonsteroidal anti-inflammatory drugs may blunt the action of diuretics, β-blockers, and ACE inhibitors.

c. Treatment of the elderly. The benefit of blood pressure lowering is evident in the elderly, with a marked **reduction in all-cause mortality and CAD mortality**, as shown in multiple trials and studies. SHEP was the first study to show that antihypertensive treatment of the elderly can reduce these events. It is not clear, however, that all agents are equally effective in reducing the rate of cardiovascular events in the elderly.

d. Emerging evidence. The Systolic Blood Pressure Intervention Trial assessed blood pressure treatment targets among nondiabetic patients with HTN at high risk for cardiovascular disease, including a large proportion >75 years of age. The study showed that lowering systolic blood pressure to a goal of <120 mm Hg, as compared to 140 mm Hg, resulted in significantly lower rates of fatal and nonfatal cardiovascular events (1.65% per year vs. 2.19% per year). The intensive treatment group had increased incidence of hypotension, syncope, electrolyte disturbances, and kidney injury. In order to achieve the intensive treatment goal, substantial efforts in terms of clinical resources were required. Nonetheless, this trial strongly supports intensive antihypertensive therapy in high-risk patients. These results will undoubtedly influence revisions in forthcoming American College of Cardiology/American Heart Association (ACC/AHA) guidelines regarding treatment goals in patients with HTN. The recently published HOPE-3 trial showed that in intermediate-risk patients, the blood pressure <140/90 mm Hg was beneficial and that lowering it further did not provide additional benefit.

III. OBESITY. Rates of obesity are rising at an alarming rate both in the severe obesity cases (body mass index [BMI] > 40 kg/m^2) and in adolescents. Currently, 74% of US adults are

overweight, defined as having a BMI of >25 kg/m^2. Moreover, 36% of Americans are classified as obese, with a BMI of 30 kg/m^2 or more. This has come to be a critical problem for African American women, among whom the prevalence of obesity is >50%. The percentage of children and adolescents with obesity has doubled over the past 20 years. There are clear links between obesity and the development of cardiac risk factors: HTN, hyperlipidemia, and diabetes.

A. Link between obesity and cardiovascular disease

1. A positive association among BMI, increased total cholesterol and triglyceride levels, and a decreased high-density lipoprotein cholesterol (HDL-C) levels has been documented in various age groups.
2. Distribution of fat appears to be a more important predictor of CAD than the total amount of fat because android fat patterns are more metabolically active and highly associated with dyslipidemia. Although BMI and waist to hip ratios have indicated a linear association between obesity and CAD, the **waist to hip ratio**, which accounts for abdominal adiposity, is viewed as a more **accurate predictor of CAD**. Among obese persons, those with central adiposity are at particularly high risk. In a cohort of 1,500 women observed for 20 years, the waist to hip ratio, but not BMI, was highly predictive of the occurrence of fatal MI.
3. Obesity among adults is associated with **increased LV mass**, a powerful independent predictor of mortality and morbidity from cardiovascular disease. LV mass in persons with obesity but without diabetes probably depends, at least in part, on the degree of insulin resistance and hyperinsulinemia and not on BMI and blood pressure.
4. Central obesity is part of the **metabolic syndrome**, which is associated with increased risk for CAD in both sexes. This condition is characterized by elevated plasma triglyceride and low plasma HDL-C levels.

a. An essential feature is the presence of **dense, atherogenic LDL**.

b. Other features are HTN, impaired glucose intolerance with hyperinsulinemia, and decreased sensitivity to the action of insulin on peripheral tissues.

c. Hyperinsulinemia is associated with **lipid derangements, increased production of plasminogen activator inhibitor, and enhanced proliferation of cells in atherosclerotic plaque**. Among patients with hyperinsulinemia, an increased prevalence of CAD and a relationship among abnormal insulin levels, glucose metabolism, and severity of CAD have been reported. The physiologic response to insulin resistance is increased secretion of insulin, which may lead to glucose intolerance or frank diabetes mellitus.

B. Therapy

1. **Calorie restriction, behavior modification, and exercise** are the main treatment modalities for weight loss. The greatest weight losses have occurred with a combined regimen of diet and exercise rather than diet or exercise alone.
2. Several **medications** can be used for the temporary management of obesity. Although pharmacologic agents temporarily aid in the struggle against obesity, the National Task Force on Obesity **cautions against the use of these agents for long-term maintenance because of the potential for unknown side effects**.
3. Among morbidly obese patients (BMI > 40 kg/m^2) and obese patients (BMI between 35 and 40 kg/m^2) with coexisting conditions, **bariatric surgery** can be an effective treatment option for those who have failed noninvasive therapies.

IV.TOBACCO. Smoking, the single most preventable cause of death in the United States, is a leading risk factor for CAD, CVA, and PVD. Second-hand smoke has been shown to increase the risk for CAD. The causal role of smoking in cardiovascular disease has been derived from >20 million person-years of follow-up study (NHLBI, 1996). Nearly 17% of adults in the United States are current cigarette smokers. Rates of smoking are higher among people with lower education level and those living below the poverty level. Exposure to second-hand smoke increases the risk of death from CAD by 30%. More than 90% of current smokers began their habit before they were 21 years of age.

A. Pathophysiology. Cigarette use activates platelets, increases circulating fibrinogen, increases heart rate, and elevates blood pressure. It appears to promote plaque disruption. A strong dose–response relationship exists between smoking and CAD. The number of cigarettes smoked per day is directly proportional to the risk of MI. The adverse effect of smoking is present among men and women (but may be stronger among women) of all ages and ethnic groups with or without prior CAD. Data suggest that risk for cardiac death is two to four times greater among current smokers than nonsmokers.

B. Risk reduction and therapy. Risk for cardiovascular disease begins to decline soon after smoking cessation, irrespective of age and sex. There is a 50% reduction in cardiovascular events within the first 2 to 4 years of cigarette cessation; however, increased cardiovascular risk still exists 10 years after cessation. It is thought to take as long as 20 years to regain baseline risk. It is recommended that smokers be managed with a **combination of behavioral intervention and pharmacologic therapy**. First-line pharmacologic therapies include **nicotine replacement therapy** (transdermal patch, gum, nasal spray, lozenge, and inhaler), **varenicline, and bupropion**. Extensive materials on smoking cessation for patients and health-care provides are provided by the US Department of Health & Human Services and can be found online at www.ahrq.gov

V.SEDENTARY LIFESTYLE

A. Pathophysiology. A sedentary lifestyle is associated with increased risk for CAD. Sedentary persons have almost double the risk for CAD death as that of active persons. In five prospective exercise studies, persons at the lowest levels of exercise conditioning had an age-adjusted CAD mortality risk 2 to 10 times that of the best-conditioned participants. A sedentary lifestyle is also associated with obesity, HTN, diabetes mellitus type 2, and hypercholesterolemia. More than 50% of the US population does not exercise at least 20 minutes three times a week and 40% of adults are classified as sedentary.

B. Risk reduction. Even moderate physical activity provides a reduction in risk. Regular physical activity prevents obesity, may reduce weight, and promotes positive effects on blood pressure, LDL-C, HDL-C, and triglyceride levels. Independent of other risk factors, physical fitness has a direct protective effect against CAD events. Among patients who have had MI, controlled cardiac rehabilitation programs significantly reduce cardiovascular mortality by 20% to 25%. The AHA currently recommends that adults accumulate 30 minutes or more of moderate-intensity physical activity on most (preferably all) days of the week.

1. Mechanism

a. Exercise **improves glucose tolerance and insulin sensitivity, increases fibrinolysis, increases HDL-C levels, improves oxygen uptake** in the heart, and **increases coronary artery diameter**. Exercise reduces the sensitivity of the myocardium to

catecholamines and the risk of ventricular arrhythmias. Exercise increases HDL-C and lowers LDL-C levels and, as such, reduces cardiac events. Exercise can alter the progression of coronary atherosclerosis. Among patients with angiographically documented CAD, exercise training may increase regression and reduce the progression of coronary lesions.

b. Studies on the effect of exercise have been difficult to conduct and are known to have difficulties in quantification of exercise. Reviews on the effects of cardiac rehabilitation on morbidity and mortality demonstrated reductions in all-cause mortality of 20% to 24% and in CAD mortality of 23% to 25%.

2. **Problems with compliance.** Only 50% of persons who begin an exercise program adhere to it for more than 6 months.

a. Physicians may need to help **tailor exercise programs for individual patients** to participate in activity that is sustained in the long term.

b. As for healthy persons, **precautions** must be taken to **prevent injury**. The current guidelines may be **slightly modified for elderly exercisers** to emphasize a longer warm-up period to enable musculoskeletal and cardiorespiratory readiness for exercise and an adequate cool-down period to help dissipate heat.

VI. NONTRADITIONAL RISK FACTORS. Many patients with few traditional risk factors experience life-threatening acute coronary syndromes without prior symptoms of disease. Several potential risk factors have been identified that may enhance risk for CAD. These are levels of C-reactive protein (CRP), lipoprotein(a) or Lp(a), homocysteine, fibrinogen, and myeloperoxidase (MPO), as well as genetic mutations and single-nucleotide polymorphisms (SNPs) in a number of candidate genes.

A. **CRP** is a marker of systemic inflammation. As the role of **inflammation** in the initiation and progression of atherosclerosis becomes better understood, CRP is gaining prominence as an important parameter in the assessment of cardiovascular risk.

1. **Pathophysiology**

a. CRP has been shown to be an independent risk factor for the development of cardiovascular events in both apparently healthy individuals and in patients with established coronary heart disease. CRP binds to oxidized LDL, promoting the uptake of LDL by macrophage scavenger cells in the arterial wall and possibly enhancing the atherosclerotic process.

b. The degree of associated risk throughout various levels of CRP, often measured as high-sensitivity (hsCRP), has been evaluated in several studies.

1. 1 Men in the Physicians' Health Study with the highest quartile CRP had **three times the risk of MI** and **twice the risk of ischemic stroke** compared with men in the lowest quartile.
2. 2 In women, the difference is even more pronounced. The relative risk of cardiovascular events in the highest quartile of CRP compared with the lowest quartile of CRP in women is **4.4**.
3. 3 An increased risk of sudden cardiac death has also been seen in patients with elevated CRP levels.

2. **Clinical use**

a. Standard CRP assays are not sufficiently sensitive to discriminate within the narrow range of CRP values associated with an increase in cardiovascular events. The development of hsCRP assays, however, has made this possible. AHA/Centers for Disease Control and Prevention guidelines have established cut-points of risk for hsCRP: a level of <1 mg/L is considered low, 1.0 to 3.0 mg/L is average, and >3.0 mg/L is high and is associated with

increased cardiovascular risk. Higher levels (>10 mg/L) suggest an alternative cause for inflammation, such as infection or underlying rheumatologic illness.

b. When deciding on whether to initiate statin therapy for the primary prevention of coronary events, hsCRP measurement may prove helpful in patients with a moderate level of cardiovascular risk. In the Air Force/Texas Coronary Atherosclerosis Prevention Study, lovastatin reduced the incidence of cardiovascular events in patients with low lipid levels if CRP levels were elevated. No improvement was seen in the cohort of patients with low lipid levels and normal CRP values. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial study targeted individuals with elevated hsCRP levels without hyperlipidemia and showed that statin therapy substantially lowered cardiovascular events in this population.

c. The current ACC/AHA guidelines provide a class IIb recommendation for hsCRP in a primary prevention population when clinical decisions to initiation statin therapy are uncertain. Ongoing clinical trials are evaluating the role of targeted anti-inflammatory treatments to reduce cardiovascular event rates and initial results suggest that this approach may be successful and generate another treatment modality in CAD.

B. Lipoprotein (a) or Lp(a) is identical to LDL, except for the addition of apolipoprotein A (apoA), a highly glycosylated protein. Although it is a lipoprotein, Lp(a) is often considered a **marker of thrombosis**.

1. Pathophysiology

a. There is a striking amino acid sequence homology between apoA and plasminogen, suggesting that Lp(a) may play an important role in the connection between atherosclerosis and thrombosis. **Lp(a) may be atherogenic**; it accumulates in atherosclerotic lesions, binds to apoB-containing lipoproteins, and proteoglycans and can be taken up by foam cell precursors. It may also promote thrombosis when it binds to fibrin and blocks the fibrinolytic action of plasmin.

b. Lp(a) is modestly associated with atherosclerotic CAD and may be more predictive of CAD among younger men, women, and persons with hyperlipidemia. Lp(a) levels appear to relate to increased risk of valvular calcification.

c. Widespread Lp(a) screening is not recommended as no clinical trials have demonstrated that reducing levels reduces cardiovascular events. Lp(a) levels may be considered in patients with cardiovascular disease and no other identifiable dyslipidemia, strong family history and no other dyslipidemia, or patients with recurrent cardiovascular events despite adequate risk factor treatment.

2. Therapy. Statins are preferred therapy for patients that require LDL-C lowering therapy due to elevated Lp(a) levels. Niacin or a PCSK9 inhibitor may be added if further control is needed.

C. Homocysteine is a product of folate metabolism. It is derived from the sulfur—containing amino acid methionine and is metabolized through pathways associated with folic acid, vitamin B_6, and vitamin B_{12} as cofactors. Elevated plasma homocysteine levels (>15 μ/L) confer an **independent risk for vascular disease**, according to the cross-sectional and prospective case-control studies. The mechanism by which homocysteine appears to promote vascular disease is **unclear**. Elevated homocysteine levels seem to play a role in the production of arterial lesions, but deficiencies of other factors, such as vitamin B_{12} and folic acid, may also be involved, especially in the elderly.

1. **Trials of homocysteine lowering.** The results of three such large, prospective, randomized trials, the Vitamin Intervention for Stroke Prevention (VISP) trial, the Norwegian Vitamin Trial (NORVIT), and the HOPE-2 trial, assessed the role of folic acid, vitamin B_6, and vitamin B_{12} in the prevention of cardiovascular events. Overall, there was no convincing benefit, and therefore, such therapy is not recommended for this indication.

D. Fibrinogen, a large hepatically synthesized glycoprotein, is a clotting factor that activates thrombin, induces platelet aggregation through the glycoprotein IIb/IIIa receptor, and stimulates smooth muscle proliferation. Several prospective studies, including the Framingham Heart Study, have shown an **impressive relationship between the plasma fibrinogen level and the occurrence of CAD and stroke**. Plasma fibrinogen levels >350 mg/dL are powerful independent risk factors for stroke and MI.

1. **Risk reduction and therapy**

a. Factors associated with a decrease in fibrinogen level include smoking cessation, physical activity, moderate alcohol intake, normalization of body weight, and postmenopausal hormone replacement. No clinical trial has identified a drug that reduces fibrinogen level safely and selectively.

E. Myeloperoxidase. As discussed previously, inflammation plays a major role in the pathogenesis of CAD and the development of MI. MPO is a protein with enzymatic activity that is released during activation and degranulation of neutrophils and monocytes. For patients in the emergency department with chest pain, serum levels of MPO have been shown to predict risk for MI at 30 days and 6 months, even in the absence of myocardial necrosis. In patients with non–ST-elevation MI, MPO levels have been shown to predict 30-day risk of recurrent nonfatal MI or hospitalization for acute coronary syndrome.

F. Nonlipid genetic factors. Although a familial predisposition for CAD has been well documented, little is known about the causative factors leading to premature events in such kindreds. In one family, a seven–amino acid deletion in the gene encoding the MEF2A transcription factor was found to confer autosomal dominant susceptibility to CAD and MI. The thrombospondins are a family of glycoproteins that play a pivotal role in cell adhesion, vascular integrity, and thrombosis. SNPs in thrombospondin genes have been linked to premature atherosclerosis and MI, providing another example of how genetic variations may contribute to the development of coronary disease. The identification of genetic risk factors for cardiovascular disease and the elucidation of their mechanism of risk elevation are still among the newest and most promising areas of translational cardiology research.

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CHAPTER 44

Diabetes and the Heart

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I. INTRODUCTION.

The presence of type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) confers an increased risk of coronary artery disease (CAD). A diagnosis of T2DM in the fifth decade is associated with a 6 to 7 years decrease in longevity largely because of complications of atherosclerosis. In the United States, the prevalence of T2DM correlates closely with obesity and has shown a sharp rise over recent decades. A similar trend has been noted across the world, with urbanization, adoption of sedentary lifestyle, and changing dietary patterns playing a major contributory role. Consequently, the management of diabetes, along with hypertension, dyslipidemia, and obesity, has become a prime focus in both the primary and secondary prevention of cardiovascular events. In response to the guidance from the Food and Drug Administration (FDA), large cardiovascular outcome trials (CVOT) have evaluated the impact of newer therapies on patients with T2DM. The findings from these completed and ongoing trials have the potential to significantly alter the care and outcomes of patients with T2DM. The purpose of this chapter is to discuss the current epidemiology and pharmacotherapy of T1DM and T2DM with an emphasis on the latest evidence-based practice for the treatment and prevention of cardiovascular events in individuals with this disease.

II. EPIDEMIOLOGY

A. Epidemiology of diabetes

1. Diabetes is one of the most common chronic diseases in both developed and developing nations. This rise in prevalence is driven partly by rising levels of obesity, physical inactivity, and urbanization, coupled with the aging population and greater longevity. The International Diabetes Federation most recently reported that 415 million people are currently living with diabetes; many are yet undiagnosed and untreated. By the year 2040, the global population with diabetes is expected to rise to 642 million (Table 44.1).

TABLE 44.1 International Diabetes Federation Estimates of Prevalence of Diabetes

Location	Population with Diabetes in million (2017)	Projected Population
North America and Caribbean	46	62
Middle East and North Africa	39	67

TABLE 44.1 International Diabetes Federation Estimates of Prevalence of Diabetes		
Europe	58	67
South and Central America	26	42
Southeast Asia	82	151
Africa	16	41
Western Pacific	159	183

2. The greatest burden of diabetes lies in developing countries. India and China are notable for the exceptionally high prevalence in 2000 (31.7 and 20.8 million, respectively, compared with 17.7 million in the United States). The projected 2030 figures for individuals with diabetes are 79.4 million in India, 42.3 million in China, and 30.3 million in the United States.

3. **T2DM has grown increasingly more prevalent in childhood and in ethnic minorities such as African Americans, Hispanic Americans, and Native Americans.** Currently up to 45% of cases in adolescents are designated T2DM. **Diabetes prevalence is higher in men than in women, but there are more women in total with diabetes.**

4. In the United States, 95% of cases with diabetes are T2DM, but T1DM has also shown increased incidence over recent years. The increase occurs largely in the youngest individuals (<5 years) and those with moderate genetic susceptibility.

B. Spectrum of insulin resistance to T2DM

1. There is a continuum between the early pathologic features of disordered glucose metabolism and T2DM.

2. A **diagnosis of diabetes** can be made on the basis of a **fasting blood glucose ≥126 mg/dL** (7.0 mmol/L) or a **2-hour plasma glucose of ≥200 mg/dL** (11.1 mmol/L) during a 75-g oral glucose tolerance test. **HbA1c measurement ≥6.5%** may also be utilized to establish the diagnosis of diabetes. In the absence of unequivocal hyperglycemia, a positive result should be confirmed on repeat testing. In the setting of classic hyperglycemic symptoms, a single random glucose ≥200 mg/dL is considered diagnostic. These diagnostic criteria are summarized in Table 44.2.

a. It is now recognized that the microvascular and macrovascular complications are not limited only to individuals meeting the diagnostic criteria for established diabetes. The progression from normal glucose tolerance to T2DM involves intermediate stages of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), also collectively termed "prediabetes." This pathologic continuum arises from dysregulation of the balance between insulin sensitivity and insulin secretion.

b. There is usually a **long latent asymptomatic phase** prior to the development of overt T2DM. Longitudinal studies suggest that insulin resistance onset occurs 10 to 20 years prior to the diagnosis of diabetes and is the best predictor of whether an individual will develop T2DM in the future. Insulin resistance places pressure on the pancreatic β-cells to augment secretion of insulin and, therefore, promotes β-cell dysfunction. Once the β-cell is unable to compensate sufficiently for the peripheral insulin resistance state, progression to

T2DM will ensue. The underlying etiology of T2DM is complex, with both environmental and genetic predisposing factors promoting insulin resistance and β-cell dysfunction.

TABLE 44.2 Criteria for the Diagnosis of Diabetes

Diabetes
• **HbA1c** ≥ 6.5% (48 mmol/mol)[a]
or
• **Fasting plasma glucose** ≥ 126 mg/dL (7.0 mmol/L)[a]
or
• **2-H plasma glucose** ≥ 200 mg/dL (11.1 mmol/L) in 75-g oral glucose tolerance test[a]
or
• **In a patient with classic symptoms of hyperglycemia** or hyperglycemic crisis, a random plasma gluco
Prediabetes
• **HbA1c** 5.7%–6.4% (39–46 mmol/mol)
or
• **Fasting plasma glucose** 100–125 mg/dL (5.6–6.9 mmol/L) ≥ IFG
or
• **2-H plasma glucose** 140–199 mg/dL (7.8–11.0 mmol/L) in 75-g oral glucose tolerance test ≥ IGT

c. HbA1c, glycosylated hemoglobin; IGT, impaired glucose tolerance; IFG, impaired fasting glucose.

d. [a]In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

e. **Epidemiologic evidence** regarding the impact of prediabetes states comes from the Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe (DECODE) group. The relationship between 2-hour postload glucose and cardiovascular mortality was linear, with a continuum of risk extending into and below the prediabetes glucose range. In subjects without a diagnosis of diabetes, the investigators observed no threshold level of fasting or 2-hour postload glucose concentration above which the risk of all-cause or cardiovascular mortality death increased sharply.

3. There is evidence that the **pathogenic effect of hyperglycemia on the endothelial cells already exists in the prediabetes stage**. The full transition from the early metabolic abnormalities of prediabetes to established diabetes probably occurs in about two-thirds of individuals.

a. There is interest in determining **interventions that may decrease the likelihood of progression to diabetes.** The Diabetes Prevention Program Research Group randomly assigned 3,234 participants without diabetes, but with elevated fasting and postload

glucose concentrations, to placebo versus metformin (850 mg twice daily) versus a lifestyle modification program promoting exercise and weight loss. The incidence of diabetes over an average follow-up of 2.8 years was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. **The lifestyle intervention was significantly more successful in preventing diabetes than the metformin strategy.** Also of note is the Study to Prevent NIDDM (STOP-NIDDM)trial, which randomized individuals with IGT to acarbose (which primarily affects postprandial glycemia) or placebo. Patients in the acarbose group were observed to have a lower rate of diabetes diagnosis than those receiving placebo. Furthermore, a lower rate of cardiovascular disease (CVD) and hypertension over a 3.3-year mean follow-up period was reported in the acarbose group.

III.DIABETES AND ATHEROSCLEROSIS

A. ***Diabetes accelerates the atherosclerotic process.*** Autopsy series have revealed more diffuse coronary involvement, greater severity of vessel stenosis, and more severe left main disease in persons with diabetes, compared with those without. Similarly, adverse coronary anatomy findings have been observed in autopsy studies of patients with a history of childhood onset of T1DM who died before the age of 40 years. The pathophysiology of atherosclerosis in diabetes remains incompletely understood but is thought to involve hyperglycemia, lipid abnormalities, and dysfunctional endothelial and vascular smooth muscle function, coupled with a propensity for inflammation, thrombosis, and platelet activation.

B. It is recognized that the **synthesis of nitric oxide (NO) by the vascular endothelium is reduced in subjects with diabetes**. NO is among several key substances that maintain healthy endothelial function, which includes freedom from adhesion molecule activation, leukocyte diapedesis, platelet aggregation, and activation of thrombosis. However, the bioavailability of NO is adversely affected by hyperglycemia, high levels of free fatty acids, and insulin resistance. Current research reveals the impact of excessive oxidative stress (which can be induced by hyperglycemia, fatty acids, or insulin resistance) on NO production and also on the generation of advanced glycation end products, which are suspected to mediate various negative cellular effects in diabetes. Reactive oxygen species also activate protein kinase C with wide-ranging effects on cellular metabolism, including activation of the phosphoinositide 3-kinase (PI3K) pathway, which has a role in mediating cell adhesion and migration. The ability of NO to act on vascular smooth muscle and cause vasodilation is reduced; endothelial cell dysfunction in diabetes is coupled with increased production of vasoconstrictors such as prostanoids and endothelin.

C. Another key pathogenic feature of atherosclerosis in diabetes is the PI3K- and nuclear factor κB–stimulated **alterations in adhesion molecule expression on the endothelial surface**. This causes the endothelium to become more adherent to passing cells, and selectins on the surface of leukocytes attach to receptors such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 and migrate into the intima. Here monocytes take on oxidized low-density lipoprotein (LDL) and become macrophage foam cells, which are instrumental in the development of an atherosclerotic plaque. The tendency toward small, dense LDL particles in diabetes is another factor contributing toward atherosclerosis. Smooth muscle cell proliferation ensues, leading to deposition of collagen and other extracellular matrix proteins into the plaque.

D. **Platelet function is also abnormal in diabetes**, with overexpression of the glycoprotein IIb/IIIa receptor promoting inappropriate platelet adhesion and activation. Upregulation of multiple coagulation factors such as factor VII, thrombin, tissue factor, and plasminogen activator inhibitor-1 increases the tendency toward clotting, therefore contributing to the risk of thrombosis at the site of a plaque rupture or stent placement.

IV.IMPACT OF DIABETES ON HEART DISEASE

A. Both ***T1DM and T2DM confer significantly elevated risks of CAD, acute coronary syndrome, post–myocardial infarction (MI) complications, heart failure, and probably also sudden cardiac death***. In addition, the incidence of peripheral arterial disease, stroke, and end-stage renal failure are elevated in individuals with diabetes. The cardiovascular complications of T2DM account for the majority of the socioeconomic burden of this chronic disease on both individuals and society.

1. **As many as 80% of individuals with diabetes will die from cardiovascular causes.** Per the Framingham Heart Study, the **risk** of CAD is ***doubled*** in men and ***tripled*** in women with diabetes, compared with age-matched subjects without diabetes.
2. The Emerging Risk Factors Collaboration undertook a large meta-analysis that demonstrated a **twofold excess risk of outcomes** such as coronary heart disease, coronary death, and nonfatal MI among individuals with established diabetes. They also found diabetes to be even more strongly related to fatal than to nonfatal MI, possibly suggesting more severe manifestations of coronary disease in those with diabetes. Hazard ratios (HRs) were particularly elevated for CVD among individuals with diabetes who were female, younger, and nonsmokers or had lower-than-average blood pressure (BP).
3. **Patients with diabetes are much more likely to present with atypical symptoms in the setting of an acute coronary syndrome and experience more silent MI.**
4. Various angiographic trials have demonstrated that patients with **diabetes undergoing percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) tend to have significantly more severe CAD**, with a preponderance of multivessel disease and greater severity of lesions than those without diabetes. Despite the more severe plaque burden, diabetes correlates with lesser collateral vessel formation.
5. The residual **risk** in individuals with T2DM following their **first cardiovascular event is significantly greater** than that noted in the nondiabetic group even after revascularization.
6. Post-MI complications and mortality in patients with diabetes correlate with post-MI ejection fraction and the presence of multivessel coronary disease. **Cardiogenic shock is more common and more severe in post-MI patients with diabetes.** The higher in-hospital mortality among the postacute coronary syndrome population with diabetes is largely related to the greater incidence of acute decompensated heart failure and to a lesser extent the increased risk of reinfarction and infarct extension.
7. The CAD mortality arising from T1DM has also been studied. Laing et al. reported a prospective study of 23,751 individuals with T1DM where subjects were followed for up to 29 years. As is typical of a T1DM cohort, the relatively young age correlated with a low event rate. However, their **CAD risk was several times higher** than that of a matched population without diabetes.

V.RISK FACTOR MODIFICATION IN PATIENTS WITH DIABETES

A. The risk factors that predispose individuals with diabetes to develop CVD are the same as those that raise cardiovascular risks in those without diabetes. However, the prevalence and consequences of known major risk factors for CAD is generally amplified among persons with diabetes. Given the overall higher cardiovascular risk conferred, the benefits of tighter risk factor control is greater in those with diabetes than those without.

1. Dyslipidemia

a. This is a major risk factor among individuals with diabetes. Diabetes is associated **with small, dense LDL** particle composition, increased levels of apolipoprotein B and E, low levels of high-density lipoprotein (HDL) cholesterol, and high triglyceride (TG) levels. These lipid composition abnormalities cluster with insulin resistance and abdominal adiposity and appear to induce endothelial dysfunction and an increased susceptibility to thrombosis.

b. **LDL reduction with statin therapy** for both primary and secondary prevention is a cornerstone of T2DM management. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend primary prevention treatment with moderate- (LDL 70 to 189 mg/dL) or high-dose statin (LDL ≥ 190 mg/dL) in all patients with diabetes aged >40 years with a 10-year risk >5%. Treatment may also be initiated in select patients with diabetes who do not meet these criteria. Some of the factors that may influence decision making include family history of premature atherosclerosis, lifetime atherosclerosis risk, abnormal coronary artery calcium score or ankle-brachial index, or high-sensitive C-reactive protein ≥2 mg/L. For secondary prevention, high-dose statin for those aged <75 years is recommended, with moderate dosages suggested in those aged >75 years and intolerant of higher dosages. Although these guidelines did not support uptitration to specific LDL targets, trials of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition as well as ezetimibe have now confirmed clinical benefits achieved with LDL down to 30 mg/dL with no harm. As a result, it appears prudent to achieve LDL goals <70 mg/dL in the secondary prevention setting with addition of alternate agents (ezetimibe/PCSK9 inhibitor) when these targets are not achieved with statin alone or the patient is statin intolerant.

c. **Hypertriglyceridemia. Elevated fasting TG levels** are characteristic of the lipid panel in diabetes and constitute an independent cardiovascular risk factor. Hypertriglyceridemia correlates with abdominal adiposity and fibrates have traditionally been considered an appropriate therapy to target hypertriglyceridemia and have often been added to statin therapy for this indication. The Fenofibrate Intervention and Event Lowering in Diabetes trial, however, showed no benefit with fenofibrate therapy and the **Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial** did not demonstrate any benefit for subjects with T2DM with the addition of fenofibrate to simvastatin. A meta-analysis, however, suggested a benefit for fibrate therapy in this population in the subset with low HDL and low TG levels. High levels of ω-3 fatty acids are commonly utilized to reduce TG levels. Large outcome trials are currently underway testing the utility of this intervention.

d. **HDL.** Low HDL levels predict poor cardiovascular outcomes in a number of epidemiologic studies and are commonly present in patients with diabetes. Pharmacologic agents called **cholesterylester transfer protein inhibitors** can dramatically increase and maintain HDL levels with favorable effects on LDL (evacetrapib and anacetrapib). Large randomized clinical trials with this group of agents have failed to show a benefit with raising HDL in this manner. Similarly trials with nicotinic acid in the background of statin

utilization have also failed to impact favorably on clinical outcomes. This agent can worsen glycemic control and should not be utilized in patients with diabetes.

2. Hypertension

a. The presence of an elevated BP in patients with diabetes serves as a strong risk factor for development of atherosclerotic events. **There are multiple large trials supporting the benefit of BP lowering in subjects with diabetes.** In the UK Prospective Diabetes Study (UKPDS), lowering the BP to a modest mean of 144/82 mm Hg (compared with 154/87 mm Hg) significantly reduced strokes, diabetes-related deaths, and heart failure, as well as microvascular complications. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, a fixed dosage combination of perindopril–indapamide was tested against matching placebo. The intervention resulted in a 5.6 and 2.2 mm Hg reduction in systolic and diastolic BP respectively, which in turn translated to a 14% reduction in mortality, 14% reduction in coronary events, and a 21% reduction in renal events over 4.3 years of follow-up. Several trials since have demonstrated the renal protective effects of angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor antagonists) over alternate agents.

b. The **Hypertension Optimal Treatment trial** demonstrated the benefit of a lower diastolic target. Among the 3,000 subjects with diabetes, but not in those without diabetes, the relative cardiovascular risk was significantly reduced in the ≤80 mm Hg group, compared with the ≤90 mm Hg group. The ACCORD trial randomized subjects with diabetes to a target systolic BP of <120 mm Hg or <140 mm Hg. The lower target group showed no difference in the primary cardiovascular outcomes end point but did have a significantly lower stroke rate; however, this was at the expense of significantly more adverse drug events and an increased risk of a creatinine rise of >1.5 mg/dL. The 2017 AHA/ACC guidelines recommend initiation of treatment in hypertensive patients with diabetes if their ***BP is 130/80 mm Hg or higher.*** This assumes that the individual has either known CVD or has a >10% risk of CVD over 10 years. The 2018 American Diabetes Association (ADA) guidelines treat BP ≥ 140/90, but note a lower goal of <130/80 mm Hg in the high-risk group and those with established CVD.

3. Tobacco

a. **There is evidence that smokers with diabetes have a markedly increased risk of MI and peripheral arterial disease.** Lipid abnormalities and the development of atherosclerotic plaques appear to be promoted by smoking in the setting of diabetes.

4. Obesity

a. The prevalence of obesity has more than doubled in the United States since 1980. Obesity and overweight are typically defined in terms of body mass index (BMI), with overweight being 25 to 30 kg/m^2, class I obesity 30 to 35 kg/m^2, class II obesity 35 to 40 kg/m^2, and class III obesity > 40 kg/m^2. Waist circumference and waist-to-hip ratio better reflect abdominal adiposity and are more reliable predictors of CAD outcomes than BMI. Obesity is an important determinant of cardiovascular health and is associated with widespread alterations in cardiac and vascular structure and function. It has been shown to be an independent risk factor for the development of CVD. **T2DM correlates closely with obesity, especially central obesity.**

b. Caloric restriction, behavior modification, and increased physical activity form the basis of weight management programs. Unfortunately, sustained weight loss is

difficult to achieve with these conservative measures. Several medications have been marketed for temporary assistance with weight loss. The cardiovascular safety of these agents with the exception of liraglutide at lower dosages has not been evaluated.

1. **1 Orlistat** is currently the only drug that is available for modulation of fat digestion. It inhibits gastric and pancreatic lipases, thus increasing the proportion of fat that is not completely hydrolyzed and is fecally excreted. The recommended prescription dose is 120 mg three times daily. A 60-mg over-the-counter version is available in some countries, including the United States. Major side effects include abdominal cramps, flatus, fecal incontinence, diarrhea, and oily stools; there is a rare association with severe liver injury.
   Multiple trials have demonstrated a greater initial weight loss (approximately 3%) with orlistat, compared with placebo, and also slower weight regain in the longer term. In obese individuals with diabetes, orlistat not only promotes weight loss but also decreases HbA1c at 1 year in comparison with placebo. **Vitamin supplementation** is warranted because of the lack of absorption of fat-soluble agents.
2. **2 Lorcaserin** is a 5HT2c receptor agonist that is approved at 10 mg tablet twice daily and is thought to decrease food intake and promote satiety. Cases of serotonin syndrome or neuroleptic malignant syndrome have been reported with its use and about 2% may develop valvular regurgitant lesions. In a study of 604 patients with diabetes and BMI >27, the percentage of patients losing >5% of their body weight at 1 year was 37.5% compared with 16.1%. Overall, the weight loss with this agent is about 3% to 3.6% compared with placebo.
3. **3 Phentermine/topiramate** acts through norepinephrine release and γ-aminobutyric acid receptor modulation. It is initiated as a 3.75/23-mg extended release tablet that is then uptitrated. It was approved in 2012 and in two randomized controlled trials (RCTs), it was associated with 8.6% to 9.3% weight loss compared with placebo. Experience with utilizing this agent is critical as the combination has known adverse effects on mood as well as on cognition.
4. **4 Naltrexone/bupropion** is an opioid receptor antagonist that was approved in 2014. It is formulated as naltrexone (32 mg) and bupropion (360 mg) twice daily. The main limiting side effect is nausea and, in RCT, the use of this agent resulted in a 3.3% to 4.8% weight loss compared with placebo.
5. **5 Liraglutide** is a glucagon-like peptide-1 (GLP-1) agonist and, for weight loss, it is administered at a daily subcutaneous dosage of 0.6 mg that is uptitrated to 3 mg. It is contraindicated in the setting of medullary thyroid cancer and multiple endocrine neoplasia and its main side effects include nausea, vomiting, and risk for pancreatitis. A 4% to 5% weight loss compared with placebo can be expected with this agent.

5. **There is growing evidence regarding the beneficial effects of significant weight loss achieved by bariatric surgery on glucose metabolism.** The 2018 ADA guidelines recommend bariatric surgery as a treatment option in appropriate surgical patients with BMI ≥40 kg/m^2 (37.5 kg/m^2 Asians) regardless of the level of glycemic control. When glycemic control is a challenge, the threshold to consider surgery is 35 to 39 kg/m^2 (32.5 to 37.4 kg/m^2 in Asians). Bariatric surgery may also be considered in the group with BMI 30 to 34.9 kg/m^2 if hyperglycemia is an issue despite optimal lifestyle and treatment interventions.

a. Bariatric surgery options include malabsorptive procedures such as the Roux-en-Y gastric bypass and restrictive procedures such as laparoscopic adjustable gastric bands and sleeve gastrectomy.

b. Weight loss post bariatric surgery is typically expressed in terms of "excess weight," which refers to the difference between the actual and the ideal weights for an individual. Weight loss after malabsorptive bariatric surgery tends to reach a nadir at 12 to 18 months with an average of 70% excess body weight loss and a 35% decrease in BMI, with an approximate 10% weight regain in the following 10 years.

c. A meta-analysis of 22,000 patients demonstrated that an average excess body weight loss of 61% was accompanied by **significant improvements in T2DM**, hypertension, dyslipidemia, and obstructive sleep apnea. Indeed, bariatric surgery has demonstrated an ability to completely reverse established diabetes in a large number of subjects. In the Swedish Obese Subjects Study, a prospective, nonrandomized, intervention trial of 4,047 obese subjects, 72% of individuals with diabetes who chose the bariatric surgery option showed reversal of their diabetes at 2 years, compared with 21% of those who followed a conservative weight loss regimen of diet and exercise. At 10 years follow-up, diabetes was reversed in 36% of the bariatric surgery group and 13% of the control group. In a smaller study of 165 obese patients with diabetes by Pories, 83% showed diabetes remission at a mean of 9.4 years. In the recent Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, 150 patients with uncontrolled T2DM and a BMI between 27 and 43 kg/m^2 were randomized to intensive medical therapy alone, versus medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The proportion of patients with HbA1c ≤6.0% at 12 months was 12% in the medical therapy group, versus 42% in the gastric bypass group ($p = 0.002$) and 37% in the sleeve gastrectomy group ($p = 0.008$).

6. Multifactorial risk factor interventions should be targeted in all patients with diabetes, regardless of whether this is a primary or a secondary prevention strategy.

a. The Steno-2 trial randomized 160 patients with T2DM and microalbuminuria to intensive versus conventional therapy for a mean period of 7.8 years. The trial was designed to evaluate the effect on cardiovascular events of an intensified, targeted, multifactorial intervention comprising behavior modification and polypharmacologic therapy aimed at several modifiable risk factors in patients with T2DM. The intensive management regimen included dietary fat restriction, 30 minutes of exercise three to five times per week, smoking cessation, ACE inhibitors or angiotensin receptor blocker administration irrespective of BP, additional agents to target BP <130/80 mm Hg, 150 mg aspirin, stepwise glycemia management to target A1c <6.5%, statins for hyperlipidemia, and fibrates for isolated hypertriglyceridemia. The intensive group achieved significantly lower BP, HbA1c, LDL, and TGs. There was an absolute risk reduction of 20% in cardiovascular events. The subjects were then followed up for a further mean of 5.5 years, at which point the primary end point of all-cause mortality was assessed. Significant differences in BP, HbA1c, LDL, and TGs were absent by this later follow-up point. The primary end point at 13.3 years was time to all-cause death, and an absolute risk reduction of 20% was found. Even beyond the period of tight risk factor control, the Kaplan–Meier curves for the first cardiovascular event continued to diverge. During the mean 13.3-year follow-up period, the mortality rate among the conventional therapy subjects was 50%, a finding that highlights the poor overall outcomes in patients with diabetes who are not intensively managed. This study established that there were long-term benefits to aggressive multifaceted risk factor management, and that tight glycemic control and treatment with aspirin, antihypertensives, and lipid-lowering drugs appeared to be additive. Therefore, current society

and national guidelines stress the importance of a broad approach to targeting multiple cardiovascular risk parameters.

VI.MICROVASCULAR TRIALS

A. The role of tight control of glycemia was firmly established in the 1990s with the publication of **two large trials demonstrating decreases in microvascular complications—primarily nephropathy and retinopathy—with lower glucose goals**.

1. The Diabetes Control and Complications Trial (DCCT) recruited 1,441 patients with T1DM, of whom 726 had no retinopathy at baseline and 715 had mild retinopathy. Subjects were randomly assigned to an external insulin pump or three or more daily insulin injections to target a fasting glucose <6 mmol/L. Conventional therapy had no glucose goals beyond those needed to prevent symptoms and comprised one or two daily injections of insulin. The two treatment groups were followed for a mean of 6.5 years between 1983 and 1993, with the mean HbA1c attained being 7.4% and 9.1%, respectively. In the primary prevention cohort (those without baseline retinopathy), intensive therapy reduced the adjusted mean risk of retinopathy development by 76%. With the two cohorts combined, ***intensive glucose control reduced the occurrence of microalbuminuria by 39%.***

2. The UKPDS recruited 5,102 newly diagnosed T2DM patients from 1977 to 1991 with a median baseline HbA1c of 9.1%. The 4,209 patients who could not be controlled on diet alone were managed with differing therapies to determine if there were any specific advantages or disadvantages between glucose-lowering agents. A total of 342 obese subjects were allocated to the metformin group; of the remaining patients, 30% were randomized to conventional therapy and 70% to insulin or a sulfonylurea. The intensive group aimed for a fasting plasma glucose <6 mmol/L. The median HbA1c achieved was 7.0% in the tight control group versus 7.9% in the conventional group. There was a **significant 25% risk reduction** (95% confidence interval [CI] 7% to 40%) in the end point of renal failure or death from renal failure, vitreous hemorrhage, or photocoagulation in the intensive control group. In summary, the two large trials published in the 1990s, DCCT and UKPDS, confirmed significant improvements in microvascular outcomes with tighter glycemic control in both T1DM and T2DM.

VII.MACROVASCULAR TRIALS

A. Despite the convincing evidence for a reduction in microvascular complications, the relationship between **glycemia and cardiovascular events** was not readily apparent in earlier trials using insulin and older antihyperglycemic agents only.

B. The **UKPDS revealed a nonsignificant 16% risk reduction** (95% confidence interval [CI] 0% to 29%, $p = 0.052$) for fatal or nonfatal MI, or sudden death, with intensive management. In those subjects with >120% ideal body weight who were allocated to the metformin strategy, there were significant benefits in terms of diabetes-related end points and all-cause mortality and a 39% risk reduction in MI. However, these results should be interpreted with caution because of the small numbers in the metformin subgroup.

C. Two follow-up studies, and three trials of intensive glucose control, next sought to clarify the relationship between glucose control and cardiovascular events. Both the DCCT and the UKPDS cohorts were followed up for more than a decade from recruitment and their macrovascular outcomes assessed.

1. The DCCT follow-up, known as Epidemiology of Diabetes Interventions and Complications (EDIC), monitored 93% of the original cohort until 2005, for a mean of

17 years of follow-up. Despite the loss of metabolic separation, there was emergence of a macrovascular risk reduction in the group that had received the period of tight control earlier in the course of their T1DM; **a 42% risk reduction for all cardiovascular events** (95% CI 9 to 63, $p = 0.02$) was observed in this group.

2. Similarly, the UKPDS subjects were invited for posttrial monitoring, with 3,277 patients attending annual clinics for a further 5 years. No attempts were made to maintain their previously assigned therapies, and indeed there was no persisting difference in HbA1c between groups at 1 year after initial trial conclusion. Data were then analyzed by original trial groupings. The sulfonylurea/insulin group showed a sustained decrease at 10 years for MI (15%, $p = 0.01$) and death from any cause (13%, $p = 0.007$). The metformin group showed a significant risk reduction in MI (33%, $p = 0.005$) and all-cause mortality (27%, $p = 0.002$).

3. The DCCT/EDIC and UKPDS follow-up findings can be interpreted as showing "legacy" effects, whereby ***tighter management of glycemia*** early in the disease course confers cardiovascular and survival benefits more than a decade later.

D. Three further large trials added additional information regarding the potential relationship between glycemic control and cardiovascular outcomes (Table 44.3).

1. The ADVANCE trial randomized 11,140 patients with T2DM to standard versus intensive glucose control. Intensive control was achieved with the use of gliclazide (a sulfonylurea) plus other agents as necessary to achieve an HbA1c ≤ 6.5%. After 5 years' median follow-up, the mean A1c was 7.3% in the standard group and 6.5% in the intensive group. Insulin was prescribed for 40.5% and 24.1% of patients in the intensive group and the standard control group, respectively. There ***was a decrease in the incidence of microvascular events (primarily microalbuminuria) but no significant effect of the type of glucose control on major macrovascular events*** (HR with intensive control 0.94), death from cardiovascular causes (hazard ratio [HR] 0.88), or death from any cause (HR 0.93). Of relevance, the nonglycemic risk factors were not fully optimized in many participants, with a mean systolic BP of 135.5 ± 17.6 in the intensive glucose group and 137.9 ± 18.4 in the standard group and an LDL mean of around 120 mg/dL ± 20 in both groups.

2. The ACCORD trial also tested the effects of tight glucose control, recruiting a total of 10,251 T2DM patients who were randomized to a target HbA1c of <6% versus 7.0% to 7.9%. These participants were slightly younger than those studied in ADVANCE; they also tended to be heavier, had a higher median baseline HbA1c, and were much more likely to be using insulin prior to entry. ACCORD was discontinued at a mean follow-up of 3.5 years because of an increased risk of death in the intensive treatment arm. The primary outcome of nonfatal MI, nonfatal stroke, and cardiovascular mortality occurred in 352 patients in the intensive group versus 371 in the standard group (HR 0.90, 95% CI 0.78 to 1.04, $p = 0.16$). Hypoglycemia requiring medical attention and weight gain >10 kg were both more common in the intensive therapy group. The finding of harm with a very aggressive A1c target was surprising and could be related to adverse effects of hypoglycemia, especially in long-standing diabetes—19 of the 41 cardiovascular deaths were attributed to "unexpected or presumed CVD," and so could have been hypoglycemia related. In addition, the average weight gain of 3.5 kg in the intensive control group (presumably drug mediated) may have impacted on outcomes. It has also been noted that 91.2% of intensive therapy patients were

receiving ***rosiglitazone, which was subsequently associated in other literature with an excess cardiovascular mortality***, versus 57.2% of the standard therapy group.

3. The Veterans Affairs Diabetes Trial randomly assigned 1,791 predominantly male military veterans who had a suboptimal response to therapy for T2DM to receive either intensive or standard glucose control. The mean age was 60 years, 40% had already experienced a cardiovascular event, 52% were receiving insulin, and the mean baseline HbA1c was 9.4%. This high-risk cohort was followed for a mean of 5.6 years, during which time the mean A1c was 6.9% in the intensive group and 8.4% with standard care. ***However, there was no significant difference observed between the two groups in any component of the primary outcome or in all-cause mortality (HR 1.07, 95% CI 0.81 to 1.42; p = 0.62).***

TABLE 44.3 Characteristics of the Major Randomized Controlled Trials of Intensive Glucose Co

	UKPDS 33	ACCORD	ADVANCE	VADT
Participants (n)	3,867	10,251	11,140	1,791
Diabetes duration (y)	0	10	7.9	11.5
Mean age (y)	53	62	66	60
History of CV disease (%)	Not reported	35	32	40
Duration of intervention (y)	10.0	3.5	5.0	5.6
Intensive group treatment	Sulfonylurea or insulin	Any oral drugs, insulin (91% rosiglitazone)	Gliclazide, other drugs including insulin	Glime or i
Standard group treatment	Diet	Any oral drugs, insulin (57% rosiglitazone)	Any oral drugs, insulin	Glime or i
Intensive group goal	FPG < 6.0 mmol/L	A1c < 6.0%	A1c ≤ 6.5%	1.5% gro
Standard group goal	FPG 6.1–15.0 mmol/L	A1c 7.0%–7.9%	Local standards	Local
Baseline median A1c (%)	7.1	8.1	7.5	9.4
Achieved median A1c (%)	7.0 vs. 7.9	6.4 vs. 7.5	6.5 vs. 7.3 (mean)	6.9 vs
Primary CV outcome	MI and sudden cardiac death	Nonfatal MI or stroke, or CV mortality	Nonfatal MI or stroke, or CV mortality	Nonfa failu amp
HR for primary	16% risk reduction	0.90 (95% CI 0.78–1.04)	Macrovascular 0.94	0.88 (

TABLE 44.3 Characteristics of the Major Randomized Controlled Trials of Intensive Glucose Co				
outcome	($p \geq 0.052$)		(95% CI 0.84–1.06)	
HR for death	0.87 ($p \geq 0.006$)	1.22 (95% CI 1.01–1.46)	0.93 (95% CI 0.83–1.06)	1.07 (

E. ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; FPG, fasting plasma glucose; HR, hazards ratio; MI, myocardial infarction; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

F. Data from Kelly TN, Bazzano LA, Fonseca VA, et al. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med*. 2009;151(6):394–403. Copyright © 2009 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

G. The lack of clear benefits in these strategy trials was likely due to a number of factors. Duration of therapy, lack of significant separation in glycemic control between the treatment and control groups, and the nature of medications utilized may all have contributed to these findings. An uncertain era began when clinicians while being able to control hyperglycemia were unable to favorably impact the cardiovascular complications that ensued. At the turn of the century, a large number of new targets to control blood sugar in diabetes were being evaluated. At this point, drug approval for newer agents simply required evidence of glycemic control. This resulted in small, short-term studies that targeted low-risk patients with DM that on occasion led to the approval/near approval of agents that could even induce harm. ***Recognizing this deficiency, the FDA issued a guidance that mandated the conduct of large CVOT in patients with established/high-risk CV profile prior to the approval of agents for T2DM.*** These trials were large in number, had significant follow-up, utilized standard definition, and had central adjudication of all clinical events. The results of completed trials are summarized in Table 44.4.

H. Trials with dipeptidyl peptidase-4 (DPP-4) inhibitors. These agents held much promise to improve macrovascular outcomes as a number of favorable mechanisms were identified in early animal and human studies. Three large CVOT with sitagliptin (Trial Evaluating Cardiovascular Outcomes with Sitagliptin, $n = 14{,}671$), alogliptin (Examination of Cardiovascular Outcomes with AlogliptIn Versus Standard of Care, $n = 5{,}380$) and saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus, $n = 16{,}492$) were conducted. In all of these trials, composite cardiovascular outcomes were similar in the treatment and control groups confirming noninferiority. An increased risk of heart failure was noted with this class of agent. The signal for heart failure was most apparent with saxagliptin, increased with alogliptin, but absent with sitagliptin.

I. Trials with sodium glucose transport protein subtype 2 (SGLT-2) inhibitors. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) Outcomes trial evaluated 7,028 patients with T2DM and high risk of cardiovascular events to empagliflozin + standard of care versus placebo + standard of care. Over a median follow-up of 3.1 years, treatment

with empagliflozin (pooled for patients receiving 10 and 25 mg once-daily empagliflozin) reduced the primary composite outcome (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) from 12.1% to 10.5%; HR 0.86, $p = 0.04$. A significant decrease in all-cause (5.7% vs. 8.3%) and cardiovascular mortality (3.7% vs. 5.9%) was noted in the treatment group along with a remarkable 35% relative risk reduction in hospitalization for heart failure. This favorable action on heart failure has led to trials in heart failure in patients with both preserved and reduced ejection fraction EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR) regardless of the presence of diabetes. The SGLT-2 inhibitor canagliflozin was evaluated in The Canagliflozin Cardiovascular Assessment Study program that enrolled 10,142 patients at high cardiovascular risk, randomized to canagliflozin + standard of care versus placebo + standard of care. Utilizing similar end points as with empagliflozin, canagliflozin resulted in a reduced event rate (26.9 vs. 31.5 participants per 1,000 patient-years; HR 0.86; $p = 0.02$ for superiority) over a mean 188 weeks of follow-up. An increased risk of amputation (6.3 vs. 3.4 participants per 1,000 patient-years; HR 1.97) was associated with canagliflozin. A large outcome trial with a third agent dapagliflozin is currently underway.

TABLE 44.4 Completed Randomized, Double-Blind, Placebo-Controlled CV Outcome Trials in T

Trial	Drug	*N*	Primary CV Outcome
DPP-4 Inhibitors			
EXAMINE	Alogliptin	5,380	Composite: CV death, nonfatal MI, or nonfatal stroke
TECOS	Sitagliptin	14,671	Composite: CV death, nonfatal MI, nonfatal hospitalization for UA
SAVOR	Saxagliptin	16,492	Composite: CV death, MI, stroke
GLP-1 Agonists			
ELIXA	Lixisenatide	6,068	Composite: CV death, MI, stroke, hospitalization for UA
LEADER	Liraglutide	9,340	Composite: CV death, nonfatal MI, or nonfatal stroke
SUSTAIN-6	Semaglutide	3,297	Composite: CV death, nonfatal MI, nonfatal stroke
SGLT-2 Inhibitors			
EMPA-REG Outcome	Empagliflozin	7,020	Composite: CV death, nonfatal MI, nonfatal stroke
CANVAS	Canagliflozin	10,142	Composite: CV death, nonfatal MI, nonfatal stroke

J. CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HR, hazards ratio; MI, myocardial infarction; SGLT-2, sodium glucose transport protein subtype 2; UA, unstable angina.

K. Trials: EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6, The preapproval Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; CANVAS, The Canagliflozin Cardiovascular Assessment Study.

L. Trials with GLP-1 receptor agonists. Three outcomes trials evaluating this group of agents have been completed. The largest trial Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results evaluated liraglutide compared with placebo in 9,340 patients over 3.8 years of clinical follow-up. The event rate for the composite end point of cardiovascular death, nonfatal MI, and nonfatal stroke was 13% versus 14.9%, HR 0.87, $p = 0.01$ for superiority. After being superimposed early, the event curves diverge over time, suggesting an antiatherosclerotic mechanism. The preapproval Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes trial reported on cardiovascular outcomes in 3,297 subjects randomized to once-a-week semaglutide compared with placebo. The primary triple end point was significantly reduced with semaglutide (6.6% vs. 8.9%, HR 0.75, $p < 0.001$ for noninferiority). Lixisenatide was tested versus 6,068 subjects with diabetes and within 6 months of an acute coronary syndrome in the Evaluation of Lixisenatide in Acute Coronary Syndrome trial. The primary end point was a composite of cardiovascular death, MI, stroke, or hospitalization for unstable angina. Over 25 months of follow-up, event rates in both groups were similar (13.4% vs. 13.2%). Outcome trials with dulaglutide, albiglutide, and exenatide are currently ongoing.

VIII. DIABETES PHARMACOTHERAPY

A. The spectrum of medications available to manage diabetes has expanded greatly over recent years. There has been increasing recognition that there may be significant differences between the cardiovascular impact of the various medications, even if the glycemic effects are equivalent. Agents with proven cardiovascular benefits should be preferentially considered in treating patients with and at high risk for CVD.

1. Insulin is available in short-, medium-, and long-acting preparations, with synthetic human insulin and analogs of human insulin differing in their rates of absorption and durations of action. Mixtures of rapid short-and intermediate-acting insulin are also commonly used. Recombinant human insulin is synthesized using *Escherichia coli* bacteria, and subtle variations in the amino acid chain deter the insulin molecules from forming aggregates, thus creating a faster-onset, shorter-acting drug than regular insulin.

2. The different **recombinant rapid-acting insulins**—lispro, aspart, and glulisine—each have differing amino acid substitutions. All three can be injected subcutaneously to prevent postprandial glucose elevations, for rapid correction of elevated glucose, and in insulin pumps. The onset of action is 15 minutes, with peak effect around 1 hour and a duration of action around 3 to 4 hours.

3. **Regular insulin** is designated as a short-acting preparation. It has onset of action within 30 to 60 minutes, a peak time of 2 to 4 hours, and a duration of action around 6 to 8 hours. It can be used in intravenous infusions, as well as subcutaneously.

4. Neutral protamine Hagedorn (NPH) is an **intermediate-acting insulin**. It's time to onset is 1 to 3 hours, and the total duration of action is 12 to 16 hours. It can be injected either once daily at bedtime to lower fasting glucose levels (typically in individuals on oral hypoglycemics who are above A1c target) or as a twice-daily basal medication in combination with a shorter-acting prandial insulin. This latter approach is known as a basal-bolus regimen and is widely used to achieve tight glucose control. In the basal-bolus regimen, a twice-daily intermediate-acting insulin, or a once-daily long-acting insulin, provides basal coverage and controls the fasting glucose levels. The three prandial insulin doses, administered just before mealtimes, cover the ingested carbohydrates and so limit postprandial glucose elevation. This is considered to be the most "physiologic" method of insulin administration, because it simulates the insulin-release patterns of the β-cells.

5. Glargine and detemir are the available **long-acting agents**, usually injected at night, and show minimal peaking. Glargine has a 24-hour profile of action, whereas detemir is more variable at 6 to 24 hours.

6. **Insulin can cause weight gain and carries a risk of severe hypoglycemia.** The hypoglycemic risk is increased in patients with renal and/or hepatic dysfunction, because the liver and kidneys are responsible for the majority of gluconeogenesis and glycogenolysis; in addition, insulin is renally excreted. The associated weight gain and hypoglycemia raised questions when the ACCORD trial revealed higher mortality in the intense therapy arm, where 77% of subjects were using insulin (vs. 55% in the standard care arm). The recent Euro Heart study also suggested harm related to insulin use. Insulin-treated patients with diabetes had an adjusted 1-year HR for mortality of 2.23 (95% CI 1.24 to 4.03, $p = 0.006$) and for cardiovascular events of 1.27 (95% CI 0.85 to 1.87, $p = 0.230$) compared with those taking oral hypoglycemic agents (predominantly sulfonylurea, metformin, or a combination of the two). However, this study was nonrandomized and the choice to prescribe insulin was made by the treating physicians. The Outcome Reduction With Initial Glargine Intervention trial was a 6.2-year dedicated cardiovascular outcomes trial of glargine which demonstrated no increased cardiovascular risk.

B. **Insulin pumps** are devices that can be programmed to release a continuous infusion of insulin into the subcutaneous tissue. An abdominal infusion site is the usual location, and the catheter should be changed every 2 to 3 days. These pumps are generally used in patients with T1DM and are most suited to knowledgeable and motivated individuals. They have been demonstrated to achieve greater success with target HbA1c levels and reduce the number of severe hypoglycemic episodes, compared with traditional subcutaneous insulin injections. A newer innovation is the subcutaneous continuous glucose-monitoring system that detects glucose levels in the interstitium of subcutaneous tissue. The real-time display of glucose levels can assist patients in anticipating insulin requirements and avoiding severe hypoglycemia. The currently marketed devices are each limited to a few days of continuous wear. Closed-loop systems that consist of both a subcutaneous continuous glucose sensor and an insulin pump are in development.

C. Metformin addresses glycemia by several mechanisms. It reduces hepatic gluconeogenesis by inhibiting glucose-6-phosphate dehydrogenase and works as a

peripheral insulin sensitizer, with promotion of insulin-induced glucose movement into skeletal myocytes and adipocytes. Because it does not stimulate insulin release, there is minimal hypoglycemic risk. This drug is considered first line in overweight patients with T2DM and is not associated with the weight gain that is encountered with insulin and the sulfonylureas. Metformin's insulin-sensitizing mechanisms have also found a role in the treatment of metabolic syndrome, polycystic ovarian syndrome, and nonalcoholic fatty liver disease, each of which is associated with insulin resistance. There is evidence for improvements in lipid profiles with metformin use. Metformin is contraindicated with impaired renal function (creatinine > 1.5 mg/dL in males and > 1.3 mg/dL in females is often quoted as the threshold) and also decompensated heart failure, where the risk of lactic acidosis may be elevated. Lactic acidosis, which can arise in the setting of reduced renal lactate clearance coupled with insufficient uptake of lactate into the liver because of gluconeogenesis inhibition, is considered to be rare. However, it is standard of care to discontinue metformin during periods of renal impairment or inpatient heart failure treatment and for 24 hours before and 48 hours after injection of iodinated contrast agents. The majority of the reported side effects are gastrointestinal and can include diarrhea, nausea, early satiety, and abdominal pain.

D. **Sulfonylureas** are **insulin-stimulating oral agents**, with action on the adenosine triphosphate (ATP)-sensitive potassium channel found on the pancreatic β-cell. Binding of a sulfonylurea causes a decrease in potassium efflux through the K^+_{ATP} channel, inducing membrane depolarization that leads to calcium influx into the β-cell. Insulin release from secretory granules results. The main side effect is hypoglycemia; weight gain can also be a complication. Questions have also been raised regarding their potential to inhibit ischemic preconditioning via blockade of myocardial K^+_{ATP} channels. The commonly used second-generation sulfonylureas, such as glipizide, glimepiride, and glyburide (also known as glibenclamide outside the United States), are largely metabolized by the liver and excreted renally. Glyburide is not recommended as first line for patients with heart failure given that it has active metabolites that can linger in patients with renal dysfunction.

E. Thiazolidinediones are a newer class of drugs that have attracted much controversy with regard to their effects on the heart. The two agents developed in this class, rosiglitazone and pioglitazone, act by increasing insulin sensitivity in target peripheral tissues. This is achieved via activation of the peroxisome proliferator–activated receptor (PPAR)-γ nuclear receptor in myocytes and adipocytes, encouraging insulin-stimulated glucose transport into the cell. Pioglitazone also acts as a partial agonist of the PPAR-α receptor, which is believed to be the reason for increased HDL and decreased LDL and TGs observed with this drug. Peripheral edema is a noted side effect; hence, this class of drugs should *not* be used in patients with New York Heart Association class III–IV heart failure because of concerns for sodium and water retention and possible precipitation of heart failure decompensation. Weight gain, by expansion of subcutaneous adipose tissues, is also an associated complication. There is some evidence, mostly using surrogate outcomes such as carotid intimal thickness and progression of coronary atherosclerosis by intravascular ultrasound, for a deterrent effect on atherosclerosis by pioglitazone in comparison with a sulfonylurea. Analysis of a database including 16,390 clinical trial participants demonstrated that pioglitazone is associated with a significantly lower risk of death, MI, or

stroke among a diverse population of patients with diabetes. However, the risk of heart failure was increased with pioglitazone, although without an associated increase in mortality. Conversely, rosiglitazone has been associated with an excess risk of MI and cardiovascular mortality in a meta-analysis. This led to the subsequent publication of the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral agent combination therapy for type 2 Diabetes (RECORD) trial, which demonstrated overall noninferiority for a combination of metformin and sulfonylurea, but an increased risk of heart failure hospital admission or death with rosiglitazone. The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, however, demonstrated that pioglitazone decreased primary cardiovascular composite outcome when compared with placebo although the result did not quite reach statistical significance. In addition, the Insulin Resistance Intervention after Stroke (IRIS) study which compared pioglitazone to placebo in insulin-resistant patients with prior transient ischemic attack or stroke showed a significant reduction in further microvascular complications.

F. Meglitinides, such as repaglinide and nateglinide, are relatively short-acting oral insulin secretagogues. They are taken just prior to a meal and help to lower postprandial glucose levels. Because of their short duration of action, meglitinides are useful in the elderly and individuals with erratic eating habits.

G. α-Glucosidase inhibitors such as acarbose and miglitol delay the absorption of complex carbohydrates via their action on the glycosidase enzymes in the brush border of the small intestine. They are generally used as an adjunctive therapy and can be useful in controlling postprandial glycemia. As described above, the STOP-NIDDM trial suggested a role for acarbose in reducing the progression of IGT to diabetes. The major side effects are flatulence and abdominal pain.

H. Amylin is also an adjunctive agent and can be combined with prandial insulin therapy in T1DM or T2DM patients not meeting glucose targets. Pramlintide is a synthetic version of endogenous amylin, which is synthesized by β-cells and secreted with insulin in response to a carbohydrate load. The major effects appear to be inhibition of gastric emptying and suppression of glucagon release. Insulin doses should be reduced on initiation of pramlintide injections to avoid potential hypoglycemia. This agent may assist in reducing body weight.

I. Incretins are a new class of agents for T2DM and include the GLP-1 and glucose-dependent insulinotropic peptide (GIP). The incretin hormones stimulate β-cell proliferation in animal models and are found at lower-than-normal levels in patients with T2DM. The active form of GLP-1 is the amide GLP-1(7 to 36), which is secreted by entero-endocrine L-cells of the ileum and colon in response to a carbohydrate load. These agents reduce HbA1c and decrease body weight, BP, and LDL cholesterol. The main side effects with this class are gastrointestinal and pruritus at the injection site. Exenatide is a synthetic short-acting GLP-1 analog that is subcutaneously injected twice daily. It works by potentiating insulin secretion, decreasing postprandial glucagon, delaying gastric emptying, and promoting weight loss. Liraglutide works in a manner similar to exenatide but has a longer half-life and is dosed once daily. Liraglutide and exenatide have demonstrated the ability to reduce systolic BP. Liraglutide also has a positive effect on the lipid profile and cardiovascular risk biomarkers. Side effects include diarrhea and vomiting, and hypoglycemia is also a concern. DPP-4) inhibitors work by deterring the DPP-4-mediated degradation of GLP-1 and GIP

into inactive metabolites. DPP-4 inhibitors are weight neutral and carry a low risk of hypoglycemia.

J. SGLT-2 inhibitors are the newest class of diabetes medications and work by inhibiting glucose reabsorption in the proximal tubule of the kidney by binding to the SGLT-2 receptor in the first part of the proximal convoluted tubule. This results in glycosuria and in weight loss along with a 1% lowering of HbA1c. It also increases insulin sensitivity in the periphery. These agents decrease BP, and decrease TG and uric acid levels while mildly increasing LDL levels. The increased amount of glucose in the urine can also worsen the infections already associated with diabetes, particularly urinary tract infections and thrush (candidiasis). There are also concerns it may increase risk of diabetic ketoacidosis. Examples of drugs in this category include dapagliflozin, canagliflozin, and empagliflozin.

IX.REVASCULARIZATION IN PATIENTS WITH DIABETES

A. The cardiovascular management of patients with diabetes incorporates not only careful consideration of medical regimens but also review of the available literature with regard to revascularization strategies. There have been many advances in evidence-based management of obstructive coronary lesions over recent decades, and many of the trials have identified strategies that confer particular benefit in individuals with diabetes. The choice of CABG versus PCI applies when the coronary anatomy and patient characteristics are amenable to both modalities of revascularization. In practice, there are significant proportions of patients in whom only one modality is realistic. A heart team approach involving a clinician, surgeon, and interventionalist should be utilized to make treatment decisions in this set of patients.

1. **CABG versus PCI.** A series of landmark trials in patients with obstructive CAD have defined current practice with regard to the decision between CABG and PCI. The finding in 1997 that **the Bypass Angioplasty Revascularization Investigation (BARI) subgroup with diabetes had a significant survival benefit in favor of CABG heralded the onset of specific coronary strategies for patients with diabetes**. The subgroup was not prespecified, but the survival benefit was considerable: In subjects receiving insulin or oral agents for diabetes (347 of the total cohort of 1,829), those randomized to CABG had a 80.6% 5-year survival, whereas balloon angioplasty was associated with 65.5% survival. This was in the interventional era prior to coronary stenting, and the explanation for the poor PCI outcomes in BARI subjects with diabetes is a presumed high rate of vessel restenosis. In addition, patients with diabetes tend to have more diffuse CAD, and lesions distant from the angioplasty site are left unprotected by a PCI strategy.

2. **CABG versus PCI with bare metal stents (BMSs) and glycoprotein IIb/IIIa inhibitors.** The widespread adoption of coronary stenting—at this stage with BMS—was successful in reducing restenosis rates. Sustained angiographic coronary patency also correlated with superior survival outcomes, symptom scores, and improved regional left ventricular systolic function. The randomized Arterial Revascularization Therapy Study of CABG versus PCI in multivessel disease showed equivalence of major outcomes for CABG and PCI strategies, with the caveat that the incidence of repeat revascularization was higher in the PCI group. This trial was also notable for its diabetes subgroup results; **there was a benefit in terms of 1-year repeat revascularization and major cardiovascular events in patients with diabetes who underwent CABG, as compared with stenting**. Other studies of

this era, including the Stent or Surgery trial published in 2002, demonstrated superiority of CABG over PCI in patients with multivessel disease in general.

3. **CABG versus drug-eluting stents (DESs).** The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial investigated the strategies of PCI with DES versus CABG in patients with triple-vessel or left main disease; approximately 26% of SYNTAX participants had diabetes. An evaluation of the 452 SYNTAX subjects with diabetes, 40% of whom received insulin, showed that mortality was significantly higher among subjects with diabetes compared with those without, regardless of the revascularization strategy. At 1 year, the only outcome difference between PCI and CABG in patients with diabetes was the excess of repeat revascularization in the PCI arm. Patients with diabetes had significantly increased repeat revascularization rates compared with those without diabetes when treated with DES, but not after CABG. Stroke was nonsignificantly higher in the SYNTAX CABG arm. The Optimal Management of Multivessel Disease (FREEDOM) trial, completed in 2010, is the largest randomized trial of diabetic patients undergoing multivessel CABG. The T2DM had to have at least three-vessel coronary disease and one-third had a recent acute coronary syndrome. The study found that FREEDOM patients had significantly improved survival free of death, MI, or stroke and increased overall survival after CABG compared with percutaneous intervention. The rate of the composite outcome in the CABG group compared with PCI was 18.7% versus 26.6%, $p = 0.005$. However, the stroke rate was greater following CABG than PCI (5.2% for CABG vs. 2.4% for PCI; $p = 0.03$).

4. **CABG outcomes. Bypass conduit attrition rates are known to be higher in patients with diabetes.** As in patients without diabetes, the use of the internal mammary arteries (IMAs) offers higher long-term patency (in the region of 90% at 10 years) compared with reversed saphenous veins (long-term patency varying between 40% and 75%). Therefore, IMAs are particularly attractive in patients with diabetes, although the practice of using bilateral IMA grafts is controversial because of the potential for sternal wound infections. In addition to wound infections, patients with diabetes have an elevated risk of perioperative stroke with CABG surgery as shown in the FREEDOM trial.

5. **Revascularization versus optimal medical therapy.** The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial raised questions regarding the relative merits of a purely medical versus medical and PCI strategy in patients with obstructive CAD and stable symptoms. This somewhat controversial study concluded that PCI added to optimal medical therapy did not reduce the primary composite end point of death and nonfatal MI or reduce major cardiovascular events over a 2.5- to 7.0-year period. A third of the participants had diabetes. The 1,605 patients with diabetes enrolled in the PCI versus optimal medical therapy stratum of BARI-2D did not show any difference in cardiovascular outcomes. However, both of these trials randomized patients after an initial angiogram that defined anatomy, and the decision to enroll in the PCI arm of BARI-2D (as opposed to the CABG arm) was made once anatomy was known and at the discretion of the investigators.

6. **Screening asymptomatic patients with diabetes for CAD.** Given the elevated risk of CAD in patients with diabetes, investigators have attempted to determine whether identification of asymptomatic CAD can improve future outcomes for patients with diabetes. The Detection of Ischemia in Asymptomatic Diabetes study used a nuclear cardiac

stress imaging protocol to identify patients likely to have CAD. At 5 years, there was no difference in nonfatal MI or mortality between the nuclear screening and standard care groups. However, the screening arm was notable for a very low rate of significant ischemia detection, and there was a very successful protocol of optimal medication therapy among trial participants.

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CHAPTER 45

Exercise Electrocardiographic Testing

Rayji S. Tsutsui

I. INTRODUCTION

A. Exercise electrocardiographic testing is a field in flux. In the past decade, it has become clear that ST-segment changes during exercise have low sensitivity and specificity in the evaluation of coronary artery disease (CAD) and are poor predictors of risk. This may be partially due to the fact that stable obstructive plaques, which typically result in exercise-mediated ischemia, are less relevant to myocardial infarction (MI) and sudden cardiac death than unstable nonobstructive plaques. Although the bulk of obstructive CAD screening has now shifted toward various stress imaging modalities, many of the physiologic parameters measured during exercise have emerged as powerful prognostic indicators. As such, the main uses of exercise electrocardiographic testing should be **evaluation of prognosis** and as **a gateway to other imaging modalities**. Stand-alone testing for CAD diagnosis is reserved for patients with **intermediate risk for CAD** and should be ordered with a careful understanding of the limitations of the test for this purpose.

1. The **advantages** of exercise electrocardiographic testing are its ability to assess a variety of prognostic markers, most importantly **functional capacity**, which is a powerful predictor of mortality, widespread availability, safety, ease of administration, and relatively low cost.

2. **Disadvantages.** As a screening test for CAD in persons without symptoms, exercise electrocardiography is generally not helpful or indicated. It has a **low sensitivity and specificity,** which can be improved with careful selection of the patient population undergoing testing.

B. **Submaximal exercise electrocardiographic testing** (i.e., testing at submaximal heart rate, discussed later) is a useful assessment before hospital discharge for **patients who have had MI**. The advantages are as follows:

1. It assists in setting **safe levels** of exercise (exercise prescription) and reassuring patients and families.

2. It is beneficial in **optimization of medical therapy**, in triage for intensity of follow-up testing and care, and in recognition of exercise-induced ischemia and arrhythmias.

3. For patients with uncomplicated MI who have received reperfusion therapy, submaximal exercise testing may be safely **performed as early as 3 days after MI**, with maximal exercise testing 3 to 6 weeks later.

II. INDICATIONS. The indications for exercise electrocardiographic testing are divided on the basis of the degree of likelihood of disease or severity of diagnosed disease, use in valvular heart disease, and use in congenital heart disease (Table 45.1).

III. CONTRAINDICATIONS. Contraindications to exercise testing are divided into absolute and relative categories (Table 45.2).

TABLE 45.1 ACC/AHA Guidelines for Exercise Testing

Exercise Testing in the Diagnosis of Obstructive CAD
Class I[a]
Adult patients (including those with complete right bundle branch block or <1 mm of resting ST- probability of CAD on the basis of sex, age, and symptoms
Class IIa
Patients with vasospastic angina
Class IIb
Patients with a high pretest probability of CAD on the basis of age, symptoms, and sex
Patients with a low pretest probability of CAD on the basis of age, symptoms, and sex
Patients with <1 mm of baseline ST-depression and taking digoxin
Patients with electrocardiographic criteria of left ventricular hypertrophy and >1 mm of baseline ST
Class III
Patients with baseline electrocardiographic abnormalities
Preexcitation (Wolff–Parkinson–White) syndrome
Electronically paced ventricular rhythm
>1 mm of resting ST-depression
Complete left bundle branch block
Patients with a documented MI or prior coronary angiographic findings of disease and an establis can be determined with testing)
Risk Assessment and Prognosis Among Patients With Symptoms or a History of CAD
Class I
Patients undergoing initial evaluation with suspected or known CAD (exceptions in class IIb), in branch block or <1 mm of resting ST- depression
Patients with suspected or known CAD previously evaluated, now presenting with marked change
Low-risk unstable angina patients 8–12 h after presentation who have been free of active ischemi
Intermediate-risk unstable angina patients 2–3 d after presentation who have been free of active i

TABLE 45.1 ACC/AHA Guidelines for Exercise Testing

Class IIa
Intermediate-risk unstable angina patients with initial cardiac markers that are normal, a repeat ele change, cardiac markers 6–12 h after symptom onset that are normal, and no other evidence of
Class IIb
Patients with baseline electrocardiographic abnormalities
Preexcitation (Wolff–Parkinson–White) syndrome
Electronically paced ventricular rhythm
1 mm or more of resting ST-depression
Complete left bundle branch block or any interventricular conduction defect with QRS duration >1
Patients with a stable clinical course who undergo periodic monitoring to guide treatment
Class III
Patients with severe comorbidity likely to limit life expectancy and/or candidacy for revascularizati
High-risk unstable angina patients
After Acute MI
Class I
Before discharge for prognostic assessment, activity prescription, or evaluation of medical therapy
Early after discharge for prognostic assessment and cardiac rehabilitation if the predischarge ex limited, about 14–21 d)
Late after discharge for prognostic assessment, activity prescription, evaluation of medical thera exercise test was submaximal (symptom limited, about 3–6 wk)
Class IIa
After discharge for activity counseling or exercise training as part of cardiac rehabilitation of revascularization
Class IIb
Patients with electrocardiographic abnormalities
Complete left bundle branch block
Preexcitation (Wolff–Parkinson–White) syndrome
Left ventricular hypertrophy
Digoxin therapy

TABLE 45.1 ACC/AHA Guidelines for Exercise Testing

Electronically paced ventricular rhythm
>1 mm of resting ST-depression
Periodic monitoring for patients who continue to participate in exercise training or cardiac rehabilit
Class III
Severe comorbidity likely to limit life expectancy or candidacy for revascularization
Patients with acute MI and uncompensated congestive heart failure, cardiac arrhythmia, or exercise ability
Before discharge, patients who have been selected for or have undergone cardiac catheterization
Exercise Testing for Persons without Symptoms or Known CAD
Class I
None
Class IIa
Asymptomatic persons with diabetes mellitus to start vigorous exercise
Class IIb
Persons with multiple risk factors
Men older than 45 y and women older than 55 y without symptoms
Who plan to start vigorous exercise (especially if sedentary)
Who are involved in occupations in which impairment might affect public safety
Who are at high risk for CAD because of other diseases
Class III
Routine screening of men or women without symptoms
Exercise Testing for Persons with Valvular Heart Disease
Class I
None
Class IIa
Patients with chronic AR and equivocal symptoms to assess functional capacity and symptomatic
Class IIb
Asymptomatic patients with AS may be considered to elicit exercise-induced symptoms and abno

TABLE 45.1 ACC/AHA Guidelines for Exercise Testing

In asymptomatic or symptomatic patients with chronic AR (with radionuclide angiography) for asse
Class III
Exercise testing should not be performed in symptomatic patients with AS
Exercise Testing for Persons with Congenital Heart Disease
Class I
None
Class IIa
Asymptomatic young adults <30 y of age to determine exercise capability, symptoms, and blood p
Adolescent or young adult patient with AS who has a Doppler mean gradient >30 mm Hg or a interested in athletic participation or if the clinical findings and Doppler findings are disparate
Asymptomatic young adult with a mean Doppler gradient >40 mm Hg or a peak Doppler gr anticipates athletic participation or pregnancy
As part of the initial evaluation of adolescent and young adult patients with TR and serially every 1
In patients with atrial septal defect with symptoms that are discrepant with clinical findings or to c patients with mild or moderate PAH
In patients with subvalvular AS testing to determine exercise capability, symptoms, ECG chan gradient is reasonable in the presence of otherwise equivocal indications for intervention
In patients with supravalvular AS (along with other imaging modalities) testing can be useful perfusion
Class IIb
In patients with aortic coarctation, testing may be performed at intervals determined in consultatio
Class III
Patients with atrial septal defect or patent ductus arteriosus with severe PAH
Symptomatic patients with AS or those with repolarization abnormality on ECG or systolic dysfunc

IV. [a] *Class I*, conditions for which there is evidence or agreement that a given procedure or treatment is useful and effective; *Class II,* conditions for which there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of a procedure or treatment; *Class IIa,* weight of evidence or opinion is in favor of usefulness and efficacy; *Class IIb,* usefulness or efficacy is less well established on the basis of evidence and opinion; *Class III,*conditions for which there is evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful.

V. ACC, American College of Cardiology; ACHD, adult congenital heart disease; AHA, American Heart Association; AR, aortic regurgitation; AS, aortic stenosis; CAD, coronary

artery disease; ECG, electrocardiogram; LVOT, left ventricular outflow tract; MI, myocardial infarction; PAH, pulmonary arterial hypertension; TR, tricuspid regurgitation.

VI. From Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol*. 2002;40:1531–1540, with permission. Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to develop guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. 2008;52:e1–e142 and from Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease). *J Am Coll Cardiol*. 2008;52:1890–1947.

TABLE 45.2 Contraindications to Exercise Testing

Absolute Contraindications
Acute myocardial infarction (within 2 d)
Ongoing unstable angina
Uncontrolled cardiac arrhythmias with hemodynamic compromise
Active endocarditis
Symptomatic severe aortic stenosis
Decompensated heart failure
Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis
Suspected or known dissecting aneurysm
Acute myocarditis or pericarditis
Acute aortic dissection
Physical disability that precludes safe and adequate testing
Relative Contraindications
Known obstructive left main coronary artery stenosis
Moderate to severe aortic stenosis with uncertain relation to symptoms
Tachyarrhythmias with uncontrolled ventricular rates
Acquired advanced or complete heart block
HOCM with severe resting gradient

TABLE 45.2 Contraindications to Exercise Testing

Recent stroke or transient ischemic attack
Mental impairment with limited ability to cooperate
Resting hypertension with systolic or diastolic blood pressure >200/100 mm Hg
Uncorrected medical conditions, such as significant anemia, important electrolyte imbalance, and h

VII. HOCM, hypertrophic obstructive cardiomyopathy; MI, myocardial infarction.

VIII. Reprinted with permission from Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training. A Scientific Statement From the American Heart Association. *Circulation*. 2013;128(8):873–934. Copyright © 2013 American Heart Association, Inc.

IX. LIMITATIONS OF EXERCISE ELECTROCARDIOGRAPHIC TESTING

A. Before ordering an exercise electrocardiography test, the physician should have an understanding of pretest probability and the limitations of the test.

B. **Bayes' theorem** states that the probability of a positive test result is affected by the likelihood (i.e., conditional probability) of a positive test result among the population that has undergone the test (i.e., pretest probability). The higher the probability that a disease is present in a given individual before a test is ordered, the higher the probability that a positive test result is a true-positive test result. Pretest probability is determined on the basis of symptoms, age, sex, and risk factors and can be divided into very low, low, intermediate, and high (Table 45.3).

C. **Sensitivity and specificity.** The likelihood that an abnormal electrocardiographic finding indicates CAD is much higher for an older person with multiple risk factors than for a young person with no risk factors. Sensitivity and specificity vary with the population being tested.

1. Exercise electrocardiographic testing is **best used** in the evaluation of a patient at intermediate risk with an atypical history or a patient at low risk with a typical history.

2. For the general population, the sensitivity is 68% and the specificity is 70%. Values are lower for persons at low risk.

3. Exercise electrocardiographic testing has a higher sensitivity and specificity for **persons at high risk**. For most of these patients, however, invasive testing is preferred for a more definitive diagnosis and possible intervention. Excluding patients with left ventricular hypertrophy or resting ST-depression and those taking digoxin also improves sensitivity and specificity.

TABLE 45.3 Pretest Probability of CAD According to Age, Sex, and Symptoms

Age (y)	Sex	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonang
30–39	Men	Intermediate	Intermediate	Low
	Women	Intermediate	Very low	Very low
40–49	Men	High	Intermediate	Interme

TABLE 45.3 Pretest Probability of CAD According to Age, Sex, and Symptoms

	Women	Intermediate	Low	Very low
50–59	Men	High	Intermediate	Interme
	Women	Intermediate	Intermediate	Low
60–69	Men	High	Intermediate	Interme
	Women	High	Intermediate	Interme

4. Reprinted from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol*. 1997;30(1):260–315. Copyright © 1997 Elsevier. With permission.

D. Positive predictive value (PPV)

1. For the general population, the sensitivity is 68% and the specificity is 70%. Values are lower for persons at low risk.
2. PPV is highly dependent on pretest probability (i.e., prevalence of disease) in the population being tested. For example, in a population at low risk, the PPV of electrocardiographic exercise testing is only 21%, but in a population at high risk, PPV rises to 83%.

X.PATIENT PREPARATION

A. Instructions. Table 45.4 provides a typical list of instructions given to patients before testing.

B. Medications

1. Before diagnostic testing, **cardiovascular drugs are withheld** at the discretion of and under the guidance of the supervising physician. This greatly increases the sensitivity of the test.

TABLE 45.4 Patient Preparation

Patients should refrain from ingesting food, alcohol, or caffeine or using tobacco products within 3 h of t
Patients should be rested for the assessment, avoiding significant exertion or exercise on the day of the
Patients should wear clothing that allows freedom of movement, including walking or running shoes, sleeves that buttons down the front. They should not wear restrictive undergarments during the test.
Outpatients should be warned that the evaluation may be fatiguing and that they may wish to have som afterward.
If the test is for diagnostic purposes, it may be helpful for patients to discontinue prescribed cardiova with their physician. Antianginal agents alter the hemodynamic response to exercise and sign electrocardiographic changes for ischemia. Patients taking intermediate- or high-dose β-blockers sh 2–4-d period to minimize hyperadrenergic withdrawal responses.
If the test is for functional purposes, patients should continue their medication regimen on their us responses will be consistent with responses expected during exercise training.

TABLE 45.4 Patient Preparation

Patients should bring a list of their medications with them to the assessment.

2. Reprinted with permission from Swain DP, Brawner CA, Chambliss, HO, eds. *ACSM's Guidelines for Exercise Testing and Prescription*. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.

a. β-Blockers pose a special problem. Patients taking β-blockers often do not have an adequate increase in heart rate to achieve the level of stress needed for the test. Abrupt withdrawal of β-blockers is to be discouraged because of reflex tachycardia. The best possible solution is to withdraw the β-blocker over several days before an exercise test, if the test is for diagnostic purposes. This is not always possible, however, because of time constraints or the necessity of drug therapy. In these cases, the records should reflect β-blocker use at the time of testing.

b. **Digoxin** may cause problems in test interpretation. To avoid a reading that cannot be used to confirm a diagnosis, digoxin should be withheld for 2 weeks before testing.

3. On the other hand, if evaluation of symptoms with exertion is the primary goal, cardiovascular medicines should be continued.

4. Patients undergoing diagnostic testing should take their **other usual medications** on the day of the test to reproduce more closely the conditions outside the exercise laboratory.

XI. EXERCISE PROTOCOLS. There are advantages and disadvantages to each exercise protocol (Table 45.5). Selection depends on the patient characteristics, the equipment available, and the familiarity and comfort of the testing personnel with the protocol.

A. An **optimal protocol** achieves peak workload and maximizes the sensitivity and specificity of the test.

1. **Workload.** An optimal protocol incorporates a **gradual increase** in the level of work, so that the patient's true peak workload can be determined. If there are large increases in workload, maximum oxygen consumption (MVO_2 max) may fall between two levels. The test is also more comfortable for the patient if the increases in workload are not large.

2. **Duration.** The optimal duration for an exercise test is **8 to 12 minutes**. Periods longer than this measure muscular endurance rather than cardiovascular fitness. Periods shorter than this do not allow adequate time for the patient to warm up and achieve maximum workloads.

3. **Stage length.** Steady-state oxygen consumption is reached after about 2 minutes of exercise at a given workload. The optimal protocol would have stage lengths of **2 to 3 minutes**.

4. **Exercise method.** Both **bicycle riding** and **treadmill testing** are used; the latter is more commonly used in the United States.

a. The primary physiologic **advantage of bicycle riding** is the ability to take **direct measurements** of workload in watts, which has direct linear relation to MVO_2. With a **treadmill**, the examiner can only **estimate workload** because workload depends on the

efficiency of walking, the weight of the patient, and the change in energy expenditure between walking and running.

B. Protocol options

1. Bruce protocol

a. Advantages. The Bruce protocol has been widely used in the past and is often the basis of older studies; therefore, **comparisons are easier**. Because the Bruce protocol has a final stage that cannot be completed, it is a good protocol for a highly fit person.

b. Disadvantages

1. **1** The main disadvantage of the Bruce protocol is the **large increments of change in workload between stages**. These large increases mean that peak workload falls somewhere between stages for many people. This is a problem in evaluating functional capacity and may result in a lower sensitivity for the test.

2. **2** The fourth stage of the Bruce protocol is an awkward stage that can be run or walked, resulting in divergent oxygen costs and workloads.

2. Modified Bruce protocol. Developed for less-fit persons, the modified Bruce protocol adds additional stages 0 and 1/2. These stages, at 1.7 mph (2.7 km/h) with 0% and 5% grades, respectively, provide a **lower workload for persons with poor cardiovascular fitness**. However, even these workloads may be too heavy for some debilitated patients and may result in premature fatigue.

TABLE 45.5 Common Exercise Protocols

			Treadmill Protocol						
Functional Class	**O_2 cost (mL/kg/min)**	**MET**	**Bruce (3-min Stages mph/grade)**		**Cornell (2-min Stages mph/grade)**		**Balke (2-min Stages mph/grade)**		**Nau**
World-class athlete	70.0	20	–	–	–	–	–	–	–
	66.5	19	6.0	22	–	–	–	–	–
	63.0	18	–	–	–	–	–	–	–
	59.5	17	5.5	20	–	–	–	–	–
Athlete	56.0	16	5.0	18	5.0	18	–	–	–
	52.5	15	–	–	–	–	4.0	20	–
	49.0	14	–	–	4.6	17	–	–	–
Fit	45.5	13	4.2	16	4.2	16	3.5	20	–
	42.0	12	–	–	–	–	–	–	–
	38.5	11	–	–	3.8	15	3.0	20.0	–
Normal and 1	35.0	10	3.4	14	3.4	14	3.0	17.5	–

TABLE 45.5 Common Exercise Protocols

	31.5	9	–	–	–	–	3.0	15.0	–
	28.0	8	–	–	3.0	13	3.0	12.5	2.0
	24.5	7	2.5	12	2.5	12	3.0	10.0	–
2	21.0	6	–	–	2.1	11	3.0	7.5	2.0
	17.5	5	1.7	10	1.7	10	3.0	5.0	2.0
	14.0	4	–	–	–	–	3.0	2.5	2.0
3	10.5	3	1.7	5	1.7	5	3.0	0	2.0
	7.0	2	1.7	0	1.7	0	–	–	2.0
4	3.5	1	–	–	–	–	–	–	1.0

MET, metabolic equivalent; mph, miles per hour.

4. Other protocols. Protocols superior to the Bruce protocol have been developed. These protocols have more gradual increases in workload and can be modified to suit the individual.

a. The **Naughton protocol** is good for older or debilitated persons and allows a gradual increase in workload.

b. The **Balke protocol** is good for younger, fit persons. It maintains a speed of 3, 3.5, or 4 mph (4.8, 5.6, or 6.4 km/h, respectively) and increases the grade every 2 minutes.

c. The **Cornell protocol** is good for a wider range of fitness levels depending on the starting grade. It allows for a gradual increase in grade and speed and may be started at 0%, 5%, or 10% grade, depending on fitness level.

d. **Ramp protocols** are computer-driven protocols that continuously increase workload until maximum exertion is reached. This is the ultimate in continuous advancement, but steady state may not be reached at any given workload.

XII. DATA

A. Electrocardiographic data. Although not the only data that should be examined, electrocardiographic changes garner the most attention in test interpretation. The **portion of the electrocardiogram (ECG) most sensitive to ischemia** is the ST-segment. The pathophysiologic mechanism of the ST-change is net depression caused by a current of ischemia from the affected myocardial cells. The TP-segment may be useful at rest and should be used when possible; however, it shortens or disappears with exercise. Baseline electrocardiographic abnormalities that can obscure the correct diagnosis of ST-changes are listed in Table 45.6.

1. ST-segment changes

a. Measurement of the ST-segment. There is no clear consensus as to where to measure the ST-segment. Traditionally, it is measured 80 ms past the J point, but some investigators suggest measuring at the J point or at the midpoint of the ST-segment (using

the end of the T-wave or the peak of the T-wave to determine the end of the segment; Fig. 45.1A).

b. **ST-segment changes** are measured from the isoelectric baseline, which can be determined from the PR interval. If the ST-segment is elevated at rest, any depression that occurs with exercise is still measured from the isoelectric line; early repolarization of the ST-segment at rest is normal. If, however, the ST-segment is depressed at rest, any further depression should be measured from the baseline ST-segment (Fig. 45.1B).

c. **Normal response.** During exercise, there is depression of the J junction that is maximal at peak exercise and returns to baseline during recovery. This normal depression is upsloping and typically <1 mm below the isoelectric line 80 ms after the J point.

d. **ST-depression** does **not** localize the area of ischemia.

1. **1** ST-depression of at least 1 mm that is horizontal or downsloping is abnormal, as is upsloping ST-depression of at least 2.0 mm.

2. **2** Baseline ST-abnormalities are less likely to represent exercise-induced myocardial ischemia, and the baseline ST-depression should be subtracted from the peak ST-depression.

TABLE 45.6 Baseline Abnormalities That May Obscure Electrocardiographic Changes during Exercise

Left bundle branch block
Left ventricular hypertrophy with repolarization abnormality
Digitalis therapy
Ventricular paced rhythm
Wolff–Parkinson–White syndrome
ST abnormality associated with supraventricular tachycardia or atrial fibrillation
ST-abnormalities with mitral valve prolapse and severe anemia

3. **FIGURE 45.1 A:** Blomqvist recommended using the end of the T-wave for measuring the midpoint of the ST-segment, but Simons used the peak of the T-wave. This change was made to have a more stable end point, because the end of the T-wave is much more difficult to find than the peak of the T-wave. **B:** The ST integral, as defined by Sheffield, required that the end of the QRS complex, or J junction, be found and that the area measurement stop as soon as the ST-segment crossed the isoelectric line or as the T-wave began. The ST integral used by most commercial systems initiates the area at a fixed period after the R wave and then ends 80 ms thereafter.

4. **3** **Criteria that increase the probability of ischemia** are the **number of leads** involved (i.e., more leads increase the probability of ischemia), the **workload** at which the ST-depression occurs (i.e., lower workload increases the probability), the **angle of the slope** (i.e., a downsloping angle has a higher probability than a horizontal one), **ST-segment adjustment relative to heart rate (ST/HR index)**, the **amount of time in recovery** before normalization of the ST-segment (i.e., longer recovery increases the probability), and possibly the **magnitude of the depression**. Changes in the lateral leads, particularly V_5, are more specific than in any of the other leads. Changes in the **inferior leads alone are likely to be a false-positive** result.

e. The **meaning of ST-elevation** depends on the presence or absence of Q-waves of prior MI.

1. 1 ST-segment elevation **with Q-waves of prior MI** is a common finding among patients who have had MI. It occurs among up to 50% of patients with anterior MI and 15% of patients with previous inferior MI, and it is not caused by ischemia. The mechanism is thought to be dyskinetic myocardium or ventricular aneurysms. There may even be reciprocal ST-segment depression. Patients with more extensive Q-waves have more pronounced ST-elevation. These patients typically have a lower ejection fraction than those without elevated ST-segment with a Q-wave. These changes do not imply ischemia (although they may imply viability) and should be interpreted as normal.
2. 2 ST-segment elevation **without Q-waves of prior MI** represents marked transmural myocardial ischemia. ST-elevation may also indicate the location of the ischemia. This finding should be interpreted as abnormal.

f. **ST-normalization,** or the lack of ST-changes during exercise, **may be a sign of ischemia.** This phenomenon occurs when ischemic ST-depression and ST-elevation cancel one another. This effect is rare, but it should be considered in tests of patients with no electrocardiographic changes but with a high likelihood of CAD.

2. **R-waves may change in amplitude** during exercise. There is no diagnostic value in these changes.
3. **T-wave and U-wave changes**

a. The **T-wave** normally decreases gradually in early exercise and begins to increase in amplitude at maximal exercise. One minute into recovery, the T-wave should be back to baseline. T-wave **inversion is not a specific marker of ischemia** and may occur normally.

b. If the U-wave is upright at baseline, **U-wave inversion** may be associated with ischemia, left ventricular hypertrophy, and valvular disease.

4. **Arrhythmias.** Table 45.7 lists abnormal arrhythmias that may occur during exercise. Ectopic atrial and ventricular beats during exercise are not predictive of outcome, but ventricular ectopy during recovery may be associated with worse outcome. Sustained ventricular tachycardia and ventricular fibrillation are abnormal but occur rarely.
5. **Time to resolution of changes.** The longer into recovery that it takes for electrocardiographic changes to resolve, the higher is the probability that they are important. Rapid recovery (<1 minute) indicates less likelihood of disease and that disease if present is less severe.
6. Bundle branch block or conduction delay. Exercise-induced left bundle branch block is predictive of a worse outcome.

B. **Age-predicted maximum heart rate (APMHR).** The two most common formulas are as follows:

$$\text{APMHR} = 220 - \text{age}$$

$$\text{APMHR} = 200 - \tfrac{1}{2}\,\text{age}$$

The APMHR may be much lower or much higher than a person's actual measured MHR. **Heart rate should not be used as an indicator of maximal exertion or in the decision to terminate testing**. If MHR does not exceed 85% of APMHR during testing and there are no substantial electrocardiographic changes, the test is usually read as

nondiagnostic. If there are substantial electrocardiographic changes, the test is read as abnormal, regardless of the heart rate achieved.

TABLE 45.7 Absolute and Relative Indications for Termination of an Exercise Test

Absolute Indications
Acute MI or suspicion of MI
Onset of moderate to severe angina or increasing anginal pain
Drop in SBP >10 mm Hg, despite an increase in workload, when accompanied by any other evidence
Serious arrhythmias (e.g., second- or third-degree atrioventricular block, sustained ventricular t ventricular contractions, and atrial fibrillation with fast ventricular response)
Signs of poor perfusion, including pallor, cyanosis, or cold and clammy skin
Unusual or severe shortness of breath
Central nervous system symptoms, including ataxia, vertigo, visual or gait problems, or confusion
Technical inability to monitor the ECG
Patient's request
Relative Indications
Pronounced electrocardiographic changes from baseline >2 mm of horizontal or downsloping ST-s segment elevation except in aVR, measured 60–80 ms after the J point in a patient with suspected
Drop in SBP >10 mm Hg (persistently below baseline) despite an increase in workload, in the absenc
Any chest pain that is increasing
Physical or oral manifestations of severe fatigue or shortness of breath, wheezing
Leg cramps or intermittent claudication (grade 3 on 4-point scale)
Hypertensive response (SBP > 250 mm Hg and diastolic blood pressure > 115 mm Hg)
Less serious arrhythmias such as supraventricular tachycardia
Exercise-induced bundle branch block that cannot be differentiated from ventricular tachycardia
General appearance

ECG, electrocardiogram; MI, myocardial infarction; SBP, systolic blood pressure.

Adapted from Swain DP, Brawner CA, Chambliss, HO, eds. *ACSM's Guidelines for Exercise Testing and Prescription*. Philadelphia, PA: Williams & Wilkins; 2013 and from Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training. A scientific statement from the American Heart Association. *Circulation*. 2013;128(8):873–934.

C. **Rating of perceived exertion (RPE)** is a better marker of maximal level of exertion.

1. A useful indicator of percentage of maximum workload achieved is the **RPE scale**. This is a subjective scale used to rate how much effort the subject feels he or she is expending during an exercise test. The subject should be advised to rate how he or she feels overall and not according to an individual element such as leg fatigue. Although subjective, the scale has been shown to be reproducible, and maximum ratings correspond well with maximum exertion.

a. The **Borg scale** is used most often. The original scale ranges from 6 to 20, which is meant to correspond to a heart rate increase from 60 to 200 beats/min during exercise.

b. The **modified Borg scale** ranges from 0 to 10. The scale includes word anchors, which are important for an accurate assessment of work level. The scales are not linear, and at higher workloads, the changes in RPE are closer together.

2. A maximal level of exertion is marked by a score >18 (Borg scale) or 9 (modified Borg scale), respiratory quotient >1.1 (if carbon dioxide exchange is monitored), and overall patient appearance.

D. In addition to electrocardiographic monitoring, **blood pressure monitoring** is an important aspect of the exercise test for safety and for the diagnosis of CAD. It should be checked in each walking stage. It may not be practical to check blood pressure while the subject is running.

1. **Systolic blood pressure** (SBP) normally rises during exercise. A **failure of SBP to rise** with increasing workload or a drop in SBP usually indicates the presence of CAD and is an indication to **terminate testing**.

2. **Diastolic blood pressure** decreases with exercise and may be audible down to 0 during vigorous activity. Unlike SBP, diastolic blood pressure is not useful in diagnosis or safety monitoring.

E. **Symptoms.** The presence or absence of symptoms and their change over time are included in the final report.

F. **Functional capacity.** Functional testing is a powerful marker for prognosis. Persons who achieve >6 metabolic equivalents (METs) of workload have a significantly lower mortality rate than those who do not achieve this workload, regardless of electrocardiographic changes. On the basis of age and workload achieved, functional capacity can be divided into five classifications (Table 45.8). Among 3,400 patients with no history of diagnosed CAD undergoing exercise testing at the Cleveland Clinic, those with average or better classifications had a 2.5-year mortality of <2% compared with 6% and 14% for those who were in the fair and poor groups, respectively. The adjusted relative risk for fair or poor functional capacity in this population was almost 4.

XIII. TERMINATION OF EXERCISE TESTING

The American Heart Association (AHA) and American College of Sports Medicine (ACSM) have developed very similar indications for exercise termination (Table 45.7). The decision when to terminate a test ultimately relies on the expertise and judgment of those performing the test.

A. **Absolute indications** are all serious findings. A drop in SBP with increasing workload is a particularly ominous sign and usually, but not always, indicates the presence of severe CAD.

B. **Relative indications** for termination of testing are findings that should increase the level of concern and vigilance among those administering the test and possibly cause

cessation of testing. Relative indications for termination rely heavily on the judgment of the personnel performing the test, and the decision to continue the test should not be made lightly (Table 45.7).

TABLE 45.8 Functional Capacity Classifications by Age and Sex

Age (y)	Low[a]	Fair	Average	Good
Women				
20–29	<7.5	8–10.3	10.3–12.5	12.5–
30–39	<7	7–9	9–11	11–15
40–49	<6	6–8	8–10	10–14
50–59	<5	5–7	7–9	9–13
60–69	<4.5	4.5–6	6–8	8–11.
Men				
20–29	<8	8–11	11–14	14–17
30–39	<7.5	7.5–10	10–12.5	12.5–
40–49	<7	7–8.5	8.5–11.5	11.5–
50–59	<6	6–8	8–11	11–14
60–69	<5.5	5.5–7	7–9.5	9.5–1

[a]Functional capacities are given in metabolic equivalents.

C.

D. Postexercise recovery

1. In **all routine exercise tests, a cool-down period** adds safety to the test. The length of the cool-down period may vary from 30 seconds to several minutes, depending on the person. A general rule is to allow enough time for the heart rate to drop to <110 beats/min. A shorter cool-down period increases the sensitivity of exercise ECG because of increased venous return; resuming the supine position leads to increased wall stress. This same mechanism also increases the risk of testing.
2. The exception to observing a cool-down period may be made for exercise echocardiography, in which it is important to image the subject when he or she is as close as possible to MHR.

XIV. INTERPRETATION OF DATA. An experienced clinician must interpret an exercise electrocardiographic test. Although the terms *positive* and *negative* are often used, these terms do not accurately describe the results of an exercise electrocardiographic test and should be avoided. The information to include in an exercise electrocardiographic report is listed in Table 45.9.

A. Exercise electrocardiographic test results can be normal, abnormal, normal except for, or nondiagnostic (Table 45.10). Nondiagnostic tests are those in which the subject does not achieve 85% of APMHR and has no abnormal electrocardiographic changes or in which baseline electrocardiographic changes are present that obscure ST-changes (Table 45.6).

B. Prognosis

1. The **Duke nomogram** (Fig. 45.2) is a simple chart that factors in ST-segment deviation, amount of angina during exercise, and exercise capacity to give an estimate of a 5-year survival and average annual mortality. This nomogram was derived by means of regression analysis and can be a useful tool in determining prognosis and the degree of aggressiveness needed in treating a patient. The **Duke treadmill score (DTS)** is a numeric form of the nomogram and has been validated in several studies as an important predictor of mortality:

TABLE 45.9 Elements of Conclusion Section of a Modern Exercise Test Report

Exercise protocol used, duration of exercise, peak treadmill speed and grade, maximum heart rate and resting and peak blood pressure, and symptoms
Negative/positive/equivocal standard ST-segment response to exercise
"The ST/HR index of ≤1.6 μV/beats/min is consistent with the absence of obstructive coronary d functionally, and prognostically important coronary disease unlikely"; "The ST/HR index >1.6 μV presence of obstructive coronary disease and predicts increased cardiovascular risk
The estimated functional capacity of (*x* METs) predicts (high/low) risk of all-cause mortality
The Duke treadmill score of (*x*) predicts a cardiac mortality of (*x*%) per year over the next 5 y. This impli
The chronotropic response index of (0.*xx*) predicts an (increased/decreased) risk of death compared patients not on β-blockers, a value ≤0.80 raises concerns; for patients on β-blockers, a value ≤0.62 is
The heart rate recovery of (*x* beats/min) further predicts an (increased/decreased) risk of death
The presence/absence of frequent ventricular ectopy during recovery further increases/decreases predi

APMHR, age-predicted maximum heart rate; HR, heart rate; MET, metabolic equivalent.

Adapted with permission from Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. *Circulation*. 2006;114(19);2070–2082.

TABLE 45.10 Guidelines for Interpretation of Results of Exercise Electrocardiography

Variable	Normal	Normal Except for	Abno
Symptoms	Neuromuscular chest pain	Angina as an isolated finding	Syncc
	Fatigue, shortness of breath, and leg or joint pain	Atypical angina	Angin wav
		Chest discomfort of questionable causation	Angin hyp
		Claudication	

TABLE 45.10 Guidelines for Interpretation of Results of Exercise Electrocardiography

		Dizziness and lightheadedness	
		Other noteworthy symptoms	
Blood pressure response (mm Hg)	SBP increases >10 but is <230 at peak	SBP ≥230 at peak exercise	Any c incr
	DBP increases ≤10 but is <120 at peak	DBP ≥120 at peak exercise	
	DBP stays the same or decreases	DBP increases ≥12 from rest if peak is ≥100	
	DBP increases ≥12 from rest but peak is <100		
Arrhythmias	Occasional PVCs	Paroxysmal SVT	Susta junc
	PACs	Increased frequency of PVCs or couplets during exercise	Nonsu
	Frequent PACs or PVCs at rest that abate during exercise	Isolated run of nonsustained VT	Secon
	Chronic AF, atrial flutter	Ventricular couplets	AV di
		Paroxysmal escape rhythms	Exerc
			Idiove
			Very a
			Susta
			VF/ca
			Asyst
ST segments	≥1.0 mm ST-depression or elevation	Borderline ST-changes (0.5–0.9 mm ST-depression)	≥1.0 r
		ST-elevation in leads in area of prior MI	≥1.5 r
		T-wave inversion	≥1.0 r with
		Pseudonormalization of resting T-wave abnormalities	≥1.0 r Q-w
			Very a

TABLE 45.10 Guidelines for Interpretation of Results of Exercise Electrocardiography

			≥2.0 r
			≥2.5 r
			≥2.0 r Q-v
Functional capacity	Normal or mildly impaired exercise tolerance	Low exercise tolerance	Inabili

AF, atrial fibrillation; AV, atrioventricular; D, downsloping; DBP, diastolic blood pressure; H, horizontal; MET, metabolic equivalent; MI, myocardial infarction; PAC, premature atrial contraction; PVC, premature ventricular contraction; SBP, systolic blood pressure; SVT, supraventricular tachycardia; U, upsloping; VF, ventricular fibrillation; VT, ventricular tachycardia.

2. The **heart rate recovery**, defined as the difference in heart rate at peak exercise and at 1 minute after cessation of exercise, has important prognostic significance. A heart rate recovery of 12 beats/min or less is considered abnormal during an upright cool-down period. For patients assuming an immediate supine position, such as during exercise echocardiography, a value of <18 beats/min is considered abnormal.

FIGURE 45.2 Duke nomogram for estimation of the prognosis. MET, metabolic equivalent.

3. The **chronotropic response index (CRI)** is a measure of MHR in relation to chronotropic reserve. A normal response is defined as a CRI of >0.8 (0.62 for patients on β-blockers):

4. **Ventricular ectopy in recovery** from exercise, including frequent ventricular ectopics (>7/min), couplets, bigeminy, trigeminy, ventricular tachycardia, and ventricular fibrillation, has been shown to be predictive of all-cause mortality. These findings in recovery are a better predictor of death than ventricular ectopy during exercise.

5. A published nomogram (1) for patients with suspected CAD and a normal ECG undergoing exercise treadmill testing demonstrates how a simple combination of clinical and stress-testing variables can be used to predict mortality.

XV. POTENTIAL COMPLICATIONS. Complications of exercise electrocardiographic testing are rare, but they do occur (Table 45.11). Exercise testing of healthy persons without CAD rarely results in cardiac complications, which are most likely to occur among persons with underlying CAD. Several researchers have looked at large numbers of unselected persons involved in various activities to determine risk.

TABLE 45.11 Potential Medical Complications of Exercise Electrocardiographic Testings

Cardiovascular Complications
Cardiac arrest

TABLE 45.11 Potential Medical Complications of Exercise Electrocardiographic Testings

Ischemia
Angina
MI
Arrhythmias
Supraventricular tachycardia
Atrial fibrillation
Ventricular tachycardia
Ventricular fibrillation
Bradyarrhythmias
Bundle branch blocks
Atrioventricular nodal blocks
Congestive heart failure
Hypertension
Hypotension
Aneurysm rupture
Underlying Medical Conditions Predisposing to Increased Complications
Hypertrophic cardiomyopathy
Coronary artery anomalies
Idiopathic left ventricular hypertrophy
Marfan syndrome
Aortic stenosis
Right ventricular dysplasia
Congenital heart defects
Myocarditis
Pericarditis
Amyloidosis
Sarcoidosis
Long QT-syndrome

TABLE 45.11 Potential Medical Complications of Exercise Electrocardiographic Testings
Sickle cell trait
Sudden death
Pulmonary Complications
Exercise-induced asthma
Bronchospasm
Pneumothorax
Exercise-induced anaphylaxis
Exacerbation of underlying pulmonary disease
Gastrointestinal Complications
Vomiting
Cramps
Diarrhea
Neurologic Complications
Dizziness
Syncope (fainting)
Cerebrovascular accident (stroke)
Musculoskeletal Complications
Mechanical injuries
Back injuries
Joint pain or injury
Muscle cramps or spasms
Exacerbation of musculoskeletal disease

XVI. MI, myocardial infarction.

A. Cardiac arrest

1. For the **general population**, there is approximately 1 cardiac arrest per 565,000 person-hours of exercise.
2. Among **persons with known CAD**, there is an estimated 1 arrest per 59,000 person-hours of vigorous activity. Exercise testing may precipitate acute coronary symptoms. Acute MI has been reported in approximately 1.4 per 10,000 exercise tests.

3. Among **persons at low risk** for CAD, however, the risk for cardiac arrest during exercise testing is much lower. In one study, no complications occurred in 380,000 exercise tests of young persons with presumably no heart disease.

B. Arrhythmic complications are a potential hazard of exercise testing (Table 45.10). Arrhythmias are more likely among persons with a history of arrhythmia. In this population, they occur in 9% of tests compared with an overall incidence of 0.1%.

1. **Atrial fibrillation** is the most common arrhythmia that occurs during testing, occurring in 9.5 per 10,000 tests.
2. **Ventricular tachycardia** is less common, occurring in 5.8 per 10,000 tests.
3. **Ventricular fibrillation** is even less common, occurring 0.67 times per 10,000 tests.

C. Deaths during exercise testing are exceedingly rare among well-monitored patients, but may occur in 1 of 25,000 tests. If death occurs, it is usually caused by sudden cardiac death or MI.

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CHAPTER 46

Nuclear Cardiac Imaging

Brett W. Sperry
Wael A. Jaber

I. INTRODUCTION. Nuclear cardiology has an integral role in the noninvasive detection of coronary artery disease (CAD), assessment of myocardial viability, and stratification of risk. In addition, novel imaging protocols have been instituted to detect and risk stratify patients with certain cardiomyopathies. With respect to CAD, nuclear stress testing imparts improved sensitivity and specificity over standard exercise stress testing. For example, the average sensitivity and specificity of single-photon emission computed tomography (SPECT) with technetium 99m have been reported to be 90% and 74%, respectively—although the exact performance characteristics depend on the prevalence of the disease in the population being studied. Nuclear imaging can provide functional and prognostic information that is quantifiable, reproducible, and readily obtainable in diverse patient populations.

II. INDICATIONS (Table 46.1)

A. Coronary artery disease

1. **Diagnosis.** Nuclear perfusion studies are performed to establish noninvasively the diagnosis of CAD in the following situations: history of **stable angina; chest pain of unclear causation; unstable angina** after stabilization; **abnormal exercise test result** without symptoms; **risk stratification** in the setting of multiple factors thought to confer a high likelihood of subclinical CAD; scheduled standard exercise testing in the setting of an **abnormal electrocardiogram** (ECG; because of left ventricular [LV] hypertrophy with associated repolarization changes, ST-depression >1 mm, manifest preexcitation pattern on ECG, digoxin use, left bundle branch block, or ventricular-paced rhythm); and previously **nondiagnostic graded exercise test**.

2. **Assessment of the physiologic importance of known coronary lesions.** Perfusion imaging can assist in the determination of the functional significance of a coronary stenosis that is in the "moderate-to-severe" (50% to 70%) range on angiographic evaluation. It can therefore be useful to evaluate a specific coronary lesion before proceeding to percutaneous intervention. This remains an accepted indication for nuclear perfusion imaging, although its use for this purpose is being supplanted by other modalities that can assess the functional significance of coronary lesions at the time of angiography (e.g., fractional flow reserve).

3. **Assessment after therapeutic intervention.** In the past, perfusion imaging was often performed as a routine follow-up procedure after percutaneous intervention

and coronary artery bypass grafting (CABG). More recent recommendations on appropriate use of this modality suggest that routine screening in ***asymptomatic*** patients who have been successfully revascularized by either method is not necessarily warranted, except in the evaluation of patients more than 5 years after CABG. On the other hand, radionuclide perfusion imaging is certainly appropriate in patients who have undergone prior revascularization and are presenting with recurrent symptoms consistent with coronary ischemia.

4. **Risk stratification.** With nuclear imaging, it is possible to stratify risk among patients with stable angina or unstable angina, those who have had myocardial infarction (MI), and those about to undergo noncardiac operations.

5. **Identification of prior MI**, particularly among patients with angiographically normal coronary arteries when thrombolysis or coronary vasospasm is suspected, is afforded by nuclear imaging.

B. Assessment of left ventricular function. Although nuclear imaging is used less often for this purpose than in the past because of the desire to reduce patients' radiation exposure when possible, gated blood pool imaging remains an accurate method of determining the ejection fraction.

C. Diagnosis of cardiomyopathy. Nuclear imaging studies with novel protocols have been utilized to detect infiltrative cardiomyopathies such as amyloidosis and sarcoidosis. Additionally, if a nonischemic cardiomyopathy is suspected, nuclear imaging is sometimes used to rule out CAD and ischemic cardiomyopathy particularly if coronary angiography is not feasible or desired.

III. CONTRAINDICATIONS.

In addition to standard contraindications to exercise stress testing, specific considerations apply uniquely to nuclear imaging in general and the subgroup of dipyridamole stress perfusion studies.

A. General contraindications to nuclear studies. Nuclear imaging is contraindicated for patients who have had **iodine 131 therapy** within 12 weeks; **technetium 99m studies** within 48 hours, including bone, lung, multigated acquisition (MUGA), liver, tagged red blood cell (to evaluate gastrointestinal bleeding), and renal scans; **indium 111 scans** within 30 days; **gallium 67 scans** within 30 days; and **oral intake**within 4 hours (except for water).

B. Contraindications to dipyridamole, adenosine, or regadenoson administration include allergy to any of these agents, allergy to aminophylline, ongoing theophylline therapy (must be discontinued for 36 hours), history of uncontrolled asthma or reactive airway disease, significant atrioventricular nodal block, and caffeine consumption within 12 to 24 hours. A relative contraindication is recent use of vasodilator medications (within 12 to 24 hours depending upon the medication) which will render the vasodilator stress agent ineffective in further dilating the coronary vasculature.

TABLE 46.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging

Patient Group	Condition	In
ER patient with chest pain	For risk stratification in patient with *possible* ACS. Initial serum markers and	R

TABLE 46.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging

	enzymes. ECG is nondiagnostic	
	For CAD diagnosis in patient with *possible* ACS and nondiagnostic ECG. Negative serum markers and enzymes or normal rest perfusion scan	S
Acute MI/unstable angina	Assessment of LV function	R
ST-elevation MI	Measurement of infarct size and residual viable myocardium, in an unrevascularized asymptomatic stable patient after completion of the infarct	R
	Thrombolysis without coronary angiogram, to identify inducible ischemia and myocardium at risk	R
Non–ST-elevation MI/unstable angina	In an unrevascularized stable asymptomatic patient after completion of the infarct, to determine the extent and severity of inducible ischemia, either in the distribution of the "culprit" vessel or in remote myocardium	R
	In individuals whose angina is stabilized on medical therapy or in whom the diagnosis is uncertain, to identify the extent and severity of inducible ischemia	R
	To assess the functional significance of a coronary stenosis on angiography	R
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease *and* able to exercise to 85% MPHR or more	Those with preexcitation, LVH, on digoxin, or >1 mm ST-segment depression on resting ECG	R
	Individuals with left bundle branch block or ventricular-paced rhythm	R
	Patients with an intermediate- or high-risk Duke	R

TABLE 46.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging

	treadmill score	
	In an individual with prior abnormal myocardial perfusion scan and new or worsening symptoms	R
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease *and* not able to exercise	To identify the extent, severity, and location of inducible ischemia	R
Detection of CAD in patients with ventricular tachycardia	Patients without known CAD or ischemic equivalent	R
Detection of CAD in patients with syncope	Patients with intermediate and high risk for CHD and no ischemic equivalent	R
Prior to intermediate- and high-risk noncardiac surgery	Initial diagnosis of CAD in those with at least one clinical risk factor for adverse perioperative CV events, and poor (<4 METS) or unknown functional capacity	In
		or
		In
	In individuals with established or suspected CAD and poor (<4 METS) or unknown functional capacity	In
		or
		In
	Diagnosis of CAD in patients with left bundle branch block or ventricular-paced rhythm and at least one risk factor for adverse	R

TABLE 46.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging

	perioperative CV events	
	In suspected or established CAD, prognostic assessment of those with left bundle branch block or ventricular-paced rhythm on rest ECG	R
Equivocal SPECT myocardial perfusion scan	Clinically indicated SPECT perfusion study is equivocal for CAD diagnosis or risk stratification purposes	R
CAD patient with systolic dysfunction and CHF, with little or no angina	Prediction of improvement in regional/global LV function following revascularization	St *or* R *or* M *or* R
	Prediction of improvement in natural history following revascularization	St *or* R *or* M

IV. ACCF, American College of Cardiology Foundation; ACR, American College of Radiology; ACS, acute coronary syndrome; AHA, American Heart Association; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; CAD, coronary artery disease; CHD, congenital heart disease; CHF, congestive heart failure; CV, cardiovascular; ECG, electrocardiogram; ER, emergency room; FDG, [18F]fluoro-2-deoxyglucose; LV, left ventricular; LVH, left ventricular hypertrophy; METS, metabolic equivalents; MI, myocardial infarction; MPHR, maximal age-predicted heart rate; PET, positron emission tomography; SCCT, Society of Cardiovascular Computed Tomography; SCMR,

Society for Cardiovascular Magnetic Resonance; SNM, Society of Nuclear Medicine; SPECT, single-photon emission computed tomography.

V. EQUIPMENT.

The most basic tool in nuclear imaging is the **gamma (γ) camera**, which is used to detect γ-rays (i.e., x-ray photons) produced by the chosen radionuclide. There are two types of γ-cameras commonly utilized in nuclear cardiology.

A. **A single-crystal camera** consists of one large sodium iodide crystal. Other essential elements of this camera include the **collimator**, a lead device that screens out background or scattered photons, and the **photomultiplier**, an electronic processor that translates photon interactions with the crystal into electric energy.

1. Electric signals from the photomultiplier are processed by the **pulse height analyzer** before reaching a final form. Only signals in a specified energy range are incorporated into the interpreted images. The range recognized by the pulse height analyzer is adjustable and is established on the basis of the radiopharmaceutical used.

2. **Digitalization** of the single-crystal camera has greatly enhanced its performance.

B. A **multicrystal camera** works with an array of crystals with increased count detection capability. Because of the availability of an individual crystal to detect scintillation at any given time, this type of camera can be used to detect many more counts than can a single-crystal camera.

Specially dedicated γ-cameras are the foundation of nuclear imaging in cardiology.

C. **SPECT** cameras utilize a single crystal to acquire multiple two-dimensional (2D) images which are reconstructed to generate a 3D image.

1. Innovations in cardiac imaging have produced **ultrafast SPECT** cameras. These cameras are able to decrease scan time and radiation dose by constraining all available cameras to image only the cardiac field of view. There is a resulting increase in count sensitivity at no loss of, or even a gain in, resolution.

D. In the case of **positron emission tomography (PET)** scanning, a **positron camera** is used to detect the photon products of positron annihilation. Interaction between a positron and an electron causes annihilation, with the generation of two high-energy photons (511 keV) that travel in opposite directions.

1. A multicrystal camera is used and oriented in multiple concentric rings. Each crystal is linked optically to multiple photomultipliers. The crystals are oriented in diametric pairs positioned exactly 180° apart such that each pair of crystals must be struck simultaneously by annihilation photons to record activity. Background interference and stray photon energy are automatically accounted for, and artifact is limited.

2. Most positron cameras contain **bismuth germanate** for annihilation photon detection.

VI. MECHANICS AND TECHNIQUES

A. **Image acquisition.** Basic perfusion imaging can be performed by means of **planar** and **tomographic** techniques. The tomographic, or SPECT, method is most commonly used today.

1. **Planar images** are acquired in three views: **anterior, left anterior oblique (LAO)**, and **steep LAO** or **left lateral (LLAT) orientation**(Fig. 46.1). The patient is supine for anterior and LAO views but is placed in the lateral decubitus position for LLAT

image acquisition. Planar imaging may superimpose vascular distributions and therefore can compromise the ability to implicate a specific vascular supply when a defect is present. For example, normally perfused myocardial segments may overlap perfusion defects in a separate distribution.

2. Using **SPECT**, a series of planar images are usually obtained over a 180° arc to reconstruct a 3D representation of the heart. The arc typically extends from the 45° right anterior oblique plane to the 45° left posterior oblique plane, with the patient in the supine position.

a. Three orientations are analyzed in the final representation: **short axis, vertical long axis**, and **horizontal long axis**. A computer-generated display, the **polar map**, is also analyzed as a quantifiable representation of count density.

b. Unlike planar imaging, **SPECT** can be used to **separate vascular territories** and improve image interpretation. SPECT, however, also **increases the time needed** for image acquisition and requires close attention to quality control issues.

B. **Radiopharmaceuticals** available for nuclear imaging include thallium 201, technetium 99m, and several positron imaging agents. Each possesses specific energy characteristics, kinetic profiles, and biodistribution (see below as well as Table 46.2 and Section X for further details).

1. **Thallium 201**

a. **General characteristics.** Thallium 201 (i.e., thallous chloride) is a metallic element in group IIIA of the periodic table; it is produced in a cyclotron. Thallium emits γ-rays at an energy range of 69 to 83 keV and has a **half-life of 73 hours**. The biologic activity of this element is very similar to that of potassium; the ionic radii of the two elements are virtually identical. Thallium is actively transported into cells by the sodium–potassium adenosine triphosphatase (Na–K ATPase) pump.

b. **Kinetics.** Approximately 5% of the administered dose of thallium 201 is distributed to the myocardium, proportionate to the blood flow delivered to the coronary circulation.

1. 1 The **initial uptake** of thallium 201 by myocardium is directly related to regional blood flow. The myocardial extraction of thallium 201, however, increases at low flow rates (<10% of basal) and decreases at high flow rates (more than twice the basal rate).

2. 2 **Washout.** Almost 85% of the thallium 201 is extracted by myocytes in the first pass. After initial uptake into myocytes, a state of continuous exchange across the cell membrane occurs. The distribution of this radiotracer changes after administration, and thallium 201 washes out from the myocytes, a process called **redistribution**. Thallium 201 washout generally approaches 30% at 2 to 2.5 hours after injection.

FIGURE 46.1 Standard planar views and vascular territories. Circ, circumflex artery; LAD, left anterior descending artery; LAO, left anterior oblique; RCA, right coronary artery.

TABLE 46.2 Characteristics of Common Perfusion Agents

Attribute	Thallium 201	Technetium 99m Sestamibi/Tetrofosmin	Rubidium 82	Nitrogen 13 Ammonia
Energy (keV)	69–83	140	511	511

TABLE 46.2 Characteristics of Common Perfusion Agents

Dose (mCi)	2.5–3.5	20–30	30–60	10–20
Half-life	74 h	6 h	76 s	10 min
Cyclotron required	Yes	No	No	Yes
Perfusion imaging	Yes	Yes	Yes	Yes
Viability evaluation	Yes	Yes	No	No
Redistribution	Yes	Yes (minimal)	No	No
Gating (electrocardiogram)	No	Yes	Yes	Yes

3. **3 Ischemic myocardium.** Uptake of thallium 201 in ischemic myocardium is lower than uptake in nonischemic segments, and washout time is slower than that from nonischemic zones.
4. **4** Over time, counts become equal in the ischemic and nonischemic regions (or thallium 201 concentration may increase in ischemic regions) so that thallium 201 concentrations in these disparate areas approach one another. This disparity is taken advantage of during thallium 201 viability imaging.

2. Technetium 99m–labeled agents

a. General characteristics. Technetium 99m is a radiopharmaceutical that can be produced on-site in molybdenum 99–technetium 99m generators. It possesses several ideal imaging characteristics.

1. **1** Technetium 99m has a **half-life of 6 hours** and emits γ-rays with a single photopeak of 140 keV. Thus, radiation exposure is decreased as compared to Thallium because of the shorter half-life.
2. **2** Technetium 99m–labeled **perfusion agents** include ^{99m}**Tc-sestamibi**, ^{99m}**Tc-tetrofosmin**, and ^{99m}**Tc-teboroxime**. Some studies suggest that ^{99m}Tc-tetrofosmin has more rapid hepatobiliary clearance than sestamibi, which reduces the impact of liver uptake and allows for imaging sooner after injection.

b. Kinetics. After administration of ^{99m}Tc-sestamibi, approximately 40% to 60% of the agent is extracted by the myocardium. Initial uptake of the agent is proportional to regional myocardial blood flow, and it is bound to the inner mitochondrial membrane. ^{99m}Tc-tetrofosmin has similar pharmacokinetics to ^{99m}Tc-sestamibi. **Myocardial washout** of ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin is very slow, and little redistribution occurs. The absence of redistribution requires two separate injections of the agent, at **rest** and at **peak stress** (either exercise or pharmacologic). This can be performed with a same-day or 2-day protocol.

VII. IMAGING PROTOCOLS

A. Thallium 201

1. General features. Stress imaging with thallium 201 involves initial **injection at peak stress** (either exercise or pharmacologic) and **immediate imaging**, followed by **redistribution images** 3 to 4 hours after injection.

a. Because of the long half-life of thallium 201 (73 hours), limited amounts are administered to reduce the total radiation exposure to the patient. Although a single injection is typically used because of the redistribution phenomenon, a second injection may be given to enhance the filling of reversible defects.

b. The low energy range of thallium 201 is marginal for imaging with the γ-camera because of scatter and diminished spatial resolution.

2. **Variations from standard protocol.** Exact imaging techniques vary among institutions. Initial thallium 201 doses range from 2 to 3.5 mCi, acquisition times vary from 20 to 40 seconds per image, and the number of images varies from 32 to 64 depending on whether 180° or 360° image acquisition is used.

a. The use of **360° versus 180° imaging** has been the subject of debate. With 180° tomography, contrast is better, there is less artifact, and imaging times are shorter. Slight variations also exist depending on the use of exercise stress testing or pharmacologic stress protocols.

b. When **exercise thallium 201 scintigraphy** is performed, the radionuclide (2 to 3.5 mCi) is usually injected approximately 1 minute before peak exercise to allow time for distribution. Initial images are obtained within 5 to 10 minutes of injection. Redistribution images are obtained 2.5 to 4 hours after the initial images.

c. This technique is not highly specific for scar at 2.5 to 4 hours because persistent defects may represent viable myocardium in some cases.

1. 1 For this reason, some advocate **delayed (late redistribution) imaging** 18 to 24 hours after injection. Some studies indicate that up to 40% of persistent defects exhibit radiotracer uptake after revascularization. Delayed imaging has resulted in further redistribution in as many as 45% of patients.

2. 2 Alternative approaches in **differentiating viable tissue from scar** include **rest reinjection** of thallium 201, in effect to boost fill-in of perfusion defects. As many as 50% of persistent defects have been shown to exhibit improved thallium 201 uptake after rest injection of 1 mCi of thallium 201, suggesting viability.

d. Minor changes in imaging protocol may be observed with **pharmacologic stress testing** with adenosine, regadenoson, dipyridamole, or dobutamine.

B. **Technetium 99m.** The relative lack of redistribution requires **two injections** of technetium 99m to obtain rest and stress images.

1. **Basic protocols**

a. **Same-day protocol.** Rest images are obtained first, and stress imaging follows to minimize residual scintigraphic activity caused by the higher dose stress injection. This is the opposite order as compared to thallium imaging.

1. 1 **Rest images** are obtained with injection of 7 to 10 mCi of technetium 99m and image acquisition up to 1 to 1.5 hours later. Imaging is delayed because of slower liver clearance with rest injection.

2. 2 At peak exercise, technetium 99m is injected at typically 3× the dose of the resting images (25 to 30 mCi). **Stress images** are obtained approximately 45 to 60 minutes after injection. Hepatic uptake of technetium 99m occurs within 15 to 30 minutes of injection, and the tracer is excreted into the gastrointestinal tract through the biliary system. Appearance of the tracer in the gastrointestinal tract can interfere with imaging of the inferior wall of the left ventricle.

b. The **separate-day protocol** allows time for decay of activity. Larger doses of technetium 99m can be administered for rest and stress images, and there is minimal interference between the images.

1. 1 Between 22 and 30 mCi of technetium 99m is injected for stress and rest imaging, separated by 1 to 2 days.

2. 2 The higher doses possible with the 2-day protocol produce increased count density and better image quality at the cost of inconvenience.

2. **Factors that affect image quality.** Consumption of a **fatty meal** can enhance biliary excretion of technetium 99m and improve image quality. Because of possible interference from noncardiac uptake, image processing with technetium 99m relies on normalization to the brightest cardiac pixel. Additional artifacts are discussed later.

C. **Dual-isotope imaging.** Use of both thallium 201 and technetium 99m substantially reduces the time required to obtain stress and rest images.

1. The patient receives thallium 201 at rest (3.5 mCi) and, immediately after rest imaging, undergoes stress. At peak stress, the patient is given an injection of 25 mCi of technetium 99m. Stress images are obtained 15 minutes later.

2. This technique makes use of the dissimilar energy levels of the two radionuclides to shorten the protocol while still allowing acquisition of ECG-gated images (because of the use of technetium 99m).

3. The sensitivity (91%) and specificity (75%) of this combination protocol are comparable to the values for conventional technetium 99m SPECT.

4. The disadvantages of the dual-isotope protocols revolve around comparing images obtained with isotopes with different characteristics. There may be more Compton scatter of thallium 201 than of technetium 99m and thus greater myocardial wall thickness and inability to assess transient ischemic dilatation of the left ventricle.

VIII.STRESS PROTOCOLS

A. **Exercise stress testing.** Standard exercise testing is frequently complemented with nuclear imaging. The radioisotope is injected at peak exercise, and time is allowed for circulation of the agents while exercising (usually at least 1 minute before termination of exercise).

B. For patients who are unable to exercise, **pharmacologic stress testing** is used in concert with nuclear imaging. Adenosine, regadenoson, and dipyridamole are vasodilators that are useful in noninvasive testing because of differences in coronary flow reserve. In the presence of marked coronary stenosis, the distal vessel is maximally dilated and therefore possesses little flow reserve.

1. **Adenosine** acts at several different receptors (A_1, A_{2A}, A_{2B}, and A_3) and thus has several physiologic effects. Its desired effect for the purpose of pharmacologic stress is to substantially enhance coronary flow in normal beds (i.e., those with normal flow reserve), although much less so in distributions supplied by a stenotic artery. The resultant disproportionate flow allows for utilization or heterogeneous radiotracer uptake.

a. **Administration.** Adenosine is infused at 140 µg/kg/min for 6 minutes. The radiotracer is then injected after 3 minutes of the start of adenosine infusion.

b. **Side effects** commonly experienced include chest pain, headache, nausea, and flushing which typically resolve in 2 to 5 minutes. Atrioventricular block and bronchoconstriction are the result of effects on the A_1 and A_3 receptors, respectively.

Aminophylline can be given intravenously to reverse intolerable or dangerous side effects if they occur.

2. **Dipyridamole** is an adenosine reuptake inhibitor, leading to increased extracellular concentrations of adenosine, and thus has very similar effects. It has a longer distribution half-life than adenosine, however, of approximately 25 minutes.

a. **Administration.** Dipyridamole is infused over a 4-minute period (0.142 mg/kg/min). The maximum vasodilatory effect is achieved 4 minutes after completion of the infusion, and the radiotracer is injected at this point. A slight increase in heart rate (10 beats/min) and decrease in blood pressure (10 mm Hg) are frequently observed.

b. **Side effects.** Headache, nausea, chest pain, hypotension, dizziness, and flushing have been reported. Severe side effects may necessitate reversal of the dipyridamole effect with aminophylline, given as a 50- to 100-mg intravenous bolus.

3. **Regadenoson** is a selective A_{2A} receptor agonist that has been Food and Drug Administration–approved for clinical use in myocardial perfusion imaging since 2008. Two randomized double-blind multicenter trials—ADVANCE-MPI 1 and 2—have demonstrated the safety of this agent in a total of 1,871 patients, as well as an efficacy similar to adenosine for the detection of reversible perfusion defects on SPECT imaging.

a. **Administration.** Regadenoson is given as a single 0.4 mg (in 5 mL) intravenous bolus and does not require adjustment for body mass index or renal or hepatic function. Its coronary hyperemic effects have an onset within 30 seconds and usually last for 2 to 5 minutes.

b. **Side effects** of chest pain, headache, nausea, and flushing do occur with regadenoson and typically resolve within 2 to 5 minutes. However, atrioventricular block and bronchoconstriction are far less common than with adenosine or dipyridamole, because of the lack of agonism of the A_1 and A_3 receptors with this A_{2A}-selective agent. Aminophylline can be given intravenously to reverse intolerable or dangerous side effects if they occur.

4. **Dobutamine** is an agonist of the β_1 and β_2 receptors and thus increases both heart rate and contractility (with a mild reduction in systemic vascular resistance).

a. **Administration.** Infusion is begun at 5 µg/kg/min and increased every 3 minutes to a maximum dose of 40 µg/kg/min. The radiotracer is injected at maximum dose (or at 85% of age-predicted maximum heart rate), and the infusion is continued for 2 to 3 minutes.

b. **Side effects** associated with dobutamine include ectopy, headache, flushing, dyspnea, paresthesias, and hypotension.

IX.IMAGE INTERPRETATION

A. **Standard view of normal anatomy.** The uptake of radiotracer is homogeneous in persons with normal myocardial perfusion. The tracer is predominantly distributed to the left ventricle; the right ventricle usually appears as a faint, thin structure. Understanding and interpreting these images, however, requires an understanding of standard planar and SPECT views of LV anatomic features.

1. **Planar images** are represented as LAO, anterior–posterior (AP), and LLAT views.

2. Standard **SPECT views** include the short axis, vertical long axis, and horizontal long axis. The short-axis view is further divided into apical, mid-ventricular, and basal views.

a. As with planar views, SPECT images in various projections **correspond with specific myocardial segments** (Fig. 46.2).

b. In addition to the standard SPECT sections, short-axis sections can be compiled into a **polar map** (so-called bull's eye display). This computer-generated polar map arranges short-axis tomographic images such that the central portion represents apical slices and the periphery consists of the basal segments.

B. Reviewing sequence. Review of nuclear images follows an organized sequence.

1. **Examine unprocessed images** for artifact, extracardiac uptake, and evidence of increased lung uptake.
2. **Examine rest images.** Document defects and their extent and severity.
3. **Examine stress images.** Document defects and their extent and severity.
4. **Evaluate the polar map** in comparison with pooled normal images (derived from a database of patients with low probability of having CAD).
5. **Compare rest and stress images** for enlargement of the LV cavity.
6. **Incorporate the gated SPECT images** to establish overall ventricular function, volumes, and wall function in areas of questionable perfusion defects. Segmental defects that demonstrate normal motion on gated SPECT images may represent artifact.
7. **Examine right ventricular (RV) size and function**

C. Characterization of defects. Given that initial perfusion images represent regional myocardial blood flow, defects in these images represent an area of myocardium with relatively less uptake and diminished regional blood flow. Defects can be characterized as **fixed, reversible, partially reversible,** or as displaying **reverse redistribution**. (Partially reversible or reverse redistribution are only pertinent with thallium 201 imaging because of redistribution imaging.)

1. **Fixed defects.** Fixed (i.e., nonreversible) defects are areas of decreased tracer uptake that appear unchanged on both rest and stress images. Fixed defects can **represent scar or viable myocardium**. With thallium 201 imaging, nonreversibility suggests similar rates of clearance from the two regions.

a. **Differentiating scar from viable myocardium** in the setting of a nonreversible defect can be accomplished through the use of **metabolic radiopharmaceuticals and PET, delayed imaging, or rest reinjection** with thallium 201. The level of tracer activity reflects viability. Severe deficits (<50% of normal counts) are less predictive of viability than are milder count deficits.

b. Differentiating viable myocardium from scar is paramount because there is clinical and experimental evidence of improved LV function after revascularization of such hibernating regions (see Chapter 50). As methods of revascularization become increasingly applicable in an arena of increasingly complex patient problems, fully defining the so-called fixed defect through metabolic imaging assumes greater importance (see Sections **VIII.D.2** and **X.D**).

2. **Reversible defects** are myocardial segments with normal perfusion at rest but decreased perfusion on stress images. This pattern is consistent with the presence of **ischemic myocardium** in the region of reversibility.

a. In the setting of **thallium 201 imaging**, normal perfusion at rest (i.e., resolution of the defect) is a function of variable tracer concentrations in ischemic and nonischemic segments, which approach one another as redistribution occurs, along with

continuous exchange of myocyte and blood pool thallium 201. **Fill-in** of reversible defects on thallium 201 images can be enhanced by means of delayed imaging or rest reinjection.

b. **Technetium 99m imaging**, which does not utilize redistribution, demonstrates reversibility on the basis of differential uptake during stress compared with rest.

3. **Partially reversible defects** (seen with thallium protocols) are defects seen on stress images that partially resolve on rest images but do not fill in completely. This type of defect is thought to reflect a **mixture of scar and ischemic myocardium**. Nonetheless, reversibility may be incomplete even in the absence of nonviable tissue and represent purely ischemic myocardium.

4. A pattern of **reverse redistribution** occurs in thallium protocols when a defect is absent on stress images but is present on rest images or appears larger on rest images than on stress.

a. Such a pattern is seen in the presence of **acute MI** when the infarct artery has been rendered patent through thrombolysis, percutaneous coronary intervention, autolysis, or another form of revascularization.

b. The pattern is thought to reflect post-MI hyperemia with excess radiotracer uptake in a region of reperfused myocardium followed by accelerated myocardial washout of radiotracer in the defect region.

c. The regions in question may demonstrate viability on PET imaging and do not indicate ischemia.

5. **Artifacts.** Apparent perfusion defects may be artifactual and attributed to soft tissue attenuation, a problem that occurs more often with thallium 201 imaging than when a higher-energy agent (technetium 99m) is used.

a. Common causes of the presence of artifacts include **breast attenuation** in women (affecting the anterolateral, septal, anteroseptal, and posterolateral walls of the ventricle) and **diaphragmatic attenuation** in men (predominantly altering the inferior and posterior walls).

b. Planar images with perfusion defects seen in only a single view are suspect, and the presence of artifact must be considered.

c. SPECT artifacts may be more elusive because of processing and reconstruction of tomographic images. However, with good technique, most are avoidable. When there is a suspicion for attenuation artifacts as above, **attenuation correction** processing techniques can be employed to account for these variables.

6. **Risk assessment.** Identifying the **extent and severity** of perfusion defects is paramount to quantifying risk. Extent refers to the number of segments affected using the 17 segment model. Severity refers to the degree of decreased radiotracer uptake in each segment. Severity is typically graded on a 0 to 4 scale with 0 being normal radiotracer uptake and 4 being absent radiotracer uptake. A **summed score** is calculated which is calculated by adding all scores for the given study. A summed score is calculated at rest and at stress, and the difference between these scores is termed the summed difference score.

a. Specific patterns of perfusion imaging that suggest high-risk coronary anatomic features include perfusion **defects in more than one vascular distribution, increased lung thallium uptake, and transient ischemic LV dilatation (i.e., transient ischemic dilation)**. Extent and severity of defects also predicts risk. More will be discussed regarding risk assessment in subsequent sections.

D. Quantitative analysis. The principles of image analysis rely on visual inspection, which is fraught with observer variability.

1. Computer-aided analysis of planar data involves comparison of regional radionuclide activity on stress and rest images; count discordance coincides with reversibility. **SPECT** data are quantitatively analyzed by means of comparing count densities on short-axis images (displayed as a polar map) with normal age- and sex-adjusted count profiles. Although they improve sensitivity, these methods are **used in concert with visual analysis**.

2. PET imaging, although evaluated in large part in a visual manner, also possesses great clinical utility with the application of **quantitative analysis of myocardial perfusion, myocardial blood flow, and coronary flow reserve.** Moreover, significant advances have been made in the ability to quantify ***absolute***—and not just relative—blood flow in different coronary vascular territories using PET imaging. On the basis of analysis of baseline blood flow and flow during vasodilator stress, this technique is useful in revealing functionally important coronary lesions even in the presence of multivessel coronary disease.

a. The administration of adenosine, dipyridamole, or regadenoson should induce at least a twofold to threefold increase in coronary blood flow over baseline in a normal coronary vascular bed. This "flow reserve" is not present in the setting of functionally significant epicardial coronary artery stenosis supplying this myocardial bed (as discussed earlier in the chapter). Thus, relative differences in myocardial perfusion during hyperemia (which may not be appreciated on visual inspection) may be more precisely demonstrated with quantitative analysis of flow reserve.

FIGURE 46.2 Standard tomographic projections and myocardial segments.

b. Furthermore, the ability to quantitate absolute myocardial blood flow regionally and globally may help surmount the difficulty in noninvasively diagnosing CAD in the setting of "balanced ischemia" from severe left-main or triple-vessel CAD.

X.CLINICAL APPLICATIONS

A. Coronary artery disease

1. Detection of CAD. The ability to detect CAD in a noninvasive manner offers numerous additional applications in risk stratification, prognosis, and imaging of acute infarction.

Sensitivity and specificity. Since the introduction of thallium 201 imaging in 1975, the utility of perfusion agents in the diagnosis of CAD has been well established. Quantitative planar imaging and SPECT demonstrate 90% or greater sensitivity.

a. **Sensitivity** is affected by the number of vessels involved. Single-vessel disease is most likely to produce a false-negative finding. Multivessel CAD rarely produces a normal perfusion scan result. The **specificity** of planar imaging is 83% and that of SPECT is ~70%.

b. In general, radionuclide imaging is best used to evaluate a population at intermediate risk for CAD. The choice of radionuclide agent seemingly has little effect on the accuracy of these techniques.

c. The introduction of **PET**, however, has brought with it **advanced diagnostic accuracy**, with approximately 10% to 15% improvement over SPECT.

1. 1 Causes of **false-positive** perfusion study results include attenuation defect, technical inadequacies, coronary vasospasm, anomalous coronary circulation, cardiomyopathy, conduction defects such as left bundle branch block, and recanalization of a thrombosed coronary artery.
2. 2 Causes of **false-negative** perfusion study results include a submaximal exercise stress test, anti-ischemic medical therapy, collateral or overlap circulation, inaccurate interpretation of perfusion images or angiograms, acquisition of suboptimal images, presence of balanced coronary stenoses, and delay in stress imaging.

2. **Risk stratification.** In addition to indicators of higher risk taken from perfusion images, such as increased lung uptake, determinants in the assessment of risk are as follows.

a. **Presence of reversible as opposed to fixed defects** is associated with greater likelihood of cardiac events related to acute coronary syndrome at follow-up evaluation. This relation has clinical utility in a number of settings, including risk stratification after MI or in the preoperative setting. In one study involving patients who had had MI without complications, patients with single, fixed defects on thallium 201 images had a 6% cardiac event rate, compared with a rate of 51% for those with thallium 201 scans that indicated high risk of such an event.

b. Radionuclide **imaging abnormalities** have been identified as **independent predictors of subsequent infarction or death**. In general, the extent and severity of abnormal segments identified on nuclear images can be seen as inversely proportional to survival rate. Normal findings on a nuclear perfusion study, however, suggest an excellent prognosis, with a yearly mortality rate <1% (in patients with a normal ejection fraction). The application of such prognostic information to the care of patients preparing for noncardiac operations reflects significantly on the patient's surgical risk and has an established role in preoperative evaluation and clearance. For this population, evidence of ischemia on perfusion images portends a higher risk of a perioperative cardiac event.

3. Myocardial perfusion imaging may aid in the diagnosis and risk stratification of patients with **acute coronary syndromes**.

a. Patients with **chest pain of ill-defined origin** can be given an injection at rest of thallium 201 or technetium 99m. In the presence of true ischemia, a rest defect may be documented and insight into regional distribution of ischemia and extent of myocardium involved is gained. The **absence of any perfusion defect with ongoing chest pain makes a diagnosis of angina less likely**.

In the setting of **thrombolysis**, imaging with technetium 99m can provide important information about reperfusion or lack thereof. Injection of technetium 99m before initiation of thrombolysis captures a picture of hypoperfusion, which can, because of the extensive half-life, be imaged at a later time. Subsequent injections reveal the status of perfusion as the period after thrombolysis proceeds (i.e., persistent, large defect that represents failed reperfusion). Such applications in the setting of thrombolysis and in acute coronary syndromes have limited clinical utility because of the logistics of staffing and availability of radiopharmaceuticals.

B. **Assessment of ventricular function.** In addition to its use in perfusion analysis in CAD, radionuclide imaging can establish cardiac performance. Radionuclide-based assessment of ventricular function includes first-pass radionuclide angiocardiography and gated blood pool imaging.

1. **First-pass radionuclide angiocardiography** involves injection of a radionuclide and analysis as the agent passes through the central circulation.

a. Technetium 99m–labeled agents are typically administered in bolus form, and scintigraphic data are recorded for 15 to 30 seconds after injection. Multicrystal cameras oriented in a straight anterior projection are used for detection of count rates.

b. This method of ventricular function analysis is more useful in evaluating **RV function** than is gated blood imaging. In patients with **severe LV dysfunction**, transit time through the heart may be slowed, thus proximal venous access and rapid administration may be necessary.

2. **MUGA scans** are an example of gated blood pool imaging or radionuclide angiography. This relies on ECG gating to correlate multiple individual images of the cardiac blood pool to specific phases of the cardiac cycle.

a. For the in vivo method, the patient is administered intravenous stannous chloride. Then, a 2- to 3-mL sample of the patient's blood is retrieved and bounded with technetium 99m pertechnetate. This sample is then reinjected into the patient intravenously. The stannous ions reduce the technetium, so they will not leak out of the tagged cells. The in vitro method binds the patient's blood with the stannous ion and technetium prior to reinjection into the patient.

b. A single-crystal γ-camera is used in the LAO, AP, left lateral, and sometimes left posterior oblique projections to obtain serial static images of the cardiac blood pool gated to the R–R interval.

c. Because multiple cardiac cycles are averaged to obtain the final images, this technique is not optimal for evaluating regional wall motion. For many years, though, MUGA was considered a "gold standard" technique for assessment of overall LV ejection fraction. Radionuclide angiography remains a well-validated and highly reproducible method of assessment of overall LV ejection fraction (and importantly, retains this quality especially well at low ejection fractions). The use of this technique is diminishing in the current era of echocardiography and cardiac MRI.

3. **ECG-gated perfusion imaging.** Perfusion imaging with technetium 99m–labeled tracers during standard nuclear stress testing produces gated images where LV volumes and ejection fraction may be calculated. The standard injection of 20 to 30 mCi of technetium 99m allows evaluation of **perfusion and function in a single study**.

a. The *greatest* utility of ECG-gated perfusion imaging may be in elucidating perceived artifacts on perfusion images. For example, if a region has a perceived fixed perfusion defect, yet wall motion is normal in the same region, artifact becomes a more likely consideration as the cause of the filling defect. However, wall motion abnormalities are typically not seen in ischemic segments after exercise nuclear testing because of the delay between peak stress and image acquisition.

b. Comparison of this method with two-dimensional echocardiography in the evaluation of regional wall motion has shown good correlation between the two.

C. **Cardiac amyloidosis.** Nuclear scintigraphy with 99m technetium pyrophosphate is used in the diagnosis of cardiac amyloidosis. Historically, this agent was used in cardiac disease after MI to assess infarct size, but has been repurposed for use in cardiac amyloidosis. Technetium pyrophosphate is a bone tracer that binds to the calcium in

amyloid deposits, particularly in transthyretin amyloidosis; uptake is usually absent in light chain amyloid heart disease. Thus, this test is commonly used to diagnose transthyretin amyloidosis and differentiate it from light chain disease. Uptake is graded based upon visual assessment as well as comparing uptake in the heart versus the contralateral lung on planar images.

D. Myocardial innervation imaging. Radiotracer analogues of sympathetic nervous system factors have been used to assess myocardial innervation and predict risk in certain conditions. **Iodine 123 meta-iodobenzylguanidine (MIBG)** is a radiotracer which acts as a false neurotransmitter analogue of norepinephrine and is the most frequently used radiotracer for this indication. It is utilized in both adrenal and cardiac imaging, and images are acquired using standard techniques with planar followed by SPECT images.

1. **Heart failure**: In clinical trials, decreasing MIBG uptake was found to be associated with worsening disease status and mortality. The most striking finding was the greater than 99% negative predictive value; patients with normal uptake had very few cardiac events. This tracer may be able to identify a subset of patients who do not meet ICD criteria who are at high risk for cardiac events. In addition, MIBG uptake was shown to improve after heart failure medical therapy.

XI. POSITRON EMISSION TOMOGRAPHY.

PET has bolstered the evaluation of CAD by nuclear imaging techniques, both by improving blood flow imaging and by allowing evaluation of metabolic activity. Positron imaging agents can be divided into blood flow tracers and metabolic radiopharmaceuticals.

A. Perfusion (blood flow) tracers. A number of radiopharmaceuticals exist for the assessment of myocardial blood flow. They can be produced by a cyclotron or generator.

1. **Rubidium 82**, the most readily used blood flow tracer, can be generated on-site without the use of a cyclotron. Much like thallium 201, rubidium 82 is a potassium analogue that is actively transported into myocytes through the Na–K pump. **Uptake into myocardium** is proportionate to regional blood flow. Approximately 65% of the radiotracer is extracted at first pass. Because of a short half-life (76 seconds), rubidium 82–based imaging protocols can be used to assess myocardial blood flow rapidly (within 1 hour). However, the short half-life also precludes exercise stress PET imaging with this tracer.

2. Other perfusion agents include the cyclotron-produced **nitrogen 13 ammonia** (half-life 10 minutes) and **oxygen 15 water** (half-life 123 seconds). Image quality with **oxygen 15 water** is poor and requires extensive processing to subtract the blood pool, thus is rarely used in current practice. Rb 82 and ^{13}N-ammonia are the perfusion tracers that are used in clinical practice, with Rb 82 carrying the distinct advantage of requiring only a generator instead of a cyclotron. The image quality of ^{13}N-ammonia is excellent, although the impracticality of cyclotron production in most facilities is a limiting factor for this agent. For those facilities capable of ^{13}N-ammonia generation, however, it has the "upside" of a longer half-life than rubidium 82; thus, exercise stress cardiac PET imaging could be performed if desired.

B. Metabolic radiopharmaceuticals. Metabolic imaging with PET depends on the use of radiolabeled substrates of cardiac metabolism, largely in the form of [^{18}F]fluoro-2-deoxyglucose (FDG), carbon 11 palmitate, and carbon 11 acetate.

1. **FDG** is a glucose analogue used by ischemic and hibernating myocardium because of a transition to alternative fuel sources in the hypoxic state. There is diminished oxidation of long-chain fatty acids and increased use of glucose as a secondary fuel source during ischemia or hibernation. FDG is phosphorylated to FDG-6-phosphate after transport across the cell membrane. FDG imaging therefore reflects myocardial use of exogenous glucose, and FDG is a widely used metabolic radiopharmaceutical. It has a half-life of 1.83 hours, which means it can be ordered on a daily basis by institutions that do not have an on-site cyclotron—making it the most commonly used metabolic PET imaging agent.
2. [^{11}C]Palmitate is taken up by myocytes, converted to acyl CoA, and relegated to triglyceride stores or β-oxidized to produce [^{11}C]carbon dioxide. The release of this product of β-oxidation is reflective of long-chain fatty acid oxidation in myocardium.
3. [^{11}C]Acetate is metabolized to [^{11}C]carbon dioxide after entering the tricarboxylic acid cycle. Measuring the production of [^{11}C]carbon dioxide in this setting correlates with myocardial oxygen consumption.

C. Protocols. Image acquisition with PET is similar to that with SPECT in that tomographic images are obtained in short-axis, horizontal long-axis (sagittal), and vertical long-axis (coronal) views. A positron camera consists of an array of crystals arranged in a circle. Unlike in SPECT, the camera remains stationary in PET.

1. The heart is localized with the patient's arms extended above the head. An **attenuation scan** is performed that allows the density of the surrounding thoracic structures to be subtracted to leave only cardiac count activity. This performance of attenuation correction avoids noncardiac interference which adds a great deal to the accuracy of PET.
2. After the attenuation scan, the **positron-emitting radiopharmaceutical is injected**, and **images are obtained** 2 to 5 minutes later. As mentioned earlier in the chapter, two photons are created by the annihilation of the emitted positron colliding with the nearest electron it meets in the tissue surrounding it. These two photons travel *exactly 180° apart* while the patient is lying in the circular scanner. This is an important concept because it means there is **no need for collimation**. The detector/analyzer merely has to "accept" the signal it receives only if a simultaneous signal strikes the detector directly across from it in the scanner. This *dramatically* improves the signal-to-noise ratio that can be achieved during imaging.
3. Metabolic imaging can be undertaken after perfusion imaging with the administration of 5 to 10 mCi of FDG. Tomographic images are typically obtained 30 to 50 minutes after FDG injection.

D. Patterns of perfusion and metabolic imaging. Specific patterns of perfusion and metabolic imaging are identifiable. For example, **normal flow–normal FDG (match)** indicates normal perfusion and normal metabolic activity. **Reduced flow with normal or increased FDG ("flow–metabolism mismatch")** demonstrates viability (i.e., hibernating myocardium). **Reduced flow–reduced FDG** identifies scar tissue.

E. Clinical applications

1. **Diagnosis of CAD.** Flow imaging with PET is highly sensitive and highly specific for the detection of coronary stenosis, approaching 93% for both.

a. Higher-energy photons (511 keV), higher count densities, shorter half-life, and "built-in" attenuation correction place PET substantially ahead of SPECT in the accurate detection of CAD.

b. As mentioned before, the ability to quantitate absolute blood flow regionally and globally may help improve the diagnosis of coronary ischemia in the setting of severe multivessel disease and balanced ischemia.

2. **Assessment of myocardial viability** (see Chapter 50). The use of **PET with metabolic radiotracers is the standard for identifying viable myocardium.** The presence of a flow–metabolism mismatch, which indicates underperfusion in the presence of metabolically active myocytes, suggests hibernating myocardium. Revascularization of these zones as identified with PET has been shown to result in improvement in wall motion. This utility of nuclear imaging has found increasing application in the selection of patients for revascularization who have ischemic cardiomyopathy and heart failure with low ejection fraction.

3. **Cardiac sarcoidosis.** FDG-PET imaging is useful in detection and prognosis in patients suspected of having cardiac sarcoidosis. Normal myocardium utilizes glucose and fatty acids for metabolism. Under fasting conditions, myocardial cells shift to utilizing predominantly fatty acids. Inflammatory cells in cardiac sarcoidosis utilize glucose because of high metabolic demands, even during fasting.

a. Sarcoidosis nuclear protocols vary among institutions, but attempt to **minimize physiologic glucose uptake** in normal myocardial tissue. Patients are advised to prepare for the exam with a prolonged fast (12 to 18 hours) and high-protein, low-carbohydrate diet the day before the exam. Rubidium 82 is injected at rest to evaluate for perfusion defects. FDG is injected and a prolonged delay is utilized (usually 60 minutes) prior to image acquisition.

b. FDG-PET demonstrating areas of decreased perfusion with increased FDG in the setting of non-obstructive CAD is suggestive of active cardiac sarcoidosis.

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CHAPTER 47

Stress Echocardiography

Jimmy L. Kerrigan

I. INTRODUCTION. Stress echocardiography (SE) is an **effective method of evaluating for myocardial ischemia**, based on the detection of **stress-induced regional wall motion abnormalities** (WMAs). Stressors include exercise, pharmacologic agents, and pacing. SE is used to **screen for coronary artery disease** (CAD), and it can help **identify the coronary vessels involved**. The accuracy of SE in the detection of significant coronary artery stenosis is 80% to 90%, which is superior to that of exercise electrocardiographic testing and comparable to that of nuclear stress imaging. In patients with left ventricular (LV) dysfunction and documented CAD, SE can **differentiate viable myocardium from scarred myocardium**, which may help predict whether LV function will improve after revascularization. As a diagnostic test for CAD, **SE is safe and relatively inexpensive** and **can be rapidly performed**. However, interpretation of SE images remains primarily subjective and requires a considerable learning curve. SE can also be used to **assess the severity of valvular disease, hypertrophic cardiomyopathy, and exercise-induced pulmonary hypertension**. In addition, it provides important prognostic information after myocardial infarction (MI) and prior to noncardiac surgery.

II. PATHOPHYSIOLOGY

A. Exercise stress testing. Myocardial ischemia results from a mismatch between oxygen supply and demand. The ischemic cascade is illustrated in Figure 47.1. Echocardiography detects ischemia by identifying new or worsening WMAs earlier in the cascade than is detected by the electrocardiogram (ECG) or the onset of symptoms but usually after the onset of worsening diastolic function. Exercise can be performed with a treadmill or a bicycle.

B. Pharmacologic stress testing. In patients who cannot exercise, pharmacologic stressors can be used. These drugs are sympathomimetic agents or vasodilators.

1. Sympathomimetic agents. Myocardial oxygen demand is determined by contractility (inotropy), heart rate (chronotropy), and wall stress (preload + afterload). Sympathomimetic agents produce stress by causing an **increase in myocardial oxygen demand through increased inotropy, chronotropy, and blood pressure (BP) (afterload)**. Although a number of agents have been evaluated in combination with echocardiography, **dobutamine** is most widely used. Low-dose dobutamine has positive inotropic effects mediated through cardiac α_1- and β_1-receptors. At higher doses, it has positive chronotropic effects mediated through β_2-receptors. The plasma half-life of dobutamine is 2 to 3 minutes. The normal response to dobutamine is an increase in heart rate and hyperdynamic

wall motion, with only minimal effect on end-diastolic LV volume. It can be **combined with atropine** to achieve the usual target of at least 85% of age-predicted maximum heart rate (APMHR).

2. A **vasodilator stress test** is performed with **dipyridamole** or **adenosine** infusion. These agents result in perfusion abnormalities by causing blood to be preferentially shunted away from myocardial segments supplied by stenotic coronary arteries (i.e., coronary steal) and into more normal coronary vessels. This may lead to WMA in the perfusion territory of the stenotic coronary artery that is seen on echocardiography. These agents are less commonly used for SE. Adenosine has fewer side effects than dipyridamole, owing to a shorter half-life. However, because of the shorter duration of action of adenosine, the echocardiographic findings tend to be less pronounced and of shorter duration, resulting in a lower sensitivity.

FIGURE 47.1 Ischemic cascade. ECG, electrocardiogram; PET, positron emission tomography.

3. **The American Society of Echocardiography (ASE) guidelines recommend dobutamine as the first-line agent for pharmacologic SE**. In addition, much of the data for preoperative risk stratification and viability assessment using SE were derived from pharmacologic studies using dobutamine.

C. **Atrial pacing.** Tachycardia induced by atrial pacing is an alternative to pharmacologic testing in patients that cannot exercise and in whom pharmacologic agents are contraindicated. In patients with a permanent pacemaker, stress is achieved by increasing the pacing rate until the target heart rate is reached. Transvenous and transesophageal pacing are options for patients without a permanent pacemaker but are rarely used in practice.

III. INDICATIONS AND CHOICE OF STRESSOR

A. The **indications and contraindications** for SE testing are similar to those used for exercise electrocardiographic stress testing. The addition of an imaging modality improves the sensitivity and specificity of exercise electrocardiographic stress testing. Table 47.1 lists factors that may limit the sensitivity of electrocardiographic stress testing to detect CAD; patients with these factors would benefit from a stress test utilizing an imaging modality (i.e., echocardiography, nuclear scintigraphy, or positron emission tomography [PET]).

B. **Additional contraindications** to SE occur **with pharmacologic stress** and depend on the underlying pharmacologic stressor. Patients with severe bronchospastic obstructive lung disease or high-grade atrioventricular (AV) block should avoid dipyridamole and adenosine. Patients with unstable ventricular arrhythmias should avoid dobutamine infusion. **Relative contraindications to SE** include unstable angina, severe baseline hypertension, uncontrolled arrhythmias, mobile LV thrombus, critical symptomatic aortic stenosis (AS), and decompensated heart failure.

TABLE 47.1 Factors Limiting the Sensitivity of Stress Electrocardiography to Detect Coronary

Left bundle branch block or other intraventricular conduction delay abnormalities
Paced rhythms

TABLE 47.1 Factors Limiting the Sensitivity of Stress Electrocardiography to Detect Coronary
Abnormal ST-segments at baseline:
Digitalis effect
Electrical left ventricular hypertrophy
Previous evidence of myocardial infarction
Nonspecific, abnormal ST-segment changes
Women (higher rate of false-positive ST-segment changes)
Left ventricular hypertrophy (even with normal-appearing electrocardiogram)

C. Exercise stress is preferred over nonexercise stress because it more closely reproduces daily activity and is more sensitive in the detection of ischemia, provided the patient is able to achieve an adequate level of stress. No single **exercise modality** has been shown to have superior sensitivity, although the **treadmill** is more widely accepted among patients and physicians. **Bicycle ergometry** can be performed in the upright and supine positions. Images with treadmill stress testing must be obtained after exercise, whereas images may be obtained at peak exercise with bicycle ergometry while the patient continues to exercise. The sensitivity of treadmill testing to detect ischemia is reduced if images are not rapidly obtained (within 90 seconds) after exercise. However, the treadmill usually results in a greater level of stress than is associated with bicycle ergometry, which is more dependent on patient effort.

D. Up to **30% of patients referred for exercise echocardiography may not be able to achieve an adequate level of exercise stress** because of peripheral vascular disease, chronic obstructive pulmonary disease, or musculoskeletal problems. **Pharmacologic stress testing is usually indicated** in these patients.

IV.METHODOLOGY

A. Patient preparation

1. Patients should avoid heavy food intake for several hours before the test.
2. Rate-slowing agents (particularly β-blockers) blunt the normal heart rate response to exercise and may limit the ability of the patient to achieve at least 85% of the APMHR. This may reduce the sensitivity of the test results. If possible, these agents should be withheld before the stress test, unless the aim of the test is to evaluate their effectiveness in preventing exercise-induced ischemia.
3. The **standard connections for a 12-lead ECG** may be used with minor modifications to allow imaging in the parasternal and apical windows without affecting the accuracy of the exercise electrocardiographic testing results.

B. Equipment. All SE studies are conducted with **exercise electrocardiographic testing and standard hemodynamic monitoring equipment**. An SE software package on the echocardiographic machine is necessary to acquire digital images and to allow side-by-side comparison of prestress images with peak stress or post–peak stress images. Resuscitation equipment and a defibrillator should be readily available.

C. Performing the test

1. **Exercise SE.** Regardless of the exercise modality, a complete **baseline** echocardiographic scan is obtained for all patients. Resting images are obtained in the parasternal long- and short-axis and apical two- and four-chamber views and stored digitally. An apical long-axis view may be substituted for a parasternal long-axis view if the parasternal images are suboptimal. If endocardial definition is suboptimal, intravenous ultrasound contrast should be given to optimize the images.

a. **Treadmill exercise** is performed with standard protocols according to the functional status of the patient. Exercise is continued until at least 85% of the APMHR is reached, but it is preferably continued to the level of maximum exertion to maximize test sensitivity. APMHR equals 220 minus the patient's age. **Post–peak stress images** are obtained as quickly as possible (in the left lateral decubitus position) after the patient transfers from the treadmill to the imaging table. Stress images in the same views as the baseline study are stored digitally and recorded on videotape. All post–peak stress images should be **obtained within 90 seconds of completing exercise** to maximize test sensitivity.

b. During **upright bicycle echocardiography**, baseline images are obtained in the standard left lateral position and are repeated with the patient in the upright position on the cycle ergometer. Adequate parasternal images may be recorded by having the patient lean forward. These images are recorded and digitized to allow comparable windows for the rest and peak stress images. Cycle ergometry is started at a workload of 25 W and increased by 25 to 50 W every 2 to 3 minutes until the patient reaches his or her level of perceived maximal effort. During upright bicycle echocardiography, **images are obtained and digitized at rest, before peak, at peak, and after peak exercise**.

c. With **supine bicycle exercise**, the entire study is performed while the patient is tilted 30° in the left lateral decubitus position, and images are obtained and digitized **at rest, before peak, at peak, and after exercise**. This exercise modality is not widely used.

d. **Study end points** for exercise SE include **target heart rate** (85% APMHR), **severe electrocardiographic ischemia** (ST-segment depression > 5 mm), **intolerable symptoms** (chest pain and dyspnea), **severe hypertension** (systolic BP > 220 mm Hg or diastolic BP > 110 mm Hg), **hypotension** (systolic BP < 90 mm Hg or a fall in systolic BP > 20 mm Hg from baseline), **ventricular tachycardia** or **sustained supraventricular tachycardia,** and the **development of new WMAs in at least two contiguous segments**.

2. **Pharmacologic SE**

a. **Dobutamine SE**

1. **1 Dobutamine infusion** is started at 10 µg/kg/min and increased every 3 minutes to 20, 30, and 40 µg/kg/min. If the patient has not reached 85% of APMHR by the end of the 40 µg/kg/min dose, a 3-minute dosage of 50 µg/kg/min may be used. Infusion is begun at lower doses (5 µg/kg/min) if baseline LV function is abnormal and myocardial viability is being sought or if assessment of valvular lesions is being pursued. Images are digitized at rest and at low dosage (5 to 10 µg/kg/min), pre–peak dosage (30 µg/kg/min), and peak dosage.
2. **2 Atropine** is used as needed to reach target heart rate >85% of APMHR if dobutamine alone is not effective. Atropine (0.25 to 0.5 mg) is given intravenously every minute, starting at the 40 µg/kg/min dobutamine dose level and continuing until an end point is reached or a total dose of 2 mg is given. Atropine should be used with caution in patients that have glaucoma or benign

prostatic hypertrophy. Isometric handgrip may be performed at the peak infusion rate to help achieve target heart rate, as well.

3. **3 Study end points** for dobutamine SE are the same as those used for exercise SE. If 85% APMHR has been achieved without any other end points, it is preferable to complete the protocol to the end of the 40 µg/kg/min infusion to increase the sensitivity of the test.
4. **4 Side effects.** The most serious potential side effect of dobutamine is arrhythmia provocation. However, serious complications (e.g., arrhythmia, MI, and cardiac arrest) are rare, occurring in about 0.3% of studies in a large series of >5,000 patients. Less serious side effects include tremor, nervousness, and marked hypertensive and hypotensive responses. The most common minor complication is hypotension, which usually responds to supportive therapy including intravenous fluids. A hypotensive response with dobutamine may be caused by ischemia and dynamic outflow tract obstruction or may result from the vasodilatory effect of dobutamine in combination with a small hyperdynamic LV and a low stroke volume.
5. **5 If angina or severe side effects develop**, the effects of dobutamine may be **reversed with intravenous β-blockade** (0.5 to 1 mg/kg esmolol given over 1 minute or 2 to 5 mg/kg metoprolol given every 2 to 5 minutes). Like dobutamine, esmolol has a very short half-life and, therefore, may be the preferred agent.

b. Dipyridamole or adenosine SE

1. **1** Patients with hypotension, AV block, or a history of severe bronchospasm **should not undergo** testing with these agents.
2. **2** Different protocols of **dipyridamole infusion** have been studied. The protocol recommended by the ASE is a low-dose, two-stage infusion. The first stage begins at 0.56 mg/kg dipyridamole over 4 minutes; if no adverse effect or clinical end points are reached, an additional 0.28 mg/kg is infused over 2 minutes. **A high-dose** regimen of 0.84 mg/kg given over 10 minutes has been developed to improve the sensitivity of the test relative to low-dose protocols.
3. **3 Adenosine** is given as a continuous infusion because of its very short half-life. A typical protocol starts at a low dose of 80 µg/kg/min and is increased every 3 minutes by 30 µg/kg/min to a peak dose of 170 to 200 µg/kg/min.
4. **4 Regadenoson** is an adenosine receptor agonist with a 2- to 3-minute half-life, as compared with adenosine's 30-second half-life. Regadenoson is administered as one 0.4-mg dose over 10 seconds.
5. **5 Study end points** for dipyridamole or adenosine SE are similar to those used for exercise SE. A notable exception is that patients are not stressed until the APMHR is achieved. Additional end points include third-degree AV block, severe hypotension, and intolerable side effects (e.g., bronchospasm). Symptoms usually start to resolve within 60 seconds after medication administration.
6. **6 If hypotension, bradycardia, or bronchospasm occurs**, the effects of dipyridamole, adenosine, and regadenoson can be **reversed with intravenous aminophylline** 50 mg over 60 seconds.

D. Imaging techniques. Modern technology allows digital image acquisition of multiple cardiac cycles and side-by-side comparison in a split screen display, enabling easy comparison of regional wall motion at rest and peak stress or after stress. Detailed frame-by-frame evaluation of wall thickening or excursion is possible, which helps in the evaluation of regional myocardial function. Obesity and lung disease remain the primary reasons for poor-quality images. **Harmonic imaging** has improved endocardial definition, which can be further optimized with **microbubble contrast agents**.

1. **Contrast echocardiography.** Microbubble contrast agents provide **improved echocardiographic resolution** and allow **real-time assessment of intracardiac blood flow**. These agents are helpful when baseline SE images are suboptimal.

a. **Intravenous agitated saline** improves visualization of the right atrium and ventricle and enables visualization of intracardiac shunts. However, intravenous agitated saline is not able to cross the pulmonary circulation and opacify the left ventricle.

b. **Second-generation microbubble contrast agents,** such as **Optison** and **Definity** incorporate perfluoropropane gas encased in an albumin-based or phospholipid shell, are more durable and are able to cross the pulmonary circulation and opacify the left ventricle.

c. **These agents are well tolerated and have a low complication rate**. **Absolute contraindications to administration include previous hypersensitivity reaction and fixed right-to-left, bidirectional, or transient right-to-left cardiac shunts.** Intra-arterial injection is contraindicated. Administration is relatively contraindicated in patients who are pregnant or nursing, although data are limited in these populations, and guidelines indicate that contrast should be given if needed.

2. **Real-time three-dimensional (3D) echocardiography.** Significant advances have been made in 3D data acquisition without the need for off-line reconstruction. 3D imaging may shorten the acquisition period of postexercise images or peak exercise images, allowing improved sensitivity and minimizing the technical strains imposed on the technologist obtaining the images. Limitations include lower spatial resolution and lower frame rates; at this time, 3D SE is not routine in clinical use and remains under investigation.

V.IMAGE INTERPRETATION

A. Qualitative versus quantitative approach

1. **Interpretation of SE findings is predominantly qualitative.** Visual assessment of LV wall thickening and motion remains the standard method of interpretation of SE but is **subject to interobserver and interinstitutional variability**. Suggestions to optimize interpretation of SE images are outlined in Table 47.2. Each myocardial segment is visually assessed for wall thickening, rather than just wall motion, which may be influenced by myocardial tethering and translation. LV wall motion normally becomes hyperdynamic with stress. Worsening of WMAs or the development of new ones is the hallmark of stress-induced myocardial ischemia. SE responses and interpretation are summarized in Table 47.3.

2. **Quantitative methods** of analysis improve the reproducibility of interpretation and enhance the detection of CAD, particularly by less experienced physicians. However, at this time, **the ASE recommends further validation and simplification of quantitative analysis methods before they can be recommended for routine use**. Examples of quantitative analysis methods include Doppler assessment of global systolic and diastolic function; automated endocardial border detection using integrated backscatter; and tissue Doppler assessment of myocardial displacement, velocity, strain, and strain rate.

a. **Tissue Doppler assessment** along the long axis using apical views allows quantification of regional longitudinal myocardial function. Tissue Doppler is thought to be a potentially sensitive marker of subendocardial ischemia because abnormalities in regional contraction occur earlier in longitudinal than radial segments.

b. **Strain rate** is a measure of the speed or velocity of regional myocardial contraction (time from QRS to the onset of regional myocardial relaxation). During

dobutamine SE, strain rate increases (interval of time from QRS to myocardial relaxation decreases) in normal hearts and is reduced in areas of myocardial ischemia. The optimal cutoff for strain rate that gives the best sensitivity and specificity has been reported to be an increment of <0.6 per second. Strain rate imaging is a reliable predictor of coronary stenosis, is **more specific** than visually assessed wall motion scoring, and may allow readers to detect intermediate severity coronary stenosis that produces only subtle WMAs. It may be **difficult to acquire technically adequate images at rest and especially at higher heart rates** following stress, which limits its applicability.

TABLE 47.2 Suggestions to Optimize Interpretation of Stress Echocardiographic Images

1. Ensure that prestress and poststress images are comparable views
2. Ensure that the apex is not foreshortened, especially in two-chamber views
3. True two-chamber views should not show any of the right ventricle
4. Use ultrasound microbubble contrast agents when resting images are suboptimal
5. Check that digital images are timed to begin at systole. If digital clips include diastole, there i positive wall motion abnormality
6. Check the heart rate for each poststress image. If images are obtained after the heart rate has r test will be reduced
7. Compare the wall motion of individual segments from rest to stress in the four-screen displ compare segments in the poststress images to identify differences in contraction and in the de
8. Confirm any wall motion abnormality in a second view if possible
9. Avoid overcalling ischemia in the basal inferior or basal septal segments
10. Avoid calling a new wall motion abnormality if it is limited to only one myocardial segment; t contiguous segments

B. EF, ejection fraction; LV, left ventricular; WMA, wall motion abnormality.

TABLE 47.3 Stress Echocardiographic Responses and Interpretation

Resting or Baseline Function	Response to Low-Dose Pharmacologic Stress	Peak Stress and Poststress Function
Normal	Normal	Hyperdynamic
Normal	Normal or new WMA	New WMA or lack of hyperdynamic resp or decreased EF (with exercise only)
WMA	No change	No change
WMA	Improved	Decreased (biphasic response)
WMA	No change	Improved

C. 17-Segment model. Regional wall motion is assessed using a 17-segment model (Fig. 47.2), with results geographically represented on a circumferential polar plot (Fig. 47.3).

1. The individual **myocardial segments can be assigned to coronary artery territories**, as illustrated in Figure 47.4. Of note, this approach is not always correct because of the anatomic variability. For instance, the left anterior descending coronary artery does not always supply the entire apex and the posterior wall is not always supplied by the left circumflex coronary artery. The system may also be problematic if multivessel disease is present, in which case the territory with the most ischemia is identified and less severe lesions may not be apparent.
2. Wall motion is **subjectively graded** as normal, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic and may be assigned a wall motion score of 1 to 4 (normal, hypokinetic, akinetic, or dyskinetic, respectively). Each myocardial segment in the rest and stress images is graded in this manner.

D. Exercise SE

1. A **normal response** to exercise stress includes a global increase in contractility, the development of hyperdynamic wall motion, and a gradual rise in the heart rate. This is manifested by increased wall thickness and increased endocardial excursion with stress.
2. **Resting WMAs** usually indicate prior MI, although regional variability may be seen in diffuse myopathic processes. Resting WMAs may be defined as hypokinetic, akinetic, or dyskinetic. Akinesia and dyskinesia usually indicate transmural infarction, whereas hypokinetic segments may be partially infarcted or viable.
3. An **abnormal response to exercise is defined by the development or worsening of regional myocardial function**. Regional myocardial dysfunction, as **manifested by decreased endocardial excursion and wall thickening**, is **specific for myocardial ischemia**. Decreased excursion alone is less specific and can occur with conduction abnormalities, with paced rhythms, and in the normal basal inferior myocardial segments.
4. **Adjunctive diagnostic criteria** for a positive SE examination include **LV cavity dilation, a decrease in global systolic function, worsening diastolic function, and new or worsening mitral regurgitation (MR)**. However, these adjunctive diagnostic criteria are **more specific for detecting severe CAD and may not be sensitive** for detecting the presence of mild or moderate CAD.

FIGURE 47.2 Diagram of vertical long-axis, horizontal long-axis, and short-axis planes showing the name, location, and anatomic landmarks for selection of the basal (tips of the mitral valve leaflets), mid-cavity (papillary muscles), and apical (beyond papillary muscles but before cavity ends) short-axis slices for the 17-segment system. (Reprinted with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation.* 2002;105(4):539–542.)

5. **False-positive findings** may occur with left bundle branch block (septal WMA) and right ventricular (RV) pacing (apical WMA). A pathologic hypertensive response

to exercise may also cause LV dilation and systolic dysfunction as can afterload mismatch in the setting of severe valvular lesions such as AS, MR, or aortic regurgitation.

6. **False-negative findings** may occur with a delay in capturing postexercise images, low workload, or inadequate heart rate response (i.e., with inadequate stress or the presence of β-blockers). Additional causes of false-positive and false-negative findings are outlined in Table 47.4.

FIGURE 47.3 Display, on a circumferential polar plot, of the 17 myocardial segments and the recommended nomenclature for tomographic imaging of the heart. (Reprinted with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105(4):539–542.)

FIGURE 47.4 Assignment of the 17 myocardial segments to coronary artery territories. LAD, left anterior descending; LCX, left circumflex coronary artery; RCA, right coronary artery. (Reprinted with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105(4):539–542.)

E. **Pharmacologic SE.** With only a few exceptions, the principles of interpretation of pharmacologic SE findings are similar to those used for exercise echocardiography.

TABLE 47.4 False-Positive and False-Negative Stress Echocardiographic Test Results

Causes of Incorrect Stress Echocardiographic Interpretation	Factors Reducing Specificity or Sensitivit
False-Positive Results	
LBBB, prior cardiac surgery (e.g., myectomy)	Reduced or abnormal septal excursion with
Right ventricular pacing	Apical WMA
Nonischemic cardiomyopathy	Regional WMAs (exact cause unknown)
Hypertensive response to exercise (SBP > 220 mm Hg, DBP > 110 mm Hg)	Nonischemic WMAs and/or LV dilation
Overinterpretation	Observer bias may result in a lower thresh important to be blinded
Basal inferior or septal WMA	Areas most likely to be overcalled becaus annular tethering effects
Poor image quality	
False-Negative Results	
Single-vessel disease	More likely to have subtle, rapidly resolving

TABLE 47.4 False-Positive and False-Negative Stress Echocardiographic Test Results

Inadequate level of stress (more likely with β-blockers)	Important to stress maximally; reach at lea heart rate
LV cavity obliteration (more likely to occur with dobutamine)	Makes segmental wall motion analysis difficu
Left circumflex disease	Lateral wall dropout; more likely to miss isch
Delay in capturing images after maximal stress	
Poor image quality	

F. DBP, diastolic blood pressure; LBBB, left bundle branch block; LV, left ventricular; SBP, systolic blood pressure; WMA, wall motion abnormality.

1. The **typical ischemic response to dobutamine** is characterized by normal resting wall motion and an initial **hyperdynamic response at low doses followed by a decline in function at higher doses**. Ischemia may also be identified on the basis of deterioration of normal wall motion without any transient hyperdynamic response.
2. **LV cavity dilation and a decrease in global systolic function are not considered adjunctive diagnostic criteria in dobutamine SE**. The LV cavity may not dilate, and global systolic function may improve with dobutamine despite new WMAs because of severe CAD.
3. Interpretation of results obtained from **dipyridamole or adenosine SE** requires detection of a new or worsening regional WMA during the infusion. There is only a mild increase in cardiac contractility during vasodilator stress.

G. Reproducibility. The person who interprets the images must be well trained in order to develop an acceptable level of accuracy and must interpret an adequate number of studies on a regular basis to maintain accuracy. Concordance within centers is generally good; however, concordance between different centers may be <80%, particularly with technically difficult studies and studies of patients with mild CAD.

H. Limitations. The ability to interpret stress echocardiograms is mitigated by image quality, the presence of arrhythmias, conduction abnormalities, respiratory interference from hyperventilation, and difficulty in reproducing the translational and rotational motion of the heart.

VI. DIAGNOSTIC ACCURACY. The **diagnostic accuracy of SE is superior to exercise electrocardiographic testing alone and similar to radionuclide perfusion techniques**. Reported sensitivities and specificities (using coronary arteriography as the gold standard) vary between studies, depending on the prevalence of disease in the study population, the angiographic definition of significant disease, and the criteria used for a positive test. Clinical factors such as age, cardiac risk factors, and symptoms that influence the pretest likelihood of CAD also influence sensitivity and specificity. For the overall detection of patients with CAD, **sensitivity ranges from 75% to 92%, depending on lesion severity**, and **specificity ranges from 64% to 100%**. As with other imaging methods, the sensitivity is less for the detection of single-vessel disease and greater for the detection of multivessel disease.

A. Exercise SE

1. **Comparison with exercise electrocardiographic testing.** Exercise electrocardiographic testing remains the first-line diagnostic test for CAD. However, **SE has greater diagnostic sensitivity and specificity**, which is predictable on the basis of the earlier occurrence of a systolic WMA before electrocardiographic changes or symptoms in the ischemic cascade (Fig. 47.1). Many factors limit the sensitivity of electrocardiographic testing alone to detect CAD (Table 47.1), and these subgroups should be considered for exercise electrocardiographic testing with an imaging modality.

2. **Comparison with myocardial perfusion scintigraphy**

a. Myocardial perfusion scintigraphy is based on the detection of a perfusion defect during maximal hyperemia, with reduced perfusion of areas subtended by significant coronary artery stenosis (>50% stenosis). Perfusion abnormalities occur at an earlier stage in the ischemic cascade than do systolic WMAs, and nuclear scintigraphy should, theoretically, have a higher sensitivity than SE for CAD.

b. Studies using **single-photon emission computed tomography (SPECT) myocardial perfusion scintigraphy have demonstrated a sensitivity of >90%, slightly higher than that for SE.** However, the **specificity of SE is superior to that of SPECT**, especially in patients with LV hypertrophy or left bundle branch block. The overall accuracy of SPECT and SE has been found to be similar in meta-analyses; the superior sensitivity of SPECT is balanced by the superior specificity of SE. The exception may be in women, where SE may be more accurate than SPECT, owing to less artifact from breast attenuation.

c. SE is **convenient** and **provides information on cardiac structure and function,** and **the results can be interpreted immediately**, with rapid feedback to the patient and referring physician. SE also **avoids exposure to radioactive tracers** and is substantially **less expensive than SPECT**.

d. SPECT allows for more objective interpretation, with quantification of perfusion abnormalities. It may also be slightly superior for patients on antianginal therapy when it is necessary to induce ischemia. SPECT appears to be more sensitive in the detection of single-vessel disease and may be superior in the detection of ischemia in the setting of resting WMAs, in which the recognition of worsening wall motion may be difficult. SPECT may also be superior in patients that have poor acoustic windows, for example, those with chronic obstructive pulmonary disease. **Local expertise, cost, exposure to radiation, and patient selection are all important factors in determining which imaging modality to use**.

B. Pharmacologic SE

1. **Dobutamine SE has a sensitivity ranging from 68% to 96% and a specificity of 80% to 85%**, similar to the values for exercise SE. **Vasodilator SE has a sensitivity of 52% to 92% and a specificity of 80% to 100%**. In general, the specificity of vasodilator SE is superior to that of other echocardiographic stress techniques. However, single-vessel disease is more difficult to detect with this technique.

2. **Myocardial perfusion scintigraphy.** Compared with dipyridamole SPECT, dipyridamole SE is believed to be less sensitive but more specific; however, few studies have compared the two tests in the same patients. As with exercise SE, dobutamine SE appears to be slightly less sensitive but more specific than SPECT.

VII.ASSESSMENT OF VIABILITY

A. Myocardial contractility ceases when 20% or more of the transmural thickness is ischemic or infarcted. Dobutamine SE can be used to detect **viable myocardium**, whether stunned or hibernating. **Myocardial stunning** after MI is common, and it is characterized by viable nonischemic noncontracting myocardium. Patients with **chronic ischemia** may experience **myocardial hibernation**. Hibernating myocardium is characterized by viable, chronically ischemic noncontracting myocardium.

B. Dobutamine infusion may result in augmentation of regional myocardial function predictive of recovery of function after revascularization. This is important prognostically, because revascularization of hypoperfused but viable myocardium improves survival. A contractile response to dobutamine requires that at least 50% of the myocytes in a given segment are viable.

C. Demonstration of a **biphasic response** to low-dose (5 to 10 µg/kg/min) dobutamine strongly suggests viable myocardium. A biphasic response is present when a **resting WMA improves in response to low-dose dobutamine and decreases in function at peak stress or poststress**. The initial improvement reflects recruitment of contractile reserve and hence viability. Higher doses lead to subendocardial ischemia and worsened WMA. A biphasic response predicts eventual functional recovery of the myocardium after revascularization. A uniphasic response is less predictive of recovery, and a classic ischemic response is not predictive of the recovery of resting function. Because the biphasic response is the most reliable finding, the preference is to induce ischemia whenever possible by proceeding to maximal stress (40 µg/kg/min).

D. **Myocardial wall thickness** is also an important marker of myocardial viability. When the wall thickness is **<6 mm**, there is **a low likelihood of recovery of function**.

E. **The negative predictive value of dobutamine SE for determining viability is lower than that of thallium stress-redistribution-reinjection SPECT and fluorodeoxyglucose-PET scanning**. However, **the positive predictive value is greater**. Concurrent use of β-blockers can reduce the number of viable segments detected and the sensitivity of testing.

F. **Assessment of myocardial perfusion with echocardiography.** Second-generation microbubble contrast agents are small in diameter and reliably traverse the myocardial microvasculature. The microbubbles are destroyed with ultrasound energy, and the rate of microbubble replenishment represents mean red blood cell velocity and myocardial perfusion. Although subject to extensive research, this technology has had limited utilization in clinical practice and is not used routinely in most echocardiography laboratories.

VIII.PROGNOSTIC ROLE OF SE

A. **Suspected or known chronic CAD.** The **major determinants of prognosis** in patients with chronic CAD are **LV function and the anatomic extent and severity of myocardial ischemia**. SE is an excellent modality for the evaluation of both.

1. **Negative test result.** Perhaps the most important aspect of the prognostic literature is that **a negative test result portends an extremely low risk of subsequent cardiovascular events, as evidenced by an event rate of <1% per year for the subsequent 4 to 5 years**. However, the risk is slightly higher in patients with diabetes or chronic kidney disease.

2. **Presence of ischemia.** Abnormal findings during SE indicate elevated risk for future cardiac events. Patients at intermediate risk for CAD who have abnormal SE findings have a 1-year cardiac event (i.e., MI, percutaneous coronary intervention, coronary artery bypass grafting, or death) rate of 10% to 30%. However, this information needs to be integrated with other stress data (i.e., exercise capacity, hemodynamic response to exercise, heart rate recovery, chronotropic index, Duke treadmill score, and the type and extent of WMA). Electrocardiographic changes and hypotension are relatively insensitive measures of ischemia during dobutamine SE. However, from the prognostic standpoint, the development of echocardiographic evidence of ischemia with dobutamine is analogous to its development during exercise.

3. **Presence of nonviable myocardium.** In patients with the same pretest probability of disease, those with evidence of nonviable myocardium during SE have higher rates of cardiac events than those with normal SE findings, but they have fewer events than those with evidence of ischemia during SE. Heart failure is a more common end point among the group of patients with nonviable myocardium.

B. Post–myocardial infarction. High-risk patients after acute MI are routinely identified by age, recurrent angina, LV failure, and shock. In addition, echocardiographic features predicting outcome after MI include LV ejection fraction, the extent of resting WMAs, inducible ischemia (detected as stress-induced WMA), and the amount of viable myocardium. All of these may be identified using SE, and several large studies (most with pharmacologic stressors) have gathered prognostic data using SE in patients post-MI.

C. Noncardiac surgery

1. Preoperative evaluation studies have been predominantly conducted with pharmacologic stress agents, primarily dobutamine. However, exercise SE should be considered if possible. A low ischemic threshold during stress (ischemia at heart rate < 70% APMHR) is the strongest predictor of perioperative cardiac events.

2. The predictive value of a positive test ranges from 7% to 25% for hard events (i.e., MI or death). The negative predictive value ranges from 93% to 100%. Only a few studies have compared SE and SPECT for the prediction of perioperative cardiac events. A meta-analysis concluded that the tests had comparable levels of accuracy, but the cost features weighted in favor of SE.

D. Cardiac transplantation. Transplant vasculopathy is a major cause of mortality after cardiac transplantation. SE appears to lack both sufficient sensitivity and specificity to be a viable alternative to routine angiography as a screening method for vasculopathy.

E. Reading beyond wall motion. Important prognostic information can be obtained beyond traditional wall motion analysis. Ischemic heart disease may cause subclinical **diastolic dysfunction**. **Left atrial enlargement** correlates with the chronicity and severity of diastolic dysfunction. A normal resting left atrial volume index (<28 mL/m^2) is strongly predictive of a normal stress echocardiogram. **RV dysfunction** is a significant predictor of events, independent of LV ischemia or ejection fraction.

IX.DIASTOLIC STRESS ECHOCARDIOGRAPHY

A. In many patients, “diastolic” heart failure is the dominant form of dysfunction, without any detectable systolic dysfunction at rest or during stress. The **transmitral peak early diastolic velocity (*E*)** and the **mitral annulus early diastolic velocity (*e*′)** are

utilized to assess the diastolic dysfunction. In the presence of normal LV systolic function and volumes, an ***E/e′* ratio >15 suggests elevated LV filling pressure and diastolic dysfunction**, whereas a ratio <8 excludes diastolic dysfunction. The primary utility of diastolic SE is to evaluate patients in whom diastolic dysfunction is suspected but the resting echocardiogram is indeterminate (i.e., *E*/*e*′ 8 to 15). Assessment for diastolic dysfunction should be completed during routine SE, because its presence and severity add to the negative prognostic value of resting or stress-induced systolic dysfunction.

B. Exercise or adrenergic stress normally results in improved myocardial lusitropy (relaxation) to allow for better filling in a shorter amount of time. The tachycardia associated with exercise results in an abbreviated diastolic filling period and an increase in the transmitral peak *E*velocity. In healthy patients, both the transmitral peak *E* velocity and the mitral annulus early diastolic velocity increase with exercise, and the *E*/*e*′ ratio is not changed. However, **in patients with diastolic dysfunction, the mitral annulus early diastolic velocity is minimally affected by the change in preload caused by exercise and the *E*/*e*′ ratio increases**.

C. Assessment of diastolic dysfunction can be difficult at rest and is even more so with stress. When diastolic function is the major indication for testing, exercise SE is optimally performed using **supine bicycle ergometry**, because it allows for the acquisition of Doppler recordings during exercise. However, evaluation is routinely performed using treadmill exercise or dobutamine. Tachycardia may result in fusion of the transmitral *E* and *A* velocities at peak stress, making the tracings impossible to interpret. Therefore, Doppler assessment of the mitral inflow velocities should be assessed at rest, during exercise, and in recovery, if possible.

X.STRESS ECHOCARDIOGRAPHY IN NONISCHEMIC CARDIAC DISEASE.

SE can be used to evaluate the functional significance of a variety of valvular lesions as well as hypertrophic cardiomyopathy. SE is especially helpful when there is a discrepancy between clinical symptoms and the assessment of valve severity at rest. In addition to the effect of exercise on wall motion, ventricular size and function, other parameters are assessed when valve disease or hypertrophic cardiomyopathy is the prime focus of the stress echocardiogram. Functional capacity, change in pressure gradients across individual stenotic valves of the LV outflow tract (LVOT), change in severity of regurgitation, and the effect of exercise on estimated RV systolic pressure may all be important in understanding the hemodynamic consequences of the lesion under study. It is important to discuss with the sonographer performing the test in what order individual valve or myocardial parameters should be assessed at peak stress to optimize the value of the study. Thus, in mitral stenosis, for instance, peak mitral gradients followed by peak TR velocity and then wall motion and LV size is the appropriate order of peak acquisition of data.

A. Aortic stenosis

1. Exercise testing is contraindicated (American College of Cardiology/American Heart Association [ACC/AHA] class III, level of evidence [LOE] B recommendation) in patients with symptomatic AS. In asymptomatic patients with a calcified aortic valve and a peak aortic velocity over 4 m/s or a mean pressure gradient over 40 mm Hg, exercise testing may be considered (ACC/AHA class IIa, LOE B recommendation) to elicit exercise-induced symptoms and abnormal BP responses. Reduced functional capacity for age

and gender is associated with worse outcomes in severe AS, especially if valve replacement is not promptly performed.

2. Dobutamine SE is reasonable (ACC/AHA class IIa, LOE B recommendation) in the diagnostic evaluation of patients with **low-flow/low-gradient AS**, defined as Doppler-derived aortic valve area < 1 cm^2, LVEF < 50%, and mean pressure gradients < 40 mm Hg or peak aortic velocity < 4 m/s. In these patients, **dobutamine is used to assess both the severity of AS and the presence of contractile reserve**.

3. In severe AS, low-dose (20 µg/kg/min) dobutamine infusion results in increased cardiac output with a parallel rise in the mean transvalvular gradient. Provided the calculated aortic valve area remains <1 cm^2, **an increase in the mean transvalvular gradient to a value >40 mm Hg or velocity >4 m/s is consistent with severe AS**. If dobutamine infusion results in an increase in the valve area (typically to >1 cm^2) with little change in the gradient, it is likely that LV dysfunction rather than AS is the primary problem, and aortic valve replacement is unlikely to be beneficial.

4. Dobutamine SE is also used to identify **contractile reserve** in patients with low-flow/low-gradient AS. Contractile reserve is defined as >20% increase in stroke volume with dobutamine infusion. Lack of contractile reserve is associated with poorer prognosis with either medical or surgical therapy.

B. Mitral regurgitation. In asymptomatic patients with severe MR, exercise SE is reasonable (AHA/ACC class IIa, LOE C recommendation) to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and severity of MR. SE can help predict latent LV dysfunction in patients with normal baseline LV systolic function, severe MR, and minimal or no symptoms. An increase in the LV cavity size or decrease in LV ejection fraction at peak stress suggests latent LV dysfunction and an increased risk of LV dysfunction after valve repair. Inability to achieve a functional response expected for age and gender is indicative of poorer outcomes in those not undergoing early surgical intervention for severe MR.

In symptomatic patients with severe MR, when there is a discrepancy between symptom severity and the severity of MR, exercise testing is reasonable (AHA/ACC class IIa, LOE B recommendation).

C. Mitral stenosis. Exercise SE should be performed (ACC/AHA class I, LOE C recommendation) to assess the hemodynamic response of the mean gradient and pulmonary artery pressure in patients with mitral stenosis when there is a discrepancy among resting Doppler echocardiographic findings, clinical findings, symptoms, and signs. An increase in the mean transmitral pressure gradient >15 mm Hg or pulmonary artery systolic wedge pressure >60 mm Hg may be indications to consider percutaneous or surgical intervention.

D. Hypertrophic cardiomyopathy. In patients with hypertrophic cardiomyopathy and high resting LVOT gradients, routine exercise testing is not performed owing to increased risks of arrhythmias and hypotension. Exercise SE provides valuable information, including exercise hemodynamics, exercise capacity, worsening of MR, and provocable gradients in patients that are asymptomatic at rest. Although these patients may have only mild to moderately elevated resting LVOT gradients, using SE to identify elevated provocable gradients may help explain their exertional symptoms and quantify their exercise tolerance. Additionally, more recent data indicate that asymptomatic or minimally

symptomatic hypertrophic cardiomyopathy patients may be accurately risk stratified by their exercise capacity, regardless of their gradients with exercise.

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CHAPTER 48

Testing for Myocardial Viability

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I. INTRODUCTION. A common consideration in patients with ischemic cardiomyopathy is the degree to which dysfunctional myocardium might recover with revascularization. Exploring this question has led to a better understanding of the continuum of changes within the myocardium seen at cellular/tissue/segmental levels in response to ischemic injury. Here, myocardial segments may exhibit a number of viable forms—"stunned" (because of aborted acute ischemia), "ischemic" (acute, classical form), "hibernating" (following chronic adaptations because of repetitive ischemia), or a nonviable form (scar). Numerous techniques have been developed, each taking advantage of distinct characteristics of dysfunctional myocardium to help predict the potential for recovery and to guide therapy.

II. DEFINITIONS (see Table 48.1)

A. ***Normal tissue*** is viable and characterized by cell membrane integrity, active myocyte metabolism, the existence of blood perfusion, preserved electrical activity, the presence of contractile reserve (increased contractility on demand), and normal ventricular wall thickness.

B. ***Stunned myocardium*** is ***transiently dysfunctional myocardium***, usually following an episode of transient ischemia (e.g., with early opening of an occluded artery). Myocardial stunning represents a physiologic response to ischemia serving to decrease demand and to limit the size of an infarction. It is characterized by a blunted contractile reserve and a lack of scar and classically normal perfusion. It may take up to 8 weeks for the region wall motion abnormality to normalize.

C. ***Ischemic myocardium*** exhibits abnormal perfusion and a classical biphasic response to stress—that is, normal contraction or mild hypokinesis at rest that augments with low-level stress and becomes more dysfunctional with high-level stress because of decreased perfusion (contraction usually recovers within 30 minutes or so after stress).

D. ***Hibernating myocardium*** represents ***ischemic myocardium that has undergone chronic adaptive changes at a cellular level*** (e.g., a loss of contractile elements) in response to long-term repetitive ischemia, such as with chronic stable angina, or recurrent acute coronary syndromes. Findings include abnormal perfusion, rest myocardial dysfunction (that typically improves with revascularization), and augmented contraction with stress.

E. ***Infarcted myocardium*** is ***nonviable scar tissue*** that has lost its cellular architecture and classically does not become functional even if revascularized.

III. TECHNIQUES TO ASSESS VIABILITY. The above-described states of myocardium may coexist in the same patient. It is difficult to discern clinically which patients are more likely to have a higher percentage of viable (hibernating, ischemic, or stunned) myocardium and which do not, and thus, there is significant reliance on imaging to help assess this. Several different techniques have been developed over the years based on echocardiograph, nuclear imaging, and magnetic resonance imaging (MRI) techniques. In general, the choice of technique is guided more by the imaging capabilities of the treating medical center rather than individual patient characteristics. Metabolic assessment with nuclear imaging using positron emission tomography (PET) and scar assessment using MRI are increasingly used techniques whereas contractile reserve assessment by nuclear imaging using single photon emission computed tomography (SPECT) or dobutamine stress echocardiography (DSE) remains the alternative viability test option.

TABLE 48.1 Rest, Stress and Perfusion Characteristics of Normal, Ischemic, and Scarred My

A. **Positron emission tomography imaging.** PET is one of the most reliable tests of myocardial viability with **better image resolution** and fewer artifacts than other nuclear methods. Positron-emitting isotopes emit two high-energy (511 keV) photons in opposite directions, each of which is detected by a camera (those that do not arrive in temporal pairs are ignored). Concomitant low-dose computed tomography imaging allows software correction of attenuation of photon counts in areas where there is more tissue between the heart and the detector and this attenuation correction is particularly useful in obese patients or in those with prominent breasts. Using a variety of agents, rest and stress perfusion as well as myocardial viability can be assessed by PET imaging.

1. **Perfusion agents**

a. **Rubidium-82 (Rb82)** is a potassium analogue with a short half-life (1 minute), rapidly taken up by intact myocardial cells via the sarcolemmal Na/K pump and is a marker for normal perfusion. When used in conjunction with pharmacologic stress testing (usually with a vasodilator such as regadenoson), it can also indicate ischemia, with reduced stress tracer counts indicating ischemia. Recently, generators have become commercially available which contain strontium-82 that decays by electron capture to produce positron-emitting rubidium-82.

b. **Nitrogen 13 ammonia (13NH3)** can be used interchangeably with Rb82, also has a short half-life (10 minutes), and needs to be produced in a cyclotron in close proximity which limits its widespread use.

c. **Oxygen 15 water** can also be used as a perfusion tracer, but needs a cyclotron and is uncommonly used in conventional practice.

2. **Metabolic agents**

a. **Fludeoxyglucose 18 (FDG)** is the metabolic agent of choice and is taken up by metabolically active cells and phosphorylated so that it cannot be further metabolized and becomes trapped in the cells. As a result, FDG is a good reflector of myocardial

metabolic activity (glucose uptake and phosphorylation). FDG is cyclotron produced but has a half-life of approximately 110 minutes so it can be produced off-site (see Fig. 48.1).

b. Other agents such as carbon 11 acetate and carbon 11 palmitate are uncommonly used.

3. **Test interpretation.** In normal myocardial cells, free fatty acids are used preferentially, but **during periods of ischemia, stunning, and hibernation, metabolism changes so that glucose is primarily used.** Therefore, ischemic and hibernating myocardium is FDG avid, in contrast to scar which does not uptake FDG. When interpreting a PET viability study, typically three sets of images are recorded: a resting perfusion image, a stress perfusion image, and a metabolic tracer image.

a. Normal tissue shows normal rest and stress perfusion with high metabolic tracer uptake.

b. Stunned tissue shows normal rest and stress perfusion with high metabolic tracer uptake and reduced regional wall motion.

c. Ischemic tissue shows normal perfusion at rest, decreased perfusion at stress, and high metabolic tracer uptake.

d. **Hibernating tissue shows decreased perfusion at stress and rest with high metabolic tracer uptake**.

e. Scar shows decreased perfusion at rest and stress with no metabolic tracer uptake (see Fig. 48.2).

4. **Limitations.** Practical limitations of PET include the availability of the radiotracers. Agents with short half-lives need to be generated on-site and therefore are limited to facilities that perform a high-enough volume of studies to justify the cost. Second, the utility of FDG can be limited in diabetic patients who have impaired cellular glucose uptake.

FIGURE 48.1 Viability testing. FDG, 18F-fluorodeoxyglucose scanning; PET, positron emission tomography. **FIGURE 48.2** Rubidium positron emission tomography (PET) followed by 18F-fluorodeoxyglucose (FDG) PET: Patient (**A**) showing metabolism mismatch and is indicative of hibernating, viable myocardium. Patient (**B**) showing impaired FDG uptake combined with reduced perfusion (flow–metabolism match) is indicative of myocardial scar.

B. Cardiac magnetic resonance imaging

1. **Technique.** This technique offers high spatial resolution to aid quantification of the extent of myocardial scar (nonviable tissue) and this explains its low false-negative rate and high negative predictive ability. MRI uses a concept called delayed enhancement to highlight areas of scar by taking advantage of the pharmacokinetics of intravenously injected gadolinium-based contrast which gets held up in scarred tissue. Images are obtained 10 to 20 minutes after gadolinium injection, at which time the contrast has already washed in and out of healthy tissue, but has not yet had time to wash out of the scarred tissue which is therefore demonstrated by hyperenhancement on imaging.

2. **Test interpretation**

a. Generally, segments with less than 25% transmural scar are considered viable.

b. Segments with >75% of transmural scar are considered nonviable tissue.

c. Segments of 25% to 75% are usually reported as intermediate (see Fig. 48.3).

3. **Limitations.** As with PET, availability of cardiac MRI remains a major limitation. There are also several patient considerations. First, viability assessment requires the use of gadolinium which generally cannot be used in patients with a glomerular filtration rate of less than 30 mL/min because of the risk of nephrogenic systemic fibrosis. More recently, repeated gadolinium exposure has also been linked to cerebral deposition whose significance is unclear. Second, MRI has traditionally been contraindicated in patients with certain implanted metallic devices, most notably cardiac pacemakers, though recent advances have allowed MRI to be performed in many of these patients. Finally, MRI requires significant patient cooperation with breath holding and a stable cardiac rhythm for good image quality. Many patients cannot adequately participate and others have unacceptable claustrophobia which can limit the exam.

C. **Single photon emission computed tomography imaging.** SPECT imaging can be used to assess for viability (although not as good as either PET or MRI). For the purpose of viability assessment, the radiotracer thallium 201 is preferred specifically because of its redistribution kinetics. As a potassium analog, it is rapidly taken up by cell membrane Na/K pumps concentrating primarily in the intracellular space with peak myocardial concentration at 10 minutes. Thereafter, the tracer undergoes continual exchange between the extracellular and intracellular spaces and redistributes to poorly perfused viable cells but not scar tissue.

FIGURE 48.3 Late gadolinium-enhanced magnetic resonance imaging (MRI): Both patients (**A**) and (**B**) have extensive akinesia in left anterior descending (LAD) territory; however, patient (**A**) has more extensive scar (>50% in multiple segments) than patient (**B**) and is less likely to have left ventricle (LV) function recovery post-revascularization.

1. **Test interpretation.** Protocols used for assessing viability with SPECT include the following:

a. *Rest/redistribution*: The tracer is injected and the heart imaged at rest approximately 10 to 45 minutes after initial injection, followed by reimaging 4 hours later. Perfusion defects on the initial image that improve on reimaging represent areas of ischemic/hibernating myocardium. Normal rest/abnormal redistribution kinetics also suggest viable myocardium. Defects that do not improve represent scar.

b. *Stress/redistribution ± reinjection*: The tracer is injected at peak pharmacologic or exercise stress with immediate imaging and reimaging 4 hours later. Perfusion defects on initial imaging that improve on reimaging represent areas of ischemic/hibernating myocardium. Defects that do not improve represent scar (although without reinjection, this protocol has a relatively lower sensitivity). A second reinjection after acquisition of the 4-hour redistribution images, with third time imaging carried out 18 to 24 hours later, increases the identification of viable myocardium that may appear as scar on the 4-hour post-stress images.

2. **Limitations** of this technique include exposure to ionizing radiation, relatively low spatial resolution, and attenuation artifacts.

D. Dobutamine stress echocardiography imaging. Assessment of contractile reserve in response to escalating dobutamine infusion forms the basis for assessing viability by echocardiography.

1. Test interpretation

a. **Normal** myocardial segments respond with increased contractility.

b. **Stunned or hibernating** myocardial segments augment with stress but typically in a somewhat blunted fashion (uniphasic response).

c. **Ischemic** myocardial segments classically exhibit an inducible biphasic response, whereby there is an initial improvement at low-dose dobutamine because of the inotropic effect, but regression at higher dose because of increased myocardial oxygen demand in the presence of a significant perfusion abnormality.

d. **Scarred** myocardial segments classically exhibit akinesis at rest and with dobutamine.

2. Limitations. Dobutamine echocardiography is limited by high interobserver variability with regard to image interpretation which is more difficult than nuclear or MRI imaging. Limited image quality particularly in obese patients may be suboptimal despite the use of echo contrast. Dobutamine can provoke ventricular arrhythmias in patients with ischemia and decreased left ventricular function. For these reasons, echocardiography is typically only used as a primary imaging modality for viability assessment when other modalities are not available or otherwise contraindicated.

IV. EVIDENCE FOR VIABILITY TESTING.

There are much observational data showing that viability is associated with better outcomes in terms of improvements in left ventricular function, VO_{2max}, and heart failure symptoms as well as fewer ischemic events post-revascularization. Although randomized controlled trials have yet to show good outcome data for strategies guided by viability compared with usual care, such studies to date have been heavily criticized. For example, viability sub-study data from the "negative" Surgical Treatment of Ischemic Heart Failure (STICH) trial were non-blinded, did not include either PET or MRI imaging, and included sick patients likely with more influential factors than viability to drive mortality. The PET and Recovery Following Revascularization study similarly reported no difference in clinical outcomes between patients managed with a strategy guided by viability compared with usual care, though there was low adherence to protocol in the study (of note, those treated per protocol did have better outcomes).

Given that the degree of reversibility of segmental postischemic myocardial dysfunction lies on a spectrum, ideally cardiac viability should be assessed as a continuous variable. Most studies to date however have assessed viability as a YES/NO dichotomous variable defined as recruitment of "n" segments. In STICH, viability was defined as >11/16 viable segments based on relative tracer activity using SPECT or >5/16 segments with abnormal resting function but contractile reserve using DSE.

The burden of scar, which dictates the potential for recovery, is largely based upon the extent and duration of the malperfusion injury. Most studies suggest at least 15% viability is required to predict event-free survival with identification of 8/16 viable segments by PET associated with an increase in LVEF by ≥5% following revascularization.

V.WHEN TO (AND WHEN NOT TO) ASSESS FOR VIABILITY. The issue of viability only arises when there is some degree of contractile malfunction, as tissue with normal contractility at rest should be assumed to be viable. In general, viability testing is informative by better characterizing patient substrate and prognosis. A somewhat separate point relates to the use of viability testing with regard to decision making regarding revascularization. **Low-risk patients with ischemic left ventricular systolic dysfunction and good coronary target vessels or those with angina despite maximal medical therapy should be considered for revascularization independent of viability testing**—in such patients, viability testing should not be used to specifically dictate decision making regarding revascularization. On the other hand, for **moderate- to high-risk patients (and in those with heart failure rather than angina), demonstration of significant myocardial viability may confer a more favorable risk–benefit ratio regarding revascularization** and thereby help with decision making. Here, viability assessment can help to inform regarding potential revascularization strategies, can provide prognostic information by providing an estimate of the probability and magnitude of recovery of ventricular dysfunction following successful revascularization, and can aid with preoperative planning such as the need for backup circulatory support. For either very high-risk patients felt to have a poor prognosis independent of revascularization or for those in whom reasonable revascularization would not be possible (poor distal targets), viability testing is again not useful because other factors may overpower viability/ischemic status and drive outcome following attempts at revascularization.

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CHAPTER 49

Cardiovascular Computed Tomography Including Calcium Scoring

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I. INTRODUCTION. Cardiovascular computed tomography (CT) has continued to rapidly evolve over the past decade, gaining new and expanded indications for noninvasive assessment of the heart, great vessels, and peripheral vasculature. Technologic improvements, including increasing numbers of detectors, improved temporal and spatial resolution, and advanced postprocessing, have broadened the clinical utility of this imaging modality. Advanced multidetector computed tomography (MDCT) scanners and new scanning protocols have significantly reduced the required radiation and contrast dosages. Numerous considerations are involved in the proper selection of cardiovascular CT protocols, and skilled operators are required to plan and interpret these examinations.

II. BASICS OF CARDIAC CT

A. CT physics. In CT, images are created by rotating an x-ray source emitting a fan-shaped beam of x-rays, which then pass through the body. Some x-rays are absorbed or scattered, but others are transmitted and subsequently sensed by detectors located directly across the x-ray source. In MDCT, the x-ray tube and detectors are mounted on a gantry that rotates rapidly around the patient as he or she passes through the scanner. As in traditional x-ray radiography, different structures **attenuate** the x-ray beam to differing extents depending on their atomic composition and density, as well as the energy of the incident photons. The data collected by the detectors then go through a complex set of mathematical reconstruction algorithms that create a set of axial images through the technique of **back projection**. Each voxel in the resulting axial image is ascribed a specific attenuation value, which is expressed in **Hounsfield units (H.U.)**. Using a reference of 0 H.U. for water, −1000 H.U. for air, and +1000 H.U. for bony cortex, different points are assigned their respective attenuation values. This information is then converted into a grayscale image that can be manipulated by the interpreting physician.

B. Technical challenges for cardiac imaging

1. The fast cyclical motion of the heart requires high **temporal resolution** to avoid blurring or degradation of images because of cardiac motion artifact. In cardiac CT, image acquisition is referenced, or **gated**, to the cardiac cycle. Although data can be acquired throughout the cardiac cycle, most image data sets are reconstructed during periods of minimal

cardiac motion, typically a brief 100- to 300-ms interval in late diastole (60% to 75% of the R–R interval).

2. High **spatial resolution** is required to image relatively small vessels such as the coronary arteries. Current MDCT scanners provide a spatial resolution of 0.3 to 0.5 mm, compared with a spatial resolution of 0.1 to 0.2 mm for invasive angiography and intravascular ultrasound.

3. Respiratory motion artifact can be minimized by having the patient hold their breath during image acquisition. Most of the prior generations of clinically available scanners can cover the entire heart in 10 to 12 seconds, whereas the current 320-detector, wide-volume MDCT scanner, as well as the current dual-source MDCT scanner (with high-pitch spiral acquisition—see subsequent text), can image the entire heart in just one heartbeat.

4. Rapid improvements in CT technology and protocoling have outpaced research in the field. Many studies investigating the diagnostic and prognostic yield of information gained from cardiac CT were not based on the latest generation MDCT scanners, but rather on single-beam or MDCT detector systems with fewer detectors (e.g., 16- to 64-detector MDCT scanners).

C. Current CT hardware

1. **MDCT** involves using an x-ray tube mounted opposite multiple detector rows on a gantry, which is then rotated around the patient at a rapid rate (220 to 400 ms/rotation). The patient is moved at either a fixed or variable speed, or **pitch**, through the scanner. An increasing number of detectors allows for an increased *z*-axis (cranial–caudal) coverage, permitting faster scans with improved image quality, because of less cardiac and respiratory motion artifact. Temporal resolution is improved by faster gantry rotation, the use of **two x-ray tubes** and detector arrays mounted at 90° angles to each other (dual-source MDCT), and special reconstruction techniques. Dual-source/dual-energy scanners provide substantial improvements by utilizing dual-source MDCT technology as well as dual-energy sources to improve temporal resolution and decrease scatter. The latest generation dual-source MDCT scanners provide a temporal resolution of 66 ms. Spatial resolution is largely determined by detector architecture (typically 0.4 mm isotropic resolution), although thicker slices (1 to 5 mm) can be acquired to reduce radiation dose according to the study indication. MDCT can be used for both cardiac and noncardiac studies, and it is now the most widely used type of CT hardware for cardiac imaging.

2. **Electron beam computed tomography (EBCT)**, although rarely used today, was specifically developed for cardiac imaging. It involves the use of a rapidly oscillating electron beam reflected onto a stationary tungsten target. Because there is no mechanical motion within the gantry, EBCT is capable of very high temporal resolution (50 to 100 ms). EBCT was used primarily for the quantitative detection of coronary artery calcification (CAC).

D. Image acquisition techniques

1. **Acquisition modes.** Both prospectively triggered axial acquisition and spiral (helical) retrospectively gated acquisition are available for most MDCT scanners. High-pitch spiral acquisition (flash mode) is unique to current generation dual-source MDCT scanners.

2. **Prospectively electrocardiogram (ECG)-triggered sequential (axial, "step-and-shoot") mode.** Single transaxial slices are sequentially acquired while the patient

table is incrementally advanced between successive rotations of the gantry. For patients with adequate heart rate control, this mode should be the acquisition mode of choice for CT coronary angiography. With prospective ECG triggering, image acquisition occurs only during a prespecified part of the R–R interval. Significant reductions in radiation exposure (up to 90%) are obtained with this mode of image acquisition, compared with retrospective ECG gating.

3. **Retrospectively ECG-gated spiral (helical) mode.** Data are continuously acquired during constant rotation of the gantry with simultaneous, constant (*z*-axis) movement of the patient through the scanner. Because the tube does not perform a complete rotation in any plane, x-ray data are interpolated from a series of sequential frames to create a single tomographic image. This mode of image acquisition should be considered in situations where patients have arrhythmias and/or tachycardia.

4. **High-pitch spiral acquisition (flash mode)**. This is a newer MDCT acquisition mode, available on current generation dual-source MDCT scanners. The latest generation dual-source scanners enable continuous sampling of the *z*-axis at a pitch value of 3.4, by interleaving data acquired from two detector systems. For a CT coronary angiography study, scan acquisition is most commonly triggered in early diastole (60% of the R–R interval) and completed in one cardiac cycle. The strength of this mode of acquisition is the low radiation dose (often <2 millisieverts [mSv]).

5. **ECG gating**

a. **Prospective triggering.** The trigger signal is derived from the patient's ECG based on a prospective estimation of the R–R interval. The scan is usually triggered to begin at a defined point after the R-wave, usually allowing image acquisition to occur during diastole. Prospective ECG triggering is one of the most dose-efficient ways of cardiac scanning, because only the very minimum scan data needed for image reconstruction are acquired. Limitations of prospective triggering (or **"gating"**) include the fact that the acquired data set will be of a limited portion (or phase) of the cardiac cycle only, limiting the opportunity for evaluating image data sets from other cardiac phases. In addition, prospective triggering depends greatly on the regularity of the patient's heart rate and can result in serious misregistration artifact in the setting of arrhythmia.

b. **Retrospective gating.** Unlike prospective triggering, retrospective ECG gating collects data during the entire cardiac cycle. Once the scan is complete, data from specific periods of the cardiac cycle are used for image reconstruction by retrospective referencing to the ECG signal. This approach allows reconstructions to be made from multiple segments of the cardiac cycle and allows assessment of ventricular function via dynamic four-dimensional imaging. However, retrospective gating results in significantly higher radiation dose exposure, although this can be somewhat mitigated by **dose modulation** (see subsequent text).

E. **Other imaging considerations**

1. **Segmented reconstruction** refers to image acquisition algorithms that use scan data from more than one cardiac cycle for image reconstruction. This can improve the effective temporal resolution of the scan at the cost of a slight increase in radiation dose.

2. **Dose (or tube current) modulation.** MDCT scanners may operate with fluctuating tube currents that increase radiation dose during portions of diastole (when diagnostic images are most likely to be obtained) and decrease during systole. Dose

modulation typically reduces effective radiation dose by approximately 33%, and it is most effective at lower heart rates.

a. **Image reconstruction and interpretation.** Images are most frequently viewed from axial and double oblique planes, in which the three-dimensional data set is manipulated by the interpreting physician so that multiple planes can be viewed to assess cardiac morphology and coronary anatomy. Additional postprocessing techniques can be performed to provide further diagnostic information or, more frequently, to present to the referring physician.

b. **Multiplanar reformation** involves creating straight or curved image planes by cutting orthogonally or obliquely through the three-dimensional acquisition. This aids in evaluating complex three-dimensional structures, such as the coronary arteries.

c. **Maximal-intensity projections** are created by compressing a predetermined volume of image data into a two-dimensional projection of the brightest voxels. This is similar in principle to the two-dimensional images created by typical invasive angiography.

d. **Three-dimensional or volume rendering** is an advanced image processing approach that uses semitransparent visualization of the outer contours of volumetric data, giving the appearance of a three-dimensional structure. Although often not as useful for assessing smaller structures, these reconstructions can be very helpful for understanding complex spatial relationships between major intrathoracic structures.

e. **Four-dimensional or cine imaging** from retrospectively ECG-gated spiral data acquisition generates cine images of the CT data for evaluating ventricular and valvular function.

3. **Contrast-enhanced imaging.** Administration of iodinated contrast media increases the attenuation of the blood pool, improving vessel delineation and tissue characterization. When using contrast, image acquisition must be timed such that images are acquired when the blood pool saturation in the target structure is maximal. Various techniques exist to time the arrival of the contrast bolus in the arterial tree and initiate imaging. The specific risks of contrast media are discussed in Section IV.

III. INDICATIONS.

The roles of cardiac CT in evaluating patients with cardiovascular disease are diverse, and continue to evolve. Generally accepted indications for cardiac CT are listed in Table 49.1 and are discussed in the context of specific clinical situations in Section VI. Appropriate-use criteria (AUC) for the use of cardiac CT have also been published and are discussed at the end of the chapter. The following is a brief listing of the more common indications for MDCT.

A. **Evaluation of chest pain** in patients with low to intermediate pretest probability of obstructive disease and ongoing symptoms (e.g., chest pain, dyspnea) with an equivocal stress test

B. **Suspicion of coronary artery anomalies:** Because of the high spatial resolution and the ability to create three-dimensional reconstructions of the vasculature, MDCT has very high sensitivity and specificity for coronary artery anomalies.

C. **Pulmonary vein evaluation:** This can be performed often before or after pulmonary vein isolation (PVI) for atrial fibrillation. This is helpful for the mapping of pulmonary venous anatomy preprocedurally and to exclude pulmonary vein stenosis postprocedurally.

D. **Evaluation of cardiac masses** in conjunction with or when other noninvasive imaging modalities, such as transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), are limited/unrevealing

E. **Evaluation of pericardial disease** in conjunction with or when other noninvasive imaging modalities, such as TTE and TEE, are not able to provide the complete set of diagnostic data (e.g., suboptimal/limited images)

F. **Assessment of anatomy in complex congenital heart disease**

TABLE 49.1 Selected Appropriate Indications for Cardiac Computed Tomography

Category	Specific Appropriate Indications
Suspected CAD with symptoms	Intermediate pretest probability of CAD with uninterpretable ECG o
	Acute chest pain with intermediate pretest probability of CAD and enzymes
	Evaluation of suspected anomalous coronary artery anatomy
Coronary artery calcium scoring	Asymptomatic patients at intermediate CAD risk Asymptomatic patients with low CAD risk, with a family history of p
Evaluation of intra- and extracardiac structures	Evaluation of a cardiac mass (suspected tumor or thrombus) in pa from other noninvasive imaging modalities (e.g., TTE, TEE)
Pericardial disease	Evaluation of pericardial anatomy
Congenital heart disease	Assessment of complex congenital heart disease including anomal
Pulmonary vein anatomy	Evaluation of pulmonary vein anatomy prior to invasive radiofreque
Biventricular pacing	Mapping of the coronary vein anatomy prior to placement of bivent
Assessment of cardiac structure	Assessment of right ventricular morphology and suspected arrhyth

G. CAD, coronary artery disease; ECG, electrocardiogram; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

H. Adapted from the Taylor AJ, Cerqueira M, Hodgson J, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/SCMR 2010 appropriate use criteria for cardiac computed tomography. *J Am Coll Cardiol*. 2010;56:1864.

I. **Presurgical evaluation, particularly before redo open heart surgery:** Noncontrast MDCT can be used to assess for the presence of significant calcification in the ascending aorta, as well as assess proximity of cardiovascular structures to the sternum.

J. **Assessment of graft patency after prior bypass surgery** may be feasible in select cases, although the study can be limited by artifacts related to calcification and surgical clips.

K. **Evaluation of aortic disease:** MDCT is the test of choice for evaluating thoracoabdominal aortic aneurysms. It is also useful in the long-term follow-up of patients who have undergone prior aortic surgery or endovascular stenting.

IV.CONTRAINDICATIONS. In comparison to cardiac magnetic resonance imaging (MRI), few absolute contraindications exist for cardiac CT. However, there are important risks associated with radiation and/or contrast exposure that must be weighed against the benefits of the study. **Relative contraindications** to CT scanning are listed below.

A. Renal insufficiency. Given the potential for contrast-induced nephropathy, patients with significant renal insufficiency (i.e., estimated glomerular filtration rate < 30 mL/min/1.73 m^2) should not undergo contrast-enhanced CT, unless the information from the scan is critical and the risks/benefits are thoroughly discussed with the patient.

B. Contrast (iodine) allergy. Patients with allergic reactions to contrast should be pretreated with diphenhydramine and steroids before contrast administration. A prior anaphylactic response to contrast is generally felt to be an absolute contraindication for intravenous iodinated contrast administration by many institutions.

C. Recent intravenous iodinated contrast administration. Patients who have received an intravenous dose of iodinated contrast should avoid contrast-enhanced CT scanning for 24 hours to reduce the risk of contrast-induced nephropathy. For younger patients with normal renal function without risk factors for contrast-induced nephropathy, contrast doses of up to 150 to 200 mL per 24 hours are generally well tolerated.

D. Hyperthyroidism. Iodinated contrast is contraindicated in the setting of uncontrolled hyperthyroidism because of possible precipitation of thyrotoxicosis.

E. Atrial fibrillation, or any significant arrhythmia, is a relative contraindication to CT coronary angiography because of image degradation from suboptimal ECG gating.

F. Inability to breath-hold for at least 10 seconds. Image quality will be significantly reduced because of respiratory motion artifact, if the patient cannot comply with breath-hold instructions.

V.SAFETY

A. Radiation exposure is an important consideration in various cardiac imaging modalities, including CT. Radiation doses of cardiac CT scans vary greatly, depending on the scan parameter settings, scan range (cranial–caudal length of the scan), gender (women receive more radiation because of breast tissue), and patient's body habitus (obesity increases exposure).

1. Estimates of radiation dose from MDCT have varied widely in the literature. **Effective dose** is an estimate of the dose to patients during an ionizing radiation procedure and is expressed in **millisieverts**. For reference, the estimated dose from a chest x-ray is 0.04 to 0.10 mSv, and the average annual background radiation in the United States is 3 to 3.6 mSv. Invasive diagnostic coronary angiography provides effective doses of 2.1 to 4 mSv. In comparison, CT coronary angiography studies have reported doses ranging from 3.6 mSv to as high as 18 mSv, depending on the scan parameters, with most estimates ranging from roughly 4 to 11 mSv.

2. Table 49.2 lists radiation dose ranges for the most commonly used cardiac imaging modalities.

3. Feasibility of low-dose CT coronary angiography. With the use of prospective ECG triggering, axial imaging modes, dose reduction, and software adaptations, recent studies have reported the feasibility of CT coronary angiography with comparable image quality and substantially reduced radiation doses (i.e., 1.1 to 3.0 mSv). This remains an

area of active investigation. For second-generation, wide-volume 320-detector row MDCT scanners, submillisievert radiation dose has been reported for CT coronary angiography studies. With the current generation, dual-source MDCT scanners utilizing the high-pitch spiral acquisition (flash mode), many CT coronary angiographic studies can be performed with less than 2 mSv of radiation dose.

TABLE 49.2 Estimated Radiation Exposure from Cardiac Imaging Procedures

Diagnostic Procedure	Typical Effective Dose (mSv)	Equivalent Radiation
Natural background radiation	3–4 (range 1.5–7.5)	1 y
Chest x-ray (PA and lateral)	0.04	6 d
Transatlantic flight	0.03	5 d
Lung ventilation (Kr-81m)	0.1	2–4 wk
Lung perfusion study (Tc-99m)	1	4–6 mo
Calcium scoring	0.8–2	3–6 mo
CT head	2	6 mo
Cardiac catheterization (diagnostic)	3–4	1 y
64-Slice MDCT (with dose modulation)	8–12	2–3 y
Second-generation, wide-volume 320-detector row MDCT Latest generation, dual-source MDCT (high-pitch spiral/flash mode)	1–2	3–6 mo
Myocardial perfusion (Tl-201)	15–18	4–5 y
CT abdomen/pelvis	10–20	3–6 y
Cardiac PET	14–20	4–6 y

4. CT, computed tomography; MDCT, multidetector computed tomography; mSv, millisievert; PA, posterolateral; PET, positron emission tomography; R, Roentgen units.

B. Contrast-induced nephropathy. Iodinated contrast media can cause renal ischemia by reducing renal blood flow or increasing oxygen demand and may also have a direct toxic effect on tubular epithelial cells. If a contrast-enhanced CT study is necessary in patients with significant renal insufficiency, prophylactic measures should be taken to reduce the risk of renal damage. Most cardiac CT studies require between 80 and 100 mL of contrast.

1. **Risk factors**
   - a. Preexisting renal insufficiency
   - b. Diabetes mellitus
   - c. Increased volume of contrast media

2. **Prophylactic measures** include saline hydration, use of low-osmolar agents, and sodium bicarbonate infusion, although the data for each of these measures remain somewhat controversial. The use of *N*-acetylcysteine has been shown to have no effect in slowing the progression of contrast-induced nephropathy.

VI. CLINICAL APPLICATIONS

A. **Coronary calcium scoring** uses the observation that coronary calcium is a surrogate marker for coronary atherosclerotic plaque. Studies have shown that the complete absence of coronary artery calcium makes the presence of significant coronary luminal obstruction highly unlikely and indicates a very low risk of future coronary events. Men tend to have higher calcium scores, and individuals of either gender with renal insufficiency or diabetes mellitus tend to have higher coronary calcium scores. Coronary calcium scoring is considered an appropriate test for patients with intermediate coronary artery disease (CAD) risk and those low-risk patients with a family history of premature CAD.

1. Either noncontrast EBCT or MDCT can be used (typically with 3.0 mm slice thickness). Contrast is not necessary because calcium is readily identified secondary to its very high x-ray attenuation coefficient (high H.U. score).

2. The **Agatston CAC volume score** is the most frequently used scoring system. It is derived by measuring the area of each calcified coronary lesion and multiplying it by a coefficient of 1 to 4, depending on the maximum CT attenuation within that lesion. It is important to note that interobserver variability exists in Agatston scores. However, with very low and very high scores, such interobserver variability has little clinical meaning. The interobserver variability can be as high as 3%.

a. The **CAC score** can be classified into five groups: (1) 0, no coronary calcification; (2) 1-100, mild coronary calcification; (3) >100 to 399, moderate calcification; (4) 400 to 999, severe calcification; and (5) ≥1,000, extensive calcification.

b. The **CAC score is age specific and gender specific**. Therefore, there has to be a comparison of the individual data with a "normal" cohort in order to produce meaningful data, usually presented as a percentile distribution (e.g., Multi-Ethic Study of Atherosclerosis Risk Score). In general, CAC develops 10 to 15 years later in life in women than in men. Similarly, CAC is generally five to seven times lower at any given age in women than in men.

c. In a typical cohort of patients with CAD, the median CAC score is 975 for men and 370 for women. In comparison with a CAC score of 0, the presence of any CAC is associated with a fourfold risk of coronary events over 3 to 5 years.

d. In patients at intermediate clinical risk for coronary events (e.g., by Framingham score), the **CAC score can help reclassify patients to a higher or lower risk group**. For instance, a CAC score of 0 confirms low risk of events. Conversely, a CAC score of >400 is observed with a significant cardiac event rate (>2% per year) in patients who appear to be of intermediate risk, according to the Framingham score.

e. Because statins have no documented effect on CAC progression, **there is no value in repeating CAC in persons with a score of >100 or the 75th percentile.**

3. However, not every atherosclerotic plaque is calcified, and even the detection of a large amount of calcium does not directly translate into the presence of significant obstructive coronary artery lesions. Therefore, CAC adds incrementally to

traditional risk factor assessment and should not be used in isolation. The test is most useful in intermediate-risk populations, in which a high or low score may reclassify individuals to a higher or lower risk group, respectively. Unselected screening is not recommended.

B. CT coronary angiography has been shown to be an accurate noninvasive modality for visualizing the coronary arteries, with high sensitivity (85% to 95%) and specificity (95% to 98%), compared with invasive coronary angiography.

1. CT coronary angiography for evaluating CAD is most useful in low- to intermediate-risk patients with angina or anginal equivalent symptoms. The **negative predictive value** of CT coronary angiography is uniformly high in clinical studies, approaching 95% to 100%; in other words, CT coronary angiography is an excellent modality for ruling out coronary disease.
2. Patients who are generally poor candidates for CT coronary angiography include those who are likely to have heavily calcified coronary arteries (older than 75 years, end-stage renal disease, and Paget disease), atrial fibrillation/flutter, frequent ventricular ectopic beats, or uncontrolled tachycardia. Quantification of stenosis severity is often impossible in densely calcified arteries, whereas image quality is significantly degraded in patients with arrhythmias or tachycardia. The negative predictive value dropped to 83% in one study, where patients with Agatston CAC score of <600 were included.
3. Known severe CAD is generally a contraindication to CT coronary angiography. However, cardiac CT has been shown to have high sensitivity and specificity for the assessment of bypass graft patency in patients with previous coronary artery bypass grafting (see subsequent text).
4. **Stent patency**. Patients with prior coronary artery stents are generally poor candidates for CAC and CT angiography, although selected patients with proximal left anterior descending or left main stents may be successfully imaged. Current CT technology does not allow for the accurate quantification of in-stent restenosis severity, because of blooming artifact from the metallic struts of the stent.
5. When assessing the coronary arteries, **noncalcified plaque** appears as a low to intermediate attenuation irregularity in the vessel wall. **Calcified plaques** are bright, high-attenuation lesions in the vessel wall and may be associated with positive remodeling of the vessel. Densely calcified plaques are often associated with **calcium blooming artifact**, which can lead to overestimation of luminal stenosis severity.
6. Certain characteristics of noncalcified plaque, such as positive remodeling, have been reported to predict atherosclerotic lesions at higher risk of developing subsequent acute coronary syndromes.
7. The accuracy of CT coronary angiography is highest in the larger proximal to medium vessels, which are more likely to benefit from an invasive management strategy. Coronary stenoses are generally categorized as mild (<50% diameter stenosis), moderate (50% to 70% diameter stenosis), or severe (>70% diameter stenosis).

C. CT coronary angiography in stable chest pain

1. Recent randomized data (PROMISE study) from 10,003 patients, comparing anatomical (with CT coronary angiography) versus functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography) for the assessment of symptoms suggestive of CAD, over a median follow-up of 25 months, found that long-term patient outcomes were equivalent with both strategies. CT coronary angiography was

associated with fewer catheterizations showing no obstructive CAD than functional testing, although more patients in the anatomical testing group underwent subsequent catheterization.

2. In a prospective, open-label, multicenter trial, 4,146 patients with stable chest pain were randomly assigned to standard care or standard care plus CT coronary angiography (SCOT-HEART). CT coronary angiography helped clarify the diagnosis of angina: At 6 weeks, CT coronary angiography reclassified the diagnosis of CAD in 558 (27%) patients and the diagnosis of angina because of CAD in 481 (23%) patients. This led to decreased functional testing, increased invasive angiography, and more focused treatment regimens for patients. After 1.7 years, CT coronary angiography was associated with an apparent, but statistically nonsignificant reduction in fatal and nonfatal myocardial infarction.

D. CT coronary angiography in acute chest pain

1. In a multicenter study of 1,000 patients presenting to the emergency department with suspected acute coronary syndrome (ROMICAT-II), early CT coronary angiography, compared with standard evaluation, reduced the mean length of stay in hospital by 7.6 hours ($p < 0.001$), and more patients were discharged directly from the emergency department (47% vs. 12%, $p < 0.001$). CT coronary angiography resulted in more downstream testing and higher radiation exposure, without a significant increase in overall costs of care.

2. Another multicenter study enrolled 1,370 patients presenting to the emergency department with a suspected acute coronary syndrome: 908 patients in the CT coronary angiography group and 462 patients in the conventional care group. Compared with conventional care, CT coronary angiography was found to be safe and enabled early discharge from the emergency department (49.6% vs. 22.7%). Of 640 patients with a negative CT coronary angiography, none died or had a myocardial infarction within 30 days.

E. Bypass graft imaging

1. **Graft location.** MDCT can accurately characterize the origin, course, and touchdown of prior bypass grafts using intermediate slice thickness (e.g., 1.5 mm). This can be important for surgical planning (see subsequent text).

2. **Graft patency.** Using a protocol similar to that used for coronary artery assessment (>1 mm slice thickness), the patency of both arterial and venous bypass grafts can be assessed. Studies have suggested that the sensitivity and specificity of MDCT for detecting stenosis or occlusion of bypass grafts, when compared with invasive angiography, are excellent (97%). Occasionally, artifacts related to metallic clips can interfere with the assessment of distal anastomosis of an arterial graft (internal mammary or radial artery graft).

FIGURE 49.1 Axial multidetector computed tomography (MDCT) reconstruction demonstrating anomalous origin of the right coronary artery (RCA; arrow) from the left coronary cusp, with an intramural course, and compression of the ostium of the vessel between the ascending aorta and pulmonary artery. Note that the ostium of the RCA has a slit-like appearance. This image is from a 68-year-old male, with recurrent chest pain, who is being considered for surgical intervention.

F. Coronary artery anomalies.

Because of the three-dimensional data acquisition, MDCT is an excellent modality for assessing patients with known or suspected coronary artery anomalies. MDCT can accurately assess the origin and course of anomalous coronaries and can delineate the relationship of the coronary artery to neighboring structures. Although MRI can also be used to assess anomalous coronaries without the need

for radiation exposure, the spatial resolution, ease of data acquisition, and reliable image quality of MDCT make it a reasonable first choice (Fig. 49.1). Intramyocardial **bridging** can also be detected with high sensitivity, although the clinical significance of this relatively common finding is uncertain.

G. Cardiac morphology/function. Contrast-enhanced MDCT can provide high-resolution morphologic images of the cardiac chambers as well as accurate assessment of right and left ventricular systolic function. However, other imaging modalities such as echocardiography or MRI, which do not require radiation exposure, are generally preferred for the initial assessment of ventricular function.

1. Patients with prior **myocardial infarction** can have fibrous replacement of myocardium with or without calcification, ventricular wall thinning, aneurysm formation, and intracavitary thrombus. Cardiac CT is rarely used as the primary imaging investigation to assess for prior ischemic damage. Delayed-enhancement imaging with cardiac MRI remains the most widely accepted imaging modality of choice for this indication.
2. **Ventricular dysplasia** is characterized by fibrous and/or fatty replacement of myocardium, ventricular wall thinning and/or focal aneurysm formation, and ventricular cavity dilation with regional or global wall motion abnormalities.
3. **Mass.** Compared with cardiac MRI, CT provides less tissue characterization, although the attenuation of a mass (in H.U.) can be helpful. For instance, lipomas have low H.U. numbers, cysts have water density (i.e., 0 to 10 H.U.), and thrombi have low to intermediate H.U. numbers. Atrial myxoma can be visualized easily in the left atrium, although right atrial masses may be more difficult to assess, because of contrast mixing at the junction of the right atrium and inferior vena cava (IVC).

H. Pericardial diseases. The pericardium appears as a thin structure (1 to 2 mm) surrounding the heart, usually visible with a small amount of adjacent epicardial/pericardial fat.

1. Findings of pericardial **constriction** on CT include irregular pericardial thickening and calcification, conical or tubular deformities of one or both ventricles, enlargement of one or both atria, dilation of the IVC, and a characteristic diastolic bounce of the interventricular septum.
2. Pericardial effusions can be reliably detected by CT, with the presence of a trivial to small amount of pericardial fluid considered physiologic. Cardiac tamponade is better evaluated by echocardiography, because of its ability to provide hemodynamic assessment.
3. A pericardial **cyst** will appear as a well-circumscribed paracardiac mass with characteristic water attenuation (H.U. = 0), usually in the right costophrenic angle.
4. Both primary **neoplasms** and, more commonly, metastatic neoplasms can be visualized in the pericardium.
5. Rare pericardial disorders such as partial or complete **congenital absence of the pericardium** can be diagnosed by CT, with the demonstration of posterolateral displacement of the left ventricular apex and interposition of lung tissue between the aorta and pulmonary artery.

I. Congenital heart disease. MDCT may be useful in select patients in whom echocardiography is nondiagnostic or inadequate and MRI is not available or contraindicated. The ability to evaluate cardiovascular anatomy in multiple planes is often

helpful for delineating cardiac morphology in congenital heart disease, particularly with regard to the relationship of the great vessels, pulmonary veins, and coronary arteries. Specific situations in which MDCT can be helpful include the detection of shunts (e.g., sinus venosus atrial septal defect, unroofed coronary sinus, patent ductus arteriosus), visualization of pulmonary arteries in cyanotic congenital heart disease, precise definition of aortic anatomy in Marfan syndrome or coarctation, and delineation of partial or total anomalous pulmonary venous drainage. Additionally, CT can be useful as the follow-up imaging modality in patients with congenital heart disease, such as L-transposition of the great arteries, who have had prior pacemaker or ICD implantation, contraindicating cardiac MRI.

J. Diseases of the aorta constitute a common and important indication for CT examinations. Contrast-enhanced MDCT is nearly 100% sensitive and specific for evaluating acute aortic syndromes. ECG gating is critically important for studies of the aortic root and ascending aorta, given the propensity for motion artifacts to mimic dissection flaps on nongated studies.

1. **Acute aortic dissection** (see Chapter 26) is characterized on CT by visualization of a dissection flap (i.e., separation of the intima from the media) that forms true and false lumens. The CT study can characterize the origin and extent of the dissection, classify it as type A or B, assess for concomitant aneurysmal aortic dilation, and identify branch vessel involvement.
2. **Aortic intramural hematomas** are believed to be caused by spontaneous hemorrhage of the vasa vasorum of the medial layer. They appear as crescent-shaped areas of increased attenuation with eccentric aortic wall thickening. Unlike dissections, hematomas do not spiral around the aorta.
3. **Aortic aneurysm** occurs when there is enlargement (≥150%) of the normal aortic caliber (usually >5 cm in the thoracic aorta and >3 cm in the abdominal aorta). Given the often tortuous course of a dilated aorta, it is important that these measurements be made in the true short axis of the aorta, because oblique cuts can result in erroneous overestimation. Quantitative measurements of an aortic aneurysm can be made for planning endovascular repair with a **stent graft**.
4. **Penetrating atherosclerotic ulcer.** These tend to be focal lesions of the descending thoracic aorta that appear as contrast-filled irregular outpouchings of the aortic wall.

K. Evaluation of pulmonary veins. In the context of electrophysiology interventions such as PVI, preprocedural MDCT can be used to define pulmonary venous anatomy and identify supernumerary veins. Postprocedural MDCT can be used to evaluate for pulmonary vein stenosis. Additionally, in the setting of congenital heart disease, CT can be used to identify anomalous pulmonary venous return.

L. Evaluation of pulmonary embolism (PE). MDCT is highly accurate in detecting PE, which appears as a filling defect in the pulmonary arteries. This modality is most sensitive for proximal (main through segmental branches) thrombi. Small, more distal emboli may be missed.

M. Valvular heart disease. Visualization of the valve leaflets, particularly the aortic valve, is feasible with newer generation scanners because of their improved temporal

resolution. Dynamic four-dimensional MDCT imaging is particularly useful for the assessment of prosthetic valves for suspected thrombus, as well as infective endocarditis.

N. Surgical planning. The utility of MDCT in surgical planning before cardiothoracic surgery, particularly for reoperations, is increasingly recognized. Preoperative scans can evaluate the proximity of mediastinal structures to the sternum (i.e., aorta, right ventricle, and bypass grafts) and the degree of aortic calcification (i.e., to guide cannulation sites) and concomitantly provide information about cardiac morphology (e.g., presence of a ventricular aneurysm).

O. Peripheral arteries. MDCT can be used to evaluate peripheral arteries, including the carotid, renal, visceral, and lower extremity vessels. Indeed, imaging these vessels is generally more straightforward than coronary imaging, because of their large caliber and minimal motion. CT can be used for planning and follow-up of vascular disease in these peripheral vascular beds. Given the larger caliber of these vessels, assessment of stent patency is often quite feasible.

P. Structural cardiac interventions. MDCT is now the accepted gold-standard imaging investigation for the assessment of the aortic annulus, as well as iliac–femoral anatomy for the purpose of planning for transcatheter aortic valve replacement. MDCT has also been increasingly used for the assessment and sizing of the mitral valve annulus, to guide transcatheter mitral valve replacement. Recent data have also emerged that MDCT assessment of the left atrial appendage ostium is superior to TEE for sizing the Watchman device for left atrial appendage occlusion.

VII. APPROPRIATENESS CRITERIA

Appropriateness criteria (AUC) for the appropriate use of cardiac CT, endorsed by multiple societies and led by the American College of Cardiology, have been published. The current iteration of AUC for cardiac CT was published in 2010. They serve as guidelines, helping clinicians with the appropriate use of cardiac CT in the context of different clinical situations. Each clinical situation is designated appropriate (A), uncertain (U), or inappropriate (I) for the use of cardiac CT. For instance, cardiac MDCT is considered an *appropriate* (A) investigation for intermediate-risk patients with suspected CAD and chest pain, but negative ECG and biomarkers; it is considered an *uncertain* (U) indication to use cardiac MDCT for routine evaluation of coronary arteries following heart transplantation; it is considered an *inappropriate* (I) indication to use cardiac CT to investigate patients with documented moderate or severe ischemia on functional testing.

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CHAPTER 50

Cardiovascular Magnetic Resonance Imaging

Serge C. Harb

I.INTRODUCTION. Magnetic resonance (MR) imaging (MRI) has become widely available as a diagnostic technique for cardiovascular imaging, and its clinical indications continue to expand. Advantages of cardiovascular MR (CMR) include its ability to produce high-resolution and three-dimensional (3D) images of the cardiac chambers and thoracic vessels without ionizing radiation (unlike nuclear imaging and cardiac computed tomography) and its ability to do tissue characterization. In contrast to echocardiography, MRI is less operator dependent and is not limited by interferences from adjacent bone or air. Clinical applications of CMR include imaging of myocardia including ischemic heart disease; valvular, pericardial, aortic, and peripheral artery; congenital heart disease; and intracardiac masses.

Common indications and components of the CMR evaluation are listed in Table 50.1.

TABLE 50.1 Cardiovascular Magnetic Resonance Imaging Indications and Applications

Indication(s)	Applications
Aortic disease	Aortic aneurysm morphology and size; acute aortic pathology (dissection, coarctation of the aorta; branch vessel disease; evidence of vasculitis; infection or leak; assessment for aortic regurgitation or other associated
Ischemic heart disease	Ventricular volumes and function; myocardial scar and viability; quantificat LV aneurysm, thrombus, VSD, and other complications
Nonischemic cardiomyopathies	Ventricular volumes and function; myocardial wall thickness; LV ou cardiomyopathy; presence and patterns of myocardial scar/fibrosis; ass suspected hemochromatosis; quantification of mitral regurgitation; evalu arrhythmias or syncope
Pericardial disease	Pericardial effusion; pericardial thickening with or without calcification; p physiology including conical/tubular deformity of the ventricles, vent bounce, and early cessation of diastolic filling
Congenital heart disease	Anatomic definition; ventricular volume and function; valve morphology an for anomalous origin of the coronary arteries; anomalies of the aorta pulmonary veins
Valvular heart	Valve morphology; regurgitation and/or stenosis etiology and severity; vent

TABLE 50.1 Cardiovascular Magnetic Resonance Imaging Indications and Applications	
disease	
Cardiac masses	Size and extent of mass; tissue characterization
Pulmonary veins	Pulmonary vein anatomy and stenosis; cardiac anatomy and function

ARVD, arrhythmogenic right ventricular dysplasia; LV, left ventricular; VSD, ventricular septal defect.

TABLE 50.2 Contraindications to Cardiovascular Magnetic Resonance Imaging

Specific Devices	Special Issues
Cerebral aneurysm clips	Certain cerebral aneurysm clips pose a danger because of the po a magnetic field. Aneurysm clips classified as "nonferromagnetic
Cardiac pacemakers and ICDs	The presence of a pacemaker/defibrillator is usually a contraind problems, including (1) movement, (2) malfunction, (3) heatin induced in the leads. In addition, artifact from the leads will of However, certain new devices are labeled "MRI safe" and patien
Cardiovascular catheters	Catheters with conductive metallic components (e.g., pulmonary excessive heating. Hence patients with such devices should not
Cochlear implants and hearing aids	Most types of implants employ a strong magnet or are electro contraindicated because of potential injury or damage to the fu aids should be removed before the MRI procedure
Intravascular coils, stents, and filters	These devices typically become incorporated securely into the ve hence, most are considered MRI safe. However, specific info obtained before MRI is planned (mrisafety.com). Intracoronary s MRI, even when performed on the day of implantation, althoug waiting 6–8 wk
ECG electrodes	MR-safe ECG electrodes are strongly recommended to ensure pa
Foley catheters	Certain Foley catheters with temperature sensors have the po generally safe if positioned properly and disconnected from the
Heart valve prostheses	The majority of prosthetic heart valves and annuloplasty rings hav not be considered a contraindication to MR examination at ≤3 T
Metallic foreign bodies	All patients with a history of injury with metallic foreign bodies thoroughly evaluated, as serious injury may result from moveme
Metallic cardiac occluders (e.g., management of PDA, ASD, or VSD)	MRI is safe for nonferromagnetic devices immediately after imp generally safe approximately 6–8 wk after placement
Retained epicardial pacing	MRI in patients with retained epicardial pacing wires after car

TABLE 50.2 Contraindications to Cardiovascular Magnetic Resonance Imaging

wires	transvenous pacing wires are usually a contraindication to CMR

ASD, atrial septal defect; CMR, cardiac magnetic resonance; ECG, electrocardiogram; ICDs, implantable cardioverter–defibrillator; MR, magnetic resonance; MRI, magnetic resonance imaging; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

II. CONTRAINDICATIONS.

Contraindications to CMR imaging (CMRI) are listed in Table 50.2.

III. BASICS OF CARDIAC MRI

A. MRI physics.

Hydrogen is the most abundant atom in the body, and it is the excitation of the hydrogen nuclei, often referred to as protons, that forms the basis for clinical MRI. The nucleus has an inherent property called "spin" giving it a small magnetic moment. When these spins are placed in a magnetic field, they align parallel to the magnetic field and precess at a certain frequency (resonant or precessional frequency) but with different phase, creating a longitudinal magnetization. Application of a radiofrequency (RF) pulse with the same precessional frequency will cause excitation or resonance of the nucleus, temporarily changing its alignment within the magnetic field (transverse magnetization). However, this is an unstable state of higher energy. As the RF pulse is switched off, the spins quickly return to their resting state, that is, aligned with the field, because this is energetically the most favorable situation. The newly established transverse magnetization starts to disappear (a process called transversal relaxation), and the longitudinal magnetization grows back to its original size (a process called longitudinal relaxation). During this process, an RF signal is generated, which can be captured by the receiving coil and readily measured. This process constitutes the underlying principle of MRI.

The signal generated by an excited proton is dependent on its molecular environment, such that the MR signal from a hydrogen atom in blood can be discriminated from the MR signal from a hydrogen atom in fat or other tissue types. An MRI machine, therefore, includes a strong magnet that creates a continuous magnetic field and RF coils for transmitting the excitation pulses and receiving the radio signals generated by the excited protons. Application of predictable variations or "gradients" in the magnetic field, using gradient coils within the magnetic bore, allows 3D spatial localization of each signal. The raw data are initially mapped in "k-space"; then a Fourier transformation is performed to generate the final MRI image.

B. T1, T2, and image contrast.

The rate of relaxation of an excited proton along the longitudinal axis (i.e., the direction of the external magnetic field) is described by its T1 time, whereas the transverse axis is described by its T2 time. T1 and T2 times depend on the molecular environment of the protons (intrinsic to the tissue characteristics) and the magnetic field strength. T1 and T2 relaxation times of different tissues are important determinants of image contrast and, although not measured directly, images can be either T1 or T2 "weighted" to facilitate tissue characterization.

C. Issues specific to CMR.

Cardiac and respiratory motion poses significant challenges to CMR. In contrast to echocardiography, which is based on real-time imaging, CMRI sequences usually acquire a single image over several heart beats to optimize the

spatial and temporal resolution. It is, therefore, necessary to gate images to the cardiac cycle with either an electrocardiographic or pulse signal. Respiratory motion is typically countered by performing breath-holds during the examination. In patients who are unable to maintain a breath-hold, averaging multiple MR signals may help decrease the noise created by respiratory motion, at the expense of increasing the examination time by a factor of the number of signals averaged. Respiratory navigator sequences that coordinate imaging with a particular phase of diaphragmatic and hence respiratory motion are also effective, and they are typically used for pulse sequences that are too long for a single breath-hold, such as free-breathing whole-heart 3D coronary magnetic resonance angiography (MRA) sequences. Finally, real-time imaging using newer ultra-fast pulse sequences can be used in the absence of electrocardiographic or respiratory gating, at the expense of a significant decrease in temporal and spatial resolution.

D. CMR pulse sequences and applications

1. **Spin echo.** Spin-echo sequences are characterized by a refocusing RF pulse after delivery of the initial excitation pulse. Rapidly flowing blood appears dark, hence they are also known as "black-blood" sequences. Spin-echo sequences provide still images, which are typically used for anatomic delineation of the heart and great vessels owing to their excellent tissue contrast and high signal-to-noise ratio (SNR). They are relatively insensitive to magnetic field inhomogeneities and artifacts related to ferromagnetic objects such as sternal wires and prosthetic heart valves. The main disadvantage of spin-echo sequences is the relatively longer time it takes to acquire an image, making them more susceptible to motion artifacts and unsuitable for cine imaging. Turbo spin echo is a newer technique that provides faster acquisition times than does standard spin echo.
2. **Gradient echo.** Gradient echo sequences are characterized by the use of refocusing gradients after the delivery of the initial excitation pulse. Rapidly flowing blood appears bright, hence they are also known as "bright blood" sequences. Gradient echo is a fast imaging technique that is relatively insensitive to motion artifacts, making it ideal for cine imaging. However, it has less tissue contrast and increased susceptibility to magnetic field inhomogeneities and ferromagnetic-related artifacts. A variety of gradient echo sequences are widely used in CMR for cine imaging, myocardial perfusion and scar assessment, coronary imaging, and MRA.
3. **Cine imaging.** The most widely used pulse sequence for cine imaging is a gradient echo sequence called balanced steady-state free precession (B-SSFP), which is characterized by high SNR, high image contrast between blood and myocardium, and low sensitivity to motion artifact. However, B-SSFP is relatively insensitive to blood flow and, therefore, can be suboptimal for imaging of valve dysfunction or intracardiac shunts, which can usually be better illustrated using other gradient echo pulse sequences, such as echo planar imaging or phase velocity mapping. In addition, B-SSFP is also more susceptible to magnetic field inhomogeneities which can be problematic in patients with mechanical valves or other cardiac implants.
4. **Myocardial tagging.** RF pulses can be applied before the excitation pulse to generate dark saturation lines or grids on cine images, which are then tagged to the myocardium and further used to assess myocardial deformation. The tags can be used to help qualitatively assess myocardial motion and pericardial tethering or to quantitatively measure myocardial strain.

5. **Perfusion imaging.** Very fast gradient echo sequences are used for dynamic imaging of left ventricular (LV) myocardial perfusion during the first pass of a gadolinium contrast agent during rest and stress states. Fast gradient echo techniques are commonly used, such as fast low-angle shot or B-SSFP with a prepulse to null or darken the myocardium. Normally perfused myocardium shows an increase in signal intensity because of gadolinium contrast, whereas abnormally perfused areas remain dark, reflecting hypoperfusion.

6. **Delayed imaging.** Delayed hyperenhancement imaging for myocardial scar or fibrosis is performed 10 to 30 minutes after injection of gadolinium contrast using gradient echo sequences with an inversion recovery prepulse to null signal from the myocardium. **Areas of myocardial scar or fibrosis have a larger extracellular space with a greater accumulation and slower washout of gadolinium and, therefore, appear bright compared with dark, normal myocardium on delayed imaging**.

7. **Phase-contrast velocity mapping.** The phase difference in the spin of protons in moving blood compared with nonmoving protons within a magnetic gradient is called the "spin phase shift" and is proportional to the velocity of the moving protons. A phase-encoded image is constructed, with the gray level of each pixel coded for velocity. Phase-contrast velocity mapping could be considered analogous to pulse wave Doppler echocardiography. It can be used to measure blood velocity and hence quantify cardiac output, shunts, and valve dysfunction. There are, however, limitations, given that the accuracy of this method is highly dependent on factors such as flow pattern, flow velocity, size, and tortuosity of the vessel. Flow-related signal loss can be a result of loss of phase coherence that can occur in cases of significant flow acceleration and even in higher orders of motion present in complex flow patterns.

8. **Magnetic resonance angiography.** MRA of the great vessels typically involves a 3D fast gradient echo acquisition after injection of gadolinium contrast. The image resolution is typically 2 × 2 × 3 mm, making MRA an excellent option for imaging of large to intermediate size arteries, but less optimal for imaging of smaller vessels.

9. **Parallel imaging.** A number of parallel imaging techniques make use of multiple receiving body coils to fasten the acquisition times. This improves temporal resolution, but at the cost of a small decrease in the SNR.

E. Contrast agents. A number of gadolinium chelates are used as contrast agents in clinical MRI. **Gadolinium significantly shortens the relaxation time of nearby protons, thereby increasing their signal intensity**. These contrast agents are safe, with a low side-effect profile. Prevalence of adverse reactions is approximately 2% and includes transient headache, nausea, vomiting, local burning or cool sensation, and hives. Anaphylactic reactions are extremely rare. However, gadolinium has been linked to a severe and rapidly progressive form of systemic sclerosis called **nephrogenic systemic fibrosis**, which appears to be related to extracellular accumulation of gadolinium after its administration in patients with end-stage renal disease. The U.S. Food & Drug Administration (FDA) has advised that **gadolinium contrast agents should not be administered to patients with a glomerular filtration rate of <15 mL/min. Caution should be exercised in patients with moderate or severe renal impairment**.

IV.PRACTICAL CONSIDERATIONS

A. Safety

1. **Magnetic force.** Cardiac MRI scanners typically utilize powerful magnets of 1.5 to 3.0 T, several tens of thousands of times stronger than the earth's magnetic field (0.00005 T). Large or small ferromagnetic objects in the vicinity of the MRI magnet bore can become fast moving projectiles, which may cause severe injury to patients and/or damage the MRI scanner. Health-care professionals working in the vicinity of an MRI scanner require MRI safety training and should be vigilant to risk posed by patients and health-care professionals not familiar with the danger.
2. **Magnetic field gradients.** Switching magnetic field gradients during a CMR study produces high acoustic noise levels (up to 115 dB) and can also lead to peripheral nerve stimulation. The FDA has determined limits to the power of magnetic field gradients and noise exposure. Headphones and earplugs are recommended to prevent discomfort and hearing loss to patients and MRI staff in the vicinity of the scanner.
3. **Bioeffects of RF energy.** The majority of RF energy to the patient is dissipated as heat and is recorded as the specific absorption rate (SAR). One SAR equals 1 J of RF energy per second per kilogram of body weight (i.e., watts per kilogram). The recommended SAR limit for the whole body is 4 W/kg.

B. Patient preparation

1. **Screening.** All patients should be screened for contraindications to MRI before the procedure (Table 50.2).
2. **Patient size.** Although the maximum table load weight limit is fairly generous (~250 kg or 550 lb), because of the fixed internal diameter of the magnet bore, very large patients may not fit within the MRI magnet. Typically, patients with a torso circumference of >60 cm cannot be imaged. Discussion with the MRI technologist before scanning is recommended for specific recommendations related to your unit.
3. **Claustrophobia.** The enclosed space of the magnet poses problems for many patients, even those who do not have a history of claustrophobia. The study can usually be successfully completed with the help of clear communication with the patient before and during the procedure and/or with light oral sedation (e.g., lorazepam 0.25 to 0.5 mg) 30 to 60 minutes before the procedure.
4. **Attire.** Patients should wear a cotton hospital gown with no metal snaps. All metal items, jewelry, and nylon undergarments should be removed for reasons of safety and possible image degradation.
5. **Body coil.** Phased array body coils are placed on the patient's torso over the imaging area of interest. These use several smaller coils to acquire RF signals simultaneously and to facilitate parallel imaging. Some of these coils, for example, enable performance of 3D cardiac cine examinations with full-ventricle coverage in a single breath-hold. The net result is not only better image quality but also reduced exam time for the patient.
6. **Electrocardiogram (ECG) monitoring.** A good electrocardiographic tracing is essential for CMR. Although three or four MRI-safe, nonmetallic electrodes are placed on the patient's chest and a single lead signal is used to trigger or gate the MRI images, the magnetic field affects the ECG tracing by inducing a voltage created by ions flowing within blood vessels (magnetohydrodynamic effect). This voltage artifact is commonly superimposed on the ST-segment (during the ejection of blood in systole), increasing its amplitude and causing false QRS detection in certain algorithms. Use of vector cardiogram allows the R–R interval to be registered as a 3D spatial vector that varies in magnitude and

direction throughout the cardiac cycle. Furthermore, the use of fiber optic cables (instead of carbon leads) has also decreased the potential ECG interference of RF pulses and/or gradient field switches.

7. **Emergencies.** CMR is not appropriate in patients who are clinically unstable because of difficulties monitoring and treating patients within the magnet bore. Although MRI-safe equipment is available, it is safer to prescreen the patient's clinical status and determine the need of CMR study before initiating the scanning.

8. **Pregnancy.** There is insufficient evidence regarding the safety of MRI in pregnant patients. Current guidelines state that MRI may be used in pregnant patients where other forms of nonionizing imaging are inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation.

9. **Children.** CMRI may be necessary in pediatric patients with congenital and acquired cardiovascular disease. Typically, children younger than 8 years will require general anesthesia.

V.CLINICAL APPLICATIONS

A. Diseases of the aorta

1. **Aortic aneurysm.** MRI can clearly visualize both the aortic vessel wall and the lumen. It is a reliable method for the identification, characterization, and follow-up of thoracic and abdominal aortic aneurysms, with accuracy comparable to that of computed tomography (CT). A combination of spin-echo sequences for characterization of the vessel wall, gradient echo cine sequences for dynamic imaging of the aorta and aortic valve, and contrast-enhanced magnetic resonance angiography (CE-MRA) for aortic and branch vessel luminography is typically used. The aorta may be highly tortuous and should be imaged in multiple planes, with double-oblique measurements performed from true short-axis cuts using reconstructed images.

2. **Aortic dissection.** MRI is a highly sensitive and specific technique for the detection of aortic dissection (sensitivity 98% to 100%, specificity 98% to 100%). Spin echo, B-SSFP, and CE-MRA are used to identify the intimal flap, true and false lumens, and involvement of aortic branch vessels, including the coronary arteries. Administration of contrast is not critical to the examination, making CMR particularly helpful in patients with significant renal impairment. In addition, potential complications of aortic dissection (e.g., pleural effusion, pericardial tamponade, and aortic regurgitation) are easily evaluated. However, the longer study acquisition time with MRI compared with CT and its unsuitability for imaging of unstable patients limit its application in the acute setting. However, MRI is well suited for follow-up of both surgically and medically treated aortic dissections.

3. **Intramural hematoma and penetrating aortic ulcer.** Intramural hematoma can be considered as the forme fruste of aortic dissection because of the spontaneous rupture of vasa vasorum within the media of the aortic wall. It occurs in up to 30% of all acute aortic syndromes and appears as a smooth crescentic area of thickened aortic wall without evidence of blood flow in the false channel on either B-SSFP or spin-echo sequences. Because of the short T1-relaxation time of fresh blood, differentiation from the adjacent mediastinal fat may be difficult. Intramural blood can be best detected on fat-saturated T1-weighted gradient echo or black-blood techniques. Furthermore, on spin-echo ("black-blood") imaging, the intramural hematoma may be isointense (acute) or hyperintense (subacute) relative to skeletal muscle. Penetrating aortic ulcers appear as deep ulcerations of

an aortic atheroma that extend through the intima to disrupt the underlying media and cause bulging of the outer aortic contour. They commonly appear at the isthmus beyond the left subclavian artery and in the distal descending thoracic aorta near the diaphragm. If acute, there may be evidence of intramural bleeding in the rim adjacent to the ulcer.

4. **Atherosclerotic disease.** MRI can clearly show irregular thickening of the aorta in atherosclerotic disease. CE-MRA has good accuracy for detecting significant peripheral stenoses and occlusions.

5. **Aortic trauma.** MRI can detect chronic or missed aortic tears, usually related to a previous motor vehicle accident. Tears are usually found in the area of the ligamentum arteriosum and diaphragmatic hiatus and are characterized by a localized saccular aneurysm, with or without associated periaortic hematoma.

6. **Aortitis.** In patients with inflammatory disorders affecting the aorta such as Takayasu disease (which tends to also involve the arch branch vessels) or giant cell arteritis, MRI can accurately detect diffuse wall thickening of the thoracic and abdominal aorta (especially after gadolinium administration in T1-weighted images) as well as stenosis and occlusion of the aortic branch vessels (CE-MRA sequences). Special imaging sequences using T2-weighting and short-tau inversion recovery for fat suppression allow assessment of wall edema and wall thickening/inflammation, respectively.

7. **Aortic stents and stent grafts.** Aortic stents and stent grafts can be safely imaged using MRI; however, both cine sequences (gradient echo and B-SSFP) are prone to ferromagnetic artifacts. Spin-echo imaging can be used successfully to evaluate stent graft morphology. Artifacts may limit assessment for endoleak using CE-MRA.

B. Assessment of ventricular function and coronary artery disease (CAD)

1. **Assessment of global ventricular function.** CMR is the gold standard for the assessment of ventricular mass, volumes, and systolic function. A significant advantage of CMR is its reproducibility and accuracy compared with 2D planar or projection techniques that depend on geometric assumptions in order to define mass and volume determinations. As a result, small changes in myocardial mass and/or volume can be detected over time or because of therapy. A typical approach is to perform a short-axis stack of B-SSFP cine sequences through the left and right ventricles. Manual or semiautomated tracing of the endocardial borders at end diastole and end systole is later performed off-line, and ventricular volumes and ejection fraction are calculated.

2. **Assessment of regional ventricular function.** As mentioned before, development of multichannel phase-array coils has enabled parallel imaging and significant improvements in temporal resolution and scan times. This has led CMR to become superior to echocardiography for precise assessment of regional wall motion. B-SSFP cine sequences provide excellent blood-myocardial contrast that permits clear definition of the endocardial border. Furthermore, myocardial tagging methods have also improved the assessment of regional myocardial function.

3. **Myocardial ischemia.** CMR stress testing can detect myocardial ischemia with either wall motion or perfusion analysis. The use of dobutamine stress CMRI for wall motion analysis is relatively more established than stress perfusion imaging with adenosine or dipyridamole. Studies of stress CMR with dobutamine have revealed good sensitivity (83% to 92%) and specificity (86%) for the detection of significant CAD on a per-patient level. Furthermore, CMR tagging may further improve the accuracy of dobutamine CMR for

ischemia detection. Stress perfusion imaging by CMR has been shown to have slightly higher accuracy than that of thallium single-photon emission computed tomography (SPECT), with a sensitivity of 91% and specificity of 81% for the detection of significant CAD. The absence of ionizing radiation with MRI is an important consideration, particularly in younger patients.

4. **Myocardial infarction (MI) and viability.** T2-weighted spin-echo sequences with fat suppression may show areas of increased signal intensity consistent with tissue edema in the acute or subacute phase of an MI. This has been gaining interest as a target for clinical trials in acute coronary syndrome. The concept is that the myocardium at risk would correspond to the edematous minus the scarred area (seen on delayed enhancement). However, this technique has potential imaging artifacts (cardiac/respiratory motion, low SNR, slow flow, coil intensity profile, etc.) which could hinder the reproducibility of results seen in single-center studies. The current state-of-the-art technique for myocardial scar detection remains delayed enhancement imaging with an inversion recovery gradient echo sequence 10 to 30 minutes after injection of a gadolinium contrast agent. This method shows areas of myocardial scarring as bright and normal myocardium as dark and has shown excellent correlation with the location and extent of scar on histopathologic analysis. The superior spatial resolution of CMR makes it more sensitive for the detection of myocardial scar, and in particular subendocardial scar, than SPECT or positron emission tomography. In addition, detection of areas of microvascular obstruction, despite adequate epicardial vessel perfusion, can also be identified with CMRI and appear to be associated with worse outcomes. The transmural extent of scar is associated with myocardial viability. Transmural or near-transmural scar (>50%) suggests nonviable myocardium, whereas the absence of myocardial scar suggests that functional recovery is likely post revascularization.

5. **LV thrombus.** CMR is more sensitive than echocardiography for the detection of LV thrombus. Because of its high spatial resolution and tissue characterization capabilities, CMR can be quite advantageous in establishing or ruling out the diagnosis of intracardiac thrombus. The typical signal characteristics would include lack of contrast perfusion on first pass of gadolinium and low signal intensity on postcontrast delayed imaging with long inversion time (dark filling defect on the endocardial surface of the left ventricle).

C. **Nonischemic cardiomyopathies.** There is increasing recognition of myocardial fibrosis occurring in a variety of conditions in the absence of ischemia, including hypertensive and diabetic heart disease, hypertrophic cardiomyopathy (HCM), and idiopathic dilated cardiomyopathy (DCM).

Several new CMR techniques have been developed for the quantification of nonischemic myocardial fibrosis, with contrast-enhanced T1 mapping using a modified Look–Locker inversion recovery sequence being the most commonly used.

1. **Dilated cardiomyopathy.** CMR is useful for precise assessment of cardiac morphology and function in patients with DCM. In addition, delayed enhancement imaging will typically show enhancement in a mid-myocardial distribution in case of idiopathic cardiomyopathy.

2. **Hypertrophic cardiomyopathy.** MRI is accurate for the evaluation of the pattern and extent of hypertrophy, systolic anterior motion of the mitral valve, resting left ventricular outflow tract (LVOT) obstruction, and secondary mitral valve pathology and regurgitation. Because of the precise anatomic definition provided by CMRI, it is particularly helpful in planning for surgical myectomy or alcohol septal ablation. CMR can also help

identify abnormal chordal or papillary muscle attachments, which may contribute to LVOT obstruction and which have been reported in up to 20% of patients with HCM. Delayed enhancement is frequently seen in patients with HCM and corresponds to areas of interstitial fibrosis. It is typically seen in areas of increased wall thickness as well as right ventricular (RV) insertion points in the interventricular septum. The extent of delayed enhancement in patients with HCM has been linked to sudden cardiac death and worse outcomes.

3. **Infiltrative cardiomyopathy.** Infiltrative cardiomyopathy is typically characterized by normal ventricular size and systolic function, increased LV and/or RV wall thickness, severe diastolic dysfunction, and biatrial enlargement. CMR can clearly visualize the typical findings of infiltrative cardiomyopathy and help distinguish it from constrictive pericarditis, the main differential diagnosis. In addition, specific causes may be identified by CMR, particularly with the use of gadolinium enhancement imaging and based on the particular pattern of enhancement. For example, **diffuse subendocardial enhancement on delayed imaging is characteristic of cardiac amyloidosis**. Also, specific CMR sequences can be used for the assessment of particular disease states. For instance, **hemochromatosis is characterized by extensive signal loss on T2-weighted images, because of iron deposition in the myocardium**. Measurement of the T2 relaxation time of the myocardium (T2* technique) allows precise detection of the amount of iron overload. In addition, this T2* technique has been shown to be prognostically important, identifying patients with thalassemia at high risk for heart failure and arrhythmia.

4. **Arrhythmogenic right ventricular dysplasia (ARVD). CMR is frequently the imaging modality of choice in patients with suspected ARVD** to assess for the presence of RV dilation, global RV dysfunction, and/or regional hypokinesia. Of note, fibrofatty replacement of the RV myocardium on CMR is not a diagnostic criterion.

The CMR examination for ARVD includes, in addition to careful assessment of RV size and function, delayed enhancement imaging for identification of myocardial fibrosis.

D. Diseases of the pericardium. The normal pericardium appears on CMR as a thin (≤2 mm) curvilinear line between the epicardial and pericardial fat. The normal pericardium is of low intensity on both T1- and T2-weighted imaging sequences.

1. **Pericardial effusions** are typically of low intensity on T1-weighted spin-echo images and of high intensity on gradient echo images. The exception is hemorrhagic effusion, which is of high intensity on T1-weighted spin-echo images and of low intensity on gradient echo images.

2. **Pericarditis and constriction.** MRI can readily define the presence and extent of pericardial thickening (≥4 mm). In **inflammatory pericarditis**, the pericardium will typically have increased signal intensity on delayed enhancement imaging, reflecting neovascularization in the inflamed pericardium. CMR has become the imaging technique of choice for the diagnosis and management of **constrictive pericarditis**. Typical features include **pericardial thickening and tethering, associated with conical and tubular deformity of the right and left ventricles, respectively**. Secondary changes include atrial enlargement, systemic and pulmonary vein dilation, hepatomegaly, ascites, and pleural effusions. Cine sequences can demonstrate features of constrictive physiology, including diastolic septal bounce and abrupt cessation of diastolic filling. Furthermore, real-time cine sequences with free breathing can demonstrate the interventricular dependence with exaggerated septal shift toward the left ventricle during inspiration. However, it is important to

note that CMR is of limited value compared with CT in the evaluation of pericardial calcification because of its inability to visualize calcium (because of its lack of hydrogen ions).

3. **Congenital absence of the pericardium.** This is often left sided and can be complete or partial. It can be relatively easily demonstrated on CMR as it is typically associated with a leftward orientation and "teardrop" appearance of the heart. Insinuation of lung tissue between the aorta and pulmonary artery and between the inferior surface of the heart and left hemidiaphragm is also characteristically seen.

4. **Pericardial cysts.** These are benign developmental lesions formed when a portion of the pericardium is pinched off during embryogenesis. Pericardial cysts are classically seen at the right cardiophrenic angle. They typically contain fluid and are well marginated. Spin-echo images demonstrate round or ovoid lesions that are often contiguous with the normal pericardium. Simple cysts demonstrate low signal intensity on T1-weighted and high signal intensity on T2-weighted images. Hemorrhagic or proteinaceous filled cysts show high signal intensity on T1-weighted images.

E. Congenital heart disease. CMR has become a crucial tool in the management and follow-up of patients with congenital heart disease, particularly in cases with complex defects. Scans can be performed safely and reliably from infancy through adulthood. CMR provides excellent anatomic definition of simple and complex heart defects and precise, noninvasive quantification of valvular function, cardiac function (both left and right ventricle), and shunts. Common applications of CMR in adult congenital heart disease include noninvasive quantification of intracardiac shunts; evaluation of pulmonary regurgitation severity, ventricular volumes and function, and pulmonary artery branch vessel stenosis in patients post tetralogy of Fallot repair; identification of RV outflow tract or branch pulmonary artery obstruction in patients who are post arterial switch for dextro transposition of the great arteries (D-TGA); evaluation of baffle stenosis or leak and RV dysfunction in patients post Mustard or Senning procedure for D-TGA; and assessment for dysfunction of the systemic ventricle in patients with congenitally corrected or levo transposition of the great arteries (L-TGA).

F. Valvular heart disease. Although echocardiography remains the primary imaging modality for the diagnosis and management of valvular heart disease, CMR can provide additional important information in select cases. Particular strengths of CMR in the evaluation of valve dysfunction include an often clearer visualization of valve morphology, valve planimetry, precise quantification of regurgitant volumes, accurate and reproducible measurement of ventricular volumes and function, and assessment of associated abnormalities (e.g., bicuspid aortic valve and ascending aortic dilation).

G. Cardiac masses. CMR plays a major role in the evaluation of cardiac masses, mainly because of its ability to provide, in addition to excellent anatomic detail, tissue characterization. Thrombus is the most common intracardiac mass. Fresh thrombus has higher signal intensity than myocardium on T1-weighted images. Older thrombi may have increased signal intensity on T1-weighted and decreased signal intensity on T2-weighted images. Thrombi usually have low signal intensity on delayed enhancement imaging and do not demonstrate delayed enhancement even with long inversion time. Myxomas are the most common intracardiac tumor and, in addition to a heterogeneous and irregular

appearance, typically have higher signal intensity than myocardium on T2-weighted spin-echo imaging. Lipomas have a distinctive short T1 and, therefore, high signal intensity on T1-weighted images. Fat saturation sequences that null lipomatous tissue would confirm the diagnosis. Fibromas are an uncommon cardiac tumor and are typically seen within the ventricular myocardium in pediatric or young adult patients. They have decreased signal intensity relative to myocardium on T2-weighted images and show rim enhancement on delayed imaging.

Primary malignant tumors of the heart are rare. Imaging findings suggestive of a malignant cardiac tumor include a right atrial location, invasiveness without regard to the anatomical borders (i.e., involvement of >1 cardiac chamber, extension into the mediastinum or great vessels), associated hemorrhagic pericardial effusion, moderate or high contrast uptake on perfusion imaging (reflecting increased vascularity), and heterogeneous delayed enhancement. The most common is angiosarcoma followed by rhabdomyosarcoma. Angiosarcomas are most commonly seen in the right atrium and have a heterogeneous appearance with hyperintense areas on T1-weighted images. Delayed hyperenhancement shows heterogeneous enhancement, most marked in the periphery of the tumor. Metastatic heart disease is more common than primary cardiac tumors and typically involves the myocardium or pericardium. One limitation of CMR, as stated before, is its reduced sensitivity for the detection of calcification in cardiac masses.

H. Pulmonary veins. Imaging of the pulmonary veins is being increasingly performed prior to and after pulmonary vein ablation, to assess pulmonary venous anatomy and patency and look for complications, particularly pulmonary vein stenosis.

VI.FUTURE APPLICATIONS

A. Coronary artery assessment. Coronary imaging with CMR is usually performed with gradient echo sequences, with either fat saturation or T2 prepulses to enhance the signal difference between the coronary lumen and the surrounding myocardium, as well as to decrease the venous signal. Three-dimensional acquisition with navigator-corrected (free-breathing) data set has higher SNR when compared with 2D sequences and has become the established approach to contrast-enhanced MR coronary angiography. Although CMR can be used reliably for the detection of coronary artery anomalies, it has not yet fulfilled its early promise for noninvasive imaging of coronary atherosclerotic disease. The coronary arteries provide significant challenges to imaging by MRI because of cardiac and respiratory motion, their small size and tortuosity, normal cyclic variations in coronary flow, and competing signal from neighboring blood pools.

B. Molecular imaging. MRI shows significant promise for the selective imaging of target cells using novel molecular contrast agents. Magnetically labeled mesenchymal stem cells have been successfully tracked by MRI in pig models used for stem cell therapy in myocardial injury. Supermagnetic nanoparticles have also been used to detect atherosclerotic plaque in both animal and human studies.

C. Interventional CMR. The use of CMR in interventional procedures is appealing because it may allow for radiation-free catheterization procedures. However, its main limitation is the availability of devices that are safe to use in an MR environment.

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RECOMMENDED WEB SITES

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CHAPTER 51

Electrophysiologic Studies

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Thomas D. Callahan

I. INTRODUCTION. Electrophysiologic studies (EPS) are a specialized form of cardiac catheterization that help identify, characterize, and manage cardiac arrhythmias. Over the past 30 years, EPS have advanced our knowledge of mechanisms of cardiac arrhythmias and revolutionized the way these arrhythmias are managed. The studies should be performed by trained clinicians with the help of skilled laboratory personnel in appropriately equipped laboratories. A joint task force of the American College of Cardiology and the American Heart Association, in collaboration with the Heart Rhythm Society, has published guidelines outlining the accepted indications and the training required for personnel performing EPS.

II. INDICATIONS. The indications for EPS can be divided into three broad categories: bradyarrhythmias, tachyarrhythmias, and syncope.

A. **Bradyarrhythmias** can be caused by sinus node dysfunction, atrioventricular (AV) nodal disease, or infranodal conduction system disease. EPS for bradyarrhythmias are rarely necessary because the decision to implant a pacemaker depends primarily on correlation between symptoms and documented bradycardia or demonstration of severe bradycardia or prolonged pauses. EPS should complement the clinical evaluation, conventional 12-lead electrocardiogram (ECG), and Holter or event monitor. EPS can be of value in identifying disorders associated with adverse outcome such as severe infranodal conduction system disease.

B. EPS are of tremendous value in evaluating **tachyarrhythmias**. They are generally more successful in reproducing reentrant cardiac rhythms than those caused by triggered activity or enhanced automaticity. Among patients with reentrant tachyarrhythmias, EPS are useful in documenting the presence of the anatomic or physiologic substrate responsible for the arrhythmia, defining the electrical mechanism of the arrhythmia and its associated hemodynamic response, as well as guiding therapy. The response of the tachyarrhythmia during an EPS to various drugs or pacing maneuvers may also be helpful in further defining the underlying substrate and prognosis.

C. Patients with **syncope** of unknown etiology may benefit from EPS because bradycardia is often identified as the underlying disorder.

III. EQUIPMENT AND SETTING

A. The most important element in the performance of a safe and useful EPS is the presence of **well-trained personnel**. The presence of at least one trained physician and

well-trained laboratory support personnel, including a nurse, as well as engineering assistance to maintain and repair the laboratory equipment is necessary. Personnel involved should be familiar with basic electrophysiologic and electropharmacologic principles, the indications for EPS, and the various diagnostic and therapeutic modalities that can be used in the laboratory.

B. It is important that the laboratory be equipped with appropriate high-quality **radiographic equipment**.

C. Appropriate selection of **tools** is a very important aspect of the performance of a safe and cost-effective EPS. The minimum instrumentation required for a complete study is a stimulator, an amplifier, display monitors, reliable recording devices, and an external defibrillator.

1. The **stimulator** must be capable of burst pacing, delivery of at least three or four extra stimuli, synchronization to appropriate electric events during intrinsic or paced rhythms, and an adjustable current output. An appropriate unit should have a constant current source and minimal current leakage. It should also be relatively easy to manipulate.

2. The **junction box** connects the electrode catheters to the recording apparatus and the stimulator.

3. The presence of at least two functioning **external defibrillators** is extremely important, particularly during studies in which ventricular arrhythmias may be induced.

4. The presence of a cardiac surgical team in the same institution is not mandatory for routine EPS or simple radiofrequency (RF) ablation procedures. However, for more complex RF ablation procedures where full heparinization is used and where cardiac perforation is a potential complication, the presence of a cardiac surgical team allows for prompt, definitive therapy when surgical intervention is required.

D. **Intracardiac signals** are recorded using various **electrode catheters**.

1. The most common catheters used are **quadripolar woven Dacron polyester** or **polyurethane**. The distal poles of these catheters can be used for pacing.

2. For general purpose sensing and pacing in the atrium or ventricle, a **nondeflectable catheter** is usually sufficient. Deflectable catheters facilitate mapping and ablation by allowing more precise movement.

3. Interelectrode distance varies from 2 to 10 mm. Smaller interelectrode distance is useful for precise mapping and timing.

4. For most EPS, **bipolar recording** is used. However, in some situations, especially during mapping of tachyarrhythmias, unipolar recording can be of value in localizing the earliest sites of activity.

IV.TECHNIQUES AND PROCEDURES

A. Preprocedure preparation

1. Before the patient is taken to the EP laboratory, a discussion of the indications and proposed procedure is conducted with the patient, and informed consent is obtained.

2. For most indications, EPS is an **elective** procedure. The patient's condition should be **clinically stable** at the time of the study. EPS on patients who are unstable, including those with active, recent, or untreated coronary disease or those with clinical heart failure, carry much higher risk for complications.

3. **Electrolytes** and a **coagulation panel** are checked and verified as being within the acceptable range.

4. Conscious sedation is administered using a mild sedative (e.g., a benzodiazepine) and analgesic.

5. The patient is attached to continuous ECG and blood pressure monitoring devices.

B. Access and catheter placement

1. The usual approach to inserting electrode catheters is through the **femoral veins under local anesthesia** unless there is a clear contraindication to this approach such as the presence of deep venous thrombosis or an inferior vena cava filter. In the latter situations or when a coronary sinus (CS) catheter is difficult to insert, a superior vein approach may be used. We routinely utilize vascular ultrasound to directly visualize the femoral venipuncture, particularly when patients are on anticoagulation. This real-time visualization clarifies anatomic variants and enables us to avoid inadvertent arterial needlesticks and multiple passes that can lead to bleeding complications. Sheaths are then introduced into the vein over guidewires via the modified Seldinger technique.

2. Up to three **introducers** are placed in each femoral vein depending on the planned procedure. For patients with **left-sided bypass tracts or left ventricular (LV) tachycardia**, access to the left side of the heart is necessary. This can be achieved through the retrograde transaortic approach via an arterial access or by transseptal puncture via femoral vein access. Systemic heparin is used for all left-sided procedures, and the activated clotting time is monitored during the procedure to achieve adequate levels of anticoagulation.

3. For a complete EPS, three catheters are needed.

a. One catheter is placed in the **CS** or **high right atrium,** preferably in the appendage or against the high lateral wall. Another is placed in the **right ventricular (RV) apex,** and the third is placed across the **tricuspid valve** to obtain a His electrogram.

b. To obtain a **His electrogram**, the electrode catheter is advanced into the right ventricle across the anterior septal portion of the tricuspid valve. Under gentle clockwise torque, the catheter is then slowly withdrawn to straddle the tricuspid valve. A high-frequency sharp deflection that precedes ventricular activation and follows septal atrial activation represents a **His** or **proximal right bundle potential**. If the catheter is withdrawn further, this sharp signal occurs slightly earlier. A satisfactory position of the His catheter is achieved when an atrial signal is recorded followed by the His potential and, finally, the ventricular potential is recorded via the same pair of electrodes.

4. In **supraventricular tachycardia (SVT)** studies, when a left-sided accessory pathway or left atrial origin is suspected, an octapolar or decapolar catheter may be placed in the CS rather than in the high right atrium. This more stable catheter position allows mapping of the left AV groove along the mitral annulus. Although the CS is easily entered from the superior venous approach, successful catheterization is expected in most attempts through the femoral approach as well. The catheter is placed in the CS with the proximal electrodes just inside the CS ostium.

C. Baseline assessment

1. When all the catheters are in place, a baseline ECG (generally leads I, aVF, V_1, and V_6) and intracardiac electrograms are obtained (Fig. 51.1).

2. In general, **cycle lengths** rather than beats per minute are measured. The following measurements are made at baseline: sinus cycle length and PR, QRS, QT, AH, and HV intervals. To convert an arrhythmia's rate from cycle length to beats per minute, divide 60,000 by the cycle length to obtain the arrhythmia rate in beats per minute.

a. The **AH interval** is measured from the onset of the local A deflection to the H deflection on the His electrogram.

b. The **HV interval** is measured from the H deflection on the His electrogram to the earliest ventricular activity in any lead (surface or intracardiac).

3. When measurements are made during pacing, it is important to **measure from the resulting deflection** rather than from the pacing artifact to avoid errors caused by latency (delay between the pacing artifact and activation at the recording site).

4. All measurements are recorded in **milliseconds**. Interpretation of baseline intervals is shown in Figure 51.2.

D. Programmed stimulation

1. After baseline measurements are made, programmed stimulation is performed. The protocol depends on the indication for the study and varies among institutions. During programmed stimulation, the **hemodynamic response** of the patient to pacing and induced tachycardia is closely monitored. For example, rapid ventricular pacing in patients with structural heart disease may result in transient hypotension. If this occurs, pacing should be limited in duration, and adequate time between pacing drive trains should be allowed for hemodynamic recovery.

2. **Pacing stimuli** are usually delivered with a 1 or 2 ms pulse width at twice diastolic pacing thresholds. This is important during ventricular stimulation because pacing at higher outputs increases the risk of inducing nonclinical rhythms. There are two main types of programmed stimulation: burst pacing and the extra stimulus technique.

a. **Burst pacing** involves continuous pacing at rates faster than the patient's intrinsic rate.

b. In the **extra stimulus technique**, premature beats are introduced either during intrinsic rhythm (sensed extra stimuli) or after a paced drive train (paced extra stimuli). Extra stimulus techniques are useful in evaluating refractory periods of the AV node, atrial tissue, ventricular tissue, and accessory pathways. It is possible to evaluate infranodal conduction system refractory periods with atrial or ventricular stimulation. Extra stimulus techniques are also useful in inducing, terminating, and identifying reentrant arrhythmias.

FIGURE 51.1 Normal baseline intervals. Typically, up to four surface ECGs (I, aVF, V_1, and V_6) are displayed along with atrial (CS), His (HBE), and ventricular (RVA) electrograms. CS7–8 refers to the proximal bipolar CS electrogram. Fast sweep speeds are used, ranging from 100 to 400 mm/s. On the time scale, each large division is 100 ms, and each minor division is 10 ms. In addition to intervals, pattern of atrial and ventricular activation should be evaluated. If the CS catheter is placed correctly (see text), the earliest A in sinus rhythm is seen on the HRA electrogram (not shown), then on the His electrogram, and progressively later along the CS electrograms. In the absence of bundle branch block or left-sided accessory pathway, the earliest ventricular activity is seen on right-sided electrograms (His and RV electrograms). CS, coronary sinus; ECG, electrocardiogram; HBE, His bundle electrogram; HRA, high right atrium; RVA, right ventricular apex. (Reprinted with permission from Griffin BP, Rimmerman CM, Topol EJ,

eds.*The Cleveland Clinic Cardiology Board Review*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.)

1. 1 In the **sensed extra stimulus** technique, a single extra stimulus (S_2) is introduced initially with a coupling interval just below the intrinsic rate. The coupling interval is reduced progressively by 10 to 20 ms until the premature stimulus no longer captures. A pause of 2 to 5 seconds is allowed between stimulation sequences. Multiple extra stimuli (S_3, S_4) can be added if necessary, and the sequence can be repeated.
2. 2 In the **paced extra stimulus** technique, a drive train of 6 to 10 beats at a fixed cycle length is followed by a premature beat. The drive train cycle length (S_1S_1) usually ranges from 350 to 800 ms (most frequently, 400 to 600 ms) but depends on the resting heart rate. When this technique is used, testing at two drive train cycle lengths is recommended. The premature stimulus (S_2) is introduced with a coupling interval just below the S_1S_1. The coupling interval of the premature stimulus is decreased progressively by 10 to 20 ms until it no longer captures. The longest coupling interval (S_1S_2) that does not capture the myocardium is the absolute refractory period. S_3 and S_4 are added if necessary. This protocol can vary depending on the indication and operator preference.

FIGURE 51.2 Programmed ventricular stimulation using double extra stimuli in a patient with atrioventricular (AV) node reentry tachycardia. Note that the earliest retrograde atrial activity is seen on the His electrogram. CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

3. **Continuous monitoring** and recording of external and intracardiac electrograms is maintained throughout programmed stimulation. When a particular event such as a tachycardia occurs, stimulation is stopped and the event evaluated. The operator should be ready to respond to the event appropriately, depending on the hemodynamic effect of the event. For example, induction of a sustained tachycardia may result in severe hypotension, angina, or loss of consciousness. In such circumstances, expeditious termination of the tachycardia is indicated through overdrive pacing or cardioversion. The operator should also be ready to perform pacing or other maneuvers to further assess the mechanisms and reentrant circuit of the induced tachycardia.

V.ATRIAL STIMULATION

A. An atrial study is an integral part of an EPS. The only time an atrial study is not performed is in the presence of persistent atrial fibrillation.

1. **Burst atrial pacing** at incremental rates causes slowing of AV nodal conduction (a process known as decremental conduction) and can induce tachycardia, including AV nodal reentry tachycardia and AV reentrant tachycardia. Other forms of tachycardia unrelated to AV nodal conduction can also be induced, such as atrial flutter, atrial fibrillation, atrial tachycardia, and certain forms of idiopathic ventricular tachycardia.
2. Burst pacing is performed by means of **continuous pacing** (e.g., 10 to 20 stimuli) at a fixed cycle length starting at 100 ms below the baseline cycle length. Repeat burst pacing is performed at progressively shorter cycle lengths until 1:1 conduction through the AV node is no longer maintained. The shortest cycle length showing consistent 1:1 conduction through the AV node is recorded. This is related to the **effective refractory period** of the AV node, which is the longest A_1–A_2 interval that fails to be conducted to the His bundle. Another interval that can be measured is the **functional refractory period** of the AV node, which is

defined as the shortest output interval from the AV node to the His bundle given any input signal.

3. If a patient is believed to have **atrial flutter** or **atrial tachycardia**, repeat burst pacing at even shorter cycle lengths is performed until 1:1 atrial capture is no longer maintained.

B. Another form of atrial stimulation that is performed is paced extra stimulus.

1. The **effect of atrial premature beats** on the AH interval is assessed. The normal response of the AH interval is to progressively prolong with shorter A_1A_2 coupling. This is a direct demonstration of the normal decremental conduction properties of the AV node.

2. At a critical A_1A_2, the AV node fails to conduct, and on the His electrogram an atrial signal is seen without a His or ventricular deflection. This indicates that a **block has occurred in the AV node**. It is important to continue stimulation until the atrial refractory period is reached because a gap phenomenon may occasionally exist.

3. The **gap phenomenon** is demonstrated by apparent achievement of the AV nodal refractory period followed by resumption of conduction at shorter A_1A_2 coupling intervals. It reflects functional differences in conduction velocity or refractoriness in several regions of the AV junction.

4. If **narrow complex tachycardia** is induced, it is evaluated with regard to type, mechanism, response to maneuvers, and method of termination (see Section IX.B.3).

C. Sinus node evaluation. For patients who may have underlying sinus node dysfunction, sinus node tests are sometimes performed.

1. **Sinus node recovery time (SNRT)** is evaluated through burst pacing at various cycle lengths in the atrium for 30 to 60 seconds, followed by abrupt termination of pacing. SNRT is the escape interval between the last paced atrial beat and the first atrial recovery beat. A **corrected sinus node recovery time (CSNRT)** is calculated by subtracting the baseline sinus cycle length from SNRT. A normal value for CSNRT is <550 ms. SNRT is used to evaluate the automaticity mechanism of the sinus node.

2. **Sinoatrial conduction time (SACT)** is a combined measure of conduction in the atrial tissue that includes the area of the sinus node and sinus node automaticity. The assumptions are, first, that the conduction times into and out of the sinus node are equal; second, that the pacing train does not alter the automaticity of the sinus node; and, third, that the pacemaker site does not change after premature stimulation. The SACT is measured with one of two methods.

a. In the **Strauss method**, a premature atrial beat is used to reset the sinus node, and the return cycle length after the premature beat is measured. The basic cycle length is subtracted from the return cycle length. The remainder is the time necessary to penetrate and leave the sinus nodal tissue. The SACT is one-half this interval.

b. In the **method proposed by Narula**, the same measurements are obtained after pacing for eight beats at a rate slightly faster than the sinus rate. The upper range of the SACT is 100 to 120 ms.

3. The sensitivity of each individual (SACT and SNRT) test in diagnosing sinus node dysfunction is approximately 50% when used alone and 65% when combined. The specificity of the two combined tests is 88%, which gives the test a high positive predictive

value. However, because of its low sensitivity, a normal test does not exclude sinus node disease.

VI.VENTRICULAR STIMULATION

A. Ventricular stimulation is performed in the evaluation of suspected SVTs or ventricular tachyarrhythmias. Some SVTs, such as unusual forms of AV nodal reentry, may be more easily induced with ventricular stimulation. To further characterize the tachycardia, the response of the tachycardia to premature ventricular beats can be assessed.

1. When ventricular stimulation is performed for the evaluation of ventricular or wide complex tachyarrhythmias, **pacing at two or more sites** may be necessary. These sites are, typically, the RV apex and the RV outflow tract.

2. Before programmed stimulation is begun, pacing thresholds are determined, and the output of the pacing stimulus is set to twice the diastolic capture threshold. Higher outputs or coupling intervals shorter than 200 ms may cause induction of nonclinical arrhythmias.

B. **Burst pacing in the right ventricle** is one of two techniques used when assessing retrograde ventriculoatrial (VA) conduction in the evaluation of SVT.

1. The presence of retrograde atrial activation is documented, and the sequence or pattern of atrial activation is evaluated.

2. The **earliest atrial activity** during retrograde conduction via the AV node is typically recorded on the His electrogram (see Fig. 51.2). This indicates that retrograde conduction has proceeded through the fast pathway of the AV node. **Absence of VA conduction**, with rare exceptions (e.g., the Mahaim type of accessory pathway, which conducts only in the antegrade direction), excludes the presence of a bypass tract. The **presence of eccentric atrial activation** (late atrial activation on the His electrogram; see Fig. 51.3) suggests the presence of a retrogradely conducting bypass tract.

3. For some patients with no evidence of retrograde VA conduction, infusion of low doses of **isoproterenol** or a small dose of atropine (0.5 mg) restores this property to the AV node.

4. The shortest paced cycle length capable of 1:1 conduction to the atrium is documented.

C. **Premature ventricular stimulation** is another technique used to evaluate retrograde conduction properties of the heart.

1. If retrograde conduction is present, the refractory periods of the conducting pathways are determined with the extra stimulus technique.

2. In patients with **retrograde VA conduction through the AV node**, conduction block of a ventricular premature beat frequently occurs in the His-Purkinje system rather than in the AV node. His-Purkinje conduction block is more likely to occur at long drive trains. Such drive trains are therefore more likely to induce AV reentry tachycardia (using a bypass tract) by facilitating retrograde His-Purkinje block and allowing a retrograde-conducted beat through the pathway to propagate antegrade through the AV node.

D. In patients being evaluated for **ventricular arrhythmias**, programmed stimulation with extra stimuli is the initial technique used. Pacing at two drive train cycle lengths (e.g., 600 and 400 ms) is performed with single, double, and triple extra stimuli. Simultaneous atrial pacing at the same drive train cycle length is sometimes necessary to avoid competition from the intrinsic atrial pacemaker.

E. Like the A_1A_2 technique described earlier, **V2 is introduced at progressively shorter coupling intervals** (V_1V_2) until V_2 no longer captures (ventricular refractory period). Then V_2 is set at a coupling interval longer than the refractory period, and **V3 is introduced** at progressively shorter coupling intervals until it no longer captures. The use of **triple extra stimuli** (V_3V_4) is usually reserved for patients being evaluated for ventricular arrhythmias. A pause of 3 to 5 seconds is allowed after each cycle to assess response and for the patient to recover after ventricular pacing. An increase in the number of extra stimuli increases the sensitivity of the study in reproducing clinical arrhythmias, but at the cost of a lower specificity due to initiation of polymorphic ventricular tachycardia or ventricular fibrillation. If programmed stimulation with ventricular extra stimuli does not induce ventricular tachycardia in a patient at very high risk, other techniques may be used. One is **burst pacing in the ventricle**. A series of about 10 paced ventricular beats are introduced at a constant cycle length. The paced cycle length is then decreased by 50 to 100 ms in successive bursts until reaching within 50 ms of the predicted refractory period of the right ventricle, when the decrements proceed at 10-ms intervals until 1:1 capture is no longer maintained or 200 ms is reached. Burst pacing in the atrium can sometimes induce idiopathic LV tachycardia in susceptible patients.

FIGURE 51.3 This is an example of a 17-year-old patient with left lateral manifest pathway. Ventricular stimulation results in retrograde atrial activation, with the earliest A seen in CS1–2 (eccentric atrial activation). CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

F. In some patients, particularly those with underlying dilated cardiomyopathy, **bundle branch reentry (BBR) tachycardia** (see Fig. 51.4) may be induced.

1. This type of tachycardia usually involves the right bundle branch as the antegrade limb and the left bundle branch as the retrograde limb of the reentrant circuit. It is usually a rapid and hemodynamically unstable tachycardia.

2. Because His bundle refractoriness increases after a pause, a short–long–short stimulation sequence can be used to cause retrograde block in the right bundle so that the paced stimulus can conduct retrograde up the left bundle branch and possibly initiate tachycardia if the right bundle branch is no longer refractory for antegrade conduction.

3. The sequence most commonly used consists of a 6-beat drive train at 400 ms, followed by V_2 coupled at 600 to 700 ms. V_3 is then introduced at a coupling interval 100 ms longer than the refractory period of the ventricle. V_2V_3 is progressively decreased until V_3 no longer captures. V_4 can be introduced if necessary.

VII. INDUCTION OF VENTRICULAR FIBRILLATION. Under certain circumstances, the operator may decide that induction of ventricular fibrillation is necessary. This is valuable when testing implantable defibrillators for detection of arrhythmias and during assessment of defibrillation thresholds. Ventricular fibrillation can be induced by means of direct application of alternating current or rapid ventricular pacing at high output. The current can be delivered through a catheter electrode or through the **implantable cardioverter–defibrillator (ICD)** lead. Another means of inducing ventricular fibrillation is to deliver a low-energy shock (around 1 J) via the intracardiac leads at the peak of the T wave.

FIGURE 51.4 Bundle branch reentry tachycardia. This example is from a 52-year-old man with dilated cardiomyopathy who presented with syncope. This ventricular tachycardia exhibits left bundle branch block morphology, and there is an H deflection preceding every V on the His electrogram. To be absolutely certain of this diagnosis (as opposed to myocardial ventricular tachycardia with retrograde His), one has to look for cycle length variation and document that changes in the H–H interval precede changes in the V–V interval. HBE, His bundle electrogram; RVA, right ventricular apex.

VIII. USE OF CARDIOACTIVE DRUGS DURING EPS. Cardioactive drugs can be used during EPS as diagnostic or therapeutic agents. The drugs most commonly used are isoproterenol, procainamide, atropine, and adenosine.

A. **Isoproterenol** in doses ranging from 0.5 to 5 µg/kg/min is used during EPS to facilitate induction of SVTs and ventricular tachyarrhythmias.

1. For patients with SVTs that are AV node dependent, isoproterenol facilitates conduction through the AV node by means of shortening its refractoriness.

2. It is not absolutely certain how isoproterenol facilitates induction of ventricular tachycardia, but possible mechanisms include enhanced conduction, altered refractoriness, and enhanced automaticity related to delayed afterdepolarization.

3. Isoproterenol is particularly useful in evaluating patients with exercise-induced ventricular tachycardia and special types of RV outflow tract tachycardia. Isoproterenol is contraindicated in the presence of critical coronary artery disease.

4. Adrenergic stimulation with high doses of isoproterenol (up to 20 µg/min) also effectively induces repetitive rapid discharges from the pulmonary veins that frequently trigger initiation of atrial fibrillation (see Section **IX.B.3**).

B. **Procainamide** is used less frequently during EPS. Among patients believed to have advanced underlying conduction disease, the response of the infranodal conduction system to procainamide infusion (10 to 15 mg/kg) is assessed during sinus rhythm and with atrial pacing.

1. Considerable prolongation of the HV interval or induction of infranodal block with atrial pacing at cycle lengths longer than 400 ms is considered by many experts to be evidence of His-Purkinje disease. Procainamide can facilitate the induction of atrial and ventricular arrhythmias by means of slowing conduction.

2. Procainamide is often used to prevent recurrent atrial fibrillation when programmed atrial stimulation is necessary. An example would be a patient with atrial flutter who is being evaluated for ablation and is easily induced into atrial fibrillation during programmed stimulation.

3. Procainamide was widely used in the past for risk assessment among patients with inducible ventricular tachycardia. Studies have shown that patients with suppressible ventricular tachycardia have better long-term prognosis (lower rate of clinical recurrence and lower mortality) than those with nonsuppressible ventricular tachycardia. However, with wider use of ICDs and evidence of their superiority even among persons with suppressible ventricular tachycardia, this application of procainamide may be of historical interest only.

C. **Adenosine**, in doses that produce transient AV block (6 to 18 mg), is used frequently in EPS of patients with SVT to define the mechanism of the tachycardia,

establish AV node dependence, or document the presence or absence of accessory pathway conduction before and after RF ablation. It may also be used after atrial fibrillation ablation to assess inducibility of atrial fibrillation.

IX. INTERPRETATION OF FINDINGS IN EPS

A. Bradyarrhythmia evaluation. EPS are ***not*** indicated when symptomatic bradycardia is documented. Among patients who have a clear indication for implantation of a permanent pacemaker, findings of EPS are unlikely to alter clinical decision making. However, EPS are more helpful in patients believed to have symptoms related to underlying **sinus node dysfunction or conduction system disease** when noninvasive monitoring has failed to document a correlation between bradycardia and symptoms. EPS are also helpful in assessing patients who continue to have symptoms after permanent pacemaker implantation.

1. Baseline evaluation. Sinus bradycardia, sinus arrest with junctional or ventricular escape, various degrees of heart block, and intraventricular conduction delay, isolated or in various combinations, may occur among patients with bradycardia and can be further evaluated by examining intracardiac recordings.

a. **Conduction intervals** are measured and evaluated. Disease in the AV node often produces prolongation in the AH interval, whereas disease in the infranodal conduction system produces prolongation in the HV interval.

b. A long HV interval is suggestive but not diagnostic of an underlying bradyarrhythmia. It is commonly associated with wide QRS on surface ECG. A long HV interval at rest can be considered an indication for prophylactic pacemaker implantation (class IIa) if it exceeds 100 ms.

c. Documentation of intermittent spontaneous infranodal block or infranodal block in response to atrial pacing (see Fig. 51.5) or upon administration of procainamide is an indication for implanting a permanent pacemaker.

2. Programmed stimulation

a. After baseline intervals are measured, **SNRT and SACT** are determined. SNRT is used to evaluate automaticity of the sinoatrial node.

FIGURE 51.5 Infrahisian block in response to slow atrial pacing. This tracing is from a 70-year-old man who presented with syncope. Baseline H–V was 110 ms. As shown in this tracing, burst pacing in the right atrium at cycle length of 700 ms resulted in intermittent infrahisian block (H deflections not followed by V). This patient had a dual-chamber pacemaker implanted. HBE, His bundle electrogram; RVA, right ventricular apex.

b. Rapid pacing causes overdrive suppression of the sinus node. Among patients with sinus node dysfunction, recovery time after cessation of pacing is prolonged. The situation is similar to sudden termination of atrial fibrillation, which can be followed by a prolonged postconversion pause.

c. After cessation of pacing, the longest SNRT following pacing at varying cycle lengths and secondary pauses is documented. Secondary pauses are those intervals related to the sinus beats that occur after the first escape beat. CSNRT, which is calculated by subtracting baseline cycle length from SNRT, is considered abnormal if it exceeds 550 ms.

d. **SACT** is used to evaluate conduction velocities in the atrium and in tissues surrounding the sinoatrial node. SACT is performed with the methods described

earlier. A normal SACT is between 50 and 125 ms. When both CSNRT and SACT are normal, symptoms are uncommon. The sensitivities of CSNRT (54%) and SACT (51%) combined are higher (64%), and the specificity is approximately 88%. The low sensitivity of these tests limits their value in predicting the development of symptoms in asymptomatic patients.

e. **AV nodal and infranodal conduction system integrity** are tested with atrial stimulation techniques. Attention is paid to the AH and HV intervals during atrial pacing.

1. 1 The refractory period of the AV node is determined at two cycle lengths. The shortest cycle length with 1:1 AV conduction is also determined.

2. 2 The normal AV nodal response to burst pacing at short cycle lengths is second-degree Mobitz I AV block. HV interval prolongation or infrahisian block is not typically observed. If it occurs at cycle lengths longer than 400 ms, HV interval prolongation suggests significant underlying His-Purkinje disease.

3. 3 Prolongation of the AV nodal refractory period is most frequently caused by high vagal tone or concomitant use of medications. It has no predictive or diagnostic value in evaluating patients believed to have bradycardia. However, a long AV nodal refractory period may mask underlying abnormal His-Purkinje refractoriness, and enhancement of AV nodal conduction with atropine or isoproterenol may be necessary during EPS.

3. **Carotid sinus massage** is performed in all patients undergoing evaluation of bradycardia or syncope.

a. Firm pressure is applied over the carotid artery pulsation behind the angle of the mandible.

b. A **positive cardioinhibitory response** is present if pauses of 3 seconds or more occur. A **vasodepressor response** is present if blood pressure decreases by >50 mm Hg in the absence of marked bradycardia. Mixed responses are common.

B. **SVT evaluation.** One of the most important elements in the evaluation of tachyarrhythmias is careful analysis of the surface ECG during clinical tachycardia. This can give several clues to the underlying diagnosis and make the EPS more focused. Most SVTs that are induced in the EPS laboratory are reentrant. They include AV nodal reentry tachycardia, orthodromic AV reentry tachycardia, atrial flutter, and reentrant atrial tachycardia. Automatic tachyarrhythmias are relatively uncommon except in acutely ill patients. They characteristically exhibit a warm-up phenomenon and are difficult to induce with extra stimulus techniques but may be induced with drugs such as isoproterenol.

1. **Baseline evaluation**

a. Resting ECG and intracardiac recordings can provide important information about a possible cause even before any tachycardia is induced. The presence of a short PR interval on the ECG and wide QRS complex with a slurred initial deflection suggests preexcitation.

b. Absence of preexcitation at rest does not rule out the presence of an accessory pathway. For the diagnosis of SVT, an atrial and a ventricular study have to be performed.

c. If tachycardia is not induced with the baseline study, programmed stimulation in the atrium and ventricle is repeated with isoproterenol.

d. Some SVTs, particularly those involving AV reentry using a bypass tract, can be induced with ventricular stimulation, whereas atrial flutter and atrial tachycardia are rarely induced by means of ventricular stimulation.

2. **Programmed stimulation** begins with burst pacing in the ventricle to document and characterize VA conduction. Absence of VA conduction practically excludes a concealed bypass tract, and ventricular extra stimulus technique may not need to be performed unless ventricular tachycardia is suspected.

a. **Earliest retrograde atrial activity** is usually seen on the His electrogram during normal retrograde atrial activation through the AV node. Early retrograde atrial activity on the distal CS electrogram, if the position of the CS catheter is correct, suggests the presence of a left-sided accessory pathway (see Fig. 51.4). Early atrial activity in the proximal CS electrodes suggests a posteroseptal pathway or AV node slow pathway conduction.

1. 1 Eccentric atrial activation is any atrial activation that does not activate the AV node and the area around the AV node first. This is frequently seen with retrograde ventricular stimulation when the retrograde impulse finds the AV node refractory. The site of earliest atrial activation is then in the distal CS catheter and not in the proximal area closest to the AV node/His bundle. Evidence of eccentric atrial activation may not be clear during burst pacing when there is fusion of retrograde impulses arriving through both the AV node and the accessory pathway.
2. 2 The retrograde 1:1 cycle length should be documented.
3. 3 Programmed ventricular stimulation is performed with single premature beats at two drive train cycle lengths (e.g., 600 and 400 ms). During programmed stimulation, the following are recorded:

1. (a) Retrograde refractory periods
2. (b) The pattern and any changes in retrograde atrial activation
3. (c) The site of retrograde VA block
4. (d) The presence of dual retrograde AV node function

4. 4 If an accessory pathway is found, its retrograde 1:1 conduction cycle length and refractory period are documented.

b. During atrial stimulation, particular attention is paid to the **AH and HV intervals.**

1. 1 Sudden prolongation of A_2H_2 of >50 ms in response to a decrement of 10 ms in A_1A_2 is called a **jump** (see Fig. 51.6) and has been classically described as a sign of dual AV nodal physiology. However, more recent reports have demonstrated that the normal AV node has dual pathways even if this "jump" is not demonstrated. Furthermore, initiation of AV nodal reentrant tachycardia does not require the presence of such a jump in the AV nodal conduction curve.
2. 2 Induction of reentrant tachycardias generally depends on the occurrence of **unidirectional block and conduction delay**. In the case of AV nodal reentry, antegrade block in the fast pathway combined with critical delay in the slow pathway allows the impulse to conduct retrograde on the fast pathway and excite the atrium. This first retrograde-conducted atrial depolarization is called an **echo beat** (see Fig. 51.6). If this echo beat succeeds in conducting antegradely down the slow pathway again and retrograde up the fast pathway, sustained AV nodal reentry occurs.
3. 3 **Induction of AV nodal reentry** is facilitated by the use of shorter drive train cycle lengths and, if necessary, use of more than one extra stimulus or rapid burst atrial pacing. Occasionally, initiation of AV nodal reentry requires ventricular pacing or premature beats.
4. 4 In the presence of an accessory pathway, the site of critical delay is also in the AV node. However, to induce orthodromic AV reentry tachycardia, antegrade block of an atrial impulse has to occur in the accessory pathway so that it is excitable by the time the same impulse propagates

through the AV node and ventricle and arrives to conduct retrogradely through the accessory pathway to the atrium (see Fig. 51.7).

3. **Evaluation of induced tachycardia**

a. If a tachycardia is induced, the first assessment is its **hemodynamic effect**. Hemodynamically unstable tachycardia should be immediately terminated. Only if the tachycardia is hemodynamically stable can further evaluations during tachycardia be conducted.

1. 1 Whether the QRS is narrow or wide, the relationship between the atrial rate and the ventricular rate is noted (AV association or dissociation).
2. 2 Lack of a 1:1 AV relation excludes AV reentry tachycardia and, for practical purposes, AV nodal reentry. In rare instances, AV node reentry tachycardia can exhibit 2:1 AV block.
3. 3 If the atrial rate is faster than the ventricular rate, the diagnosis is **atrial tachycardia or atrial flutter**, depending on the rate and pattern of atrial activation.
4. 4 If the ventricular rate is faster than the atrial rate, the diagnosis is ventricular tachycardia. Alternative causes for AV dissociation include AV nodal reentry tachycardia with block in the upper common pathway, reentry tachycardia with a nodofascicular pathway, or a junctional tachycardia with retrograde block.

b. When a **1:1 AV relationship** exists, **further evaluation** is needed. The following observations and techniques are helpful in arriving at the most likely mechanism.

1. 1 **Atrial activation.** The sequence of atrial activation during tachycardia is important in the differential diagnosis of SVT. Accurate placement of catheters is extremely important; catheter misplacement can lead to inappropriate conclusions or interventions. The **earliest site of atrial activation** is noted. As previously mentioned, if earliest atrial activation is in the distal CS, a left atrial tachycardia or AV reentry using a left-sided accessory pathway is most likely. If an accessory pathway is located in the posterior septum, the earliest A is seen in the proximal CS electrogram. This is also true if the atria are being activated through the slow pathway of the AV node, as in atypical AV nodal reentry tachycardia.

FIGURE 51.6 Atrioventricular (AV) nodal jump and echo. A 10-ms decrement in S_1S_2 resulted in marked prolongation of A_2H_2 by >300 ms. In addition, an echo beat with a short H–A is seen on the coronary sinus (CS) electrogram, a definite evidence of dual AV node physiology. The atrial premature beat, blocked antegrade in the fast pathway, was conducted with sufficient delay in the slow pathway to encounter a nonrefractory retrograde fast pathway. HBE, His bundle electrogram; RVA, right ventricular apex. **FIGURE 51.7** Orthodromic atrioventricular (AV) reentry tachycardia. In this example from a patient with a manifest right-sided accessory pathway, premature atrial stimulation (S) blocks in the accessory pathway (resulting in a narrow QRS complex), conducts with a longer A–V, and re-excites the atrium. The tachycardia is narrow complex, with an H–A interval of 180 ms. The earliest A is seen on the high right atrial catheter. AV, atrioventricular; HBE, His bundle electrogram; HR, high right atrium; RVA, right ventricular apex.

2. 2 The presence of **cycle length variation** during tachycardia helps predict the activation sequence. For example, a change in AA coupling interval before an equal change in HH or VV interval (with changing VA) suggests a diagnosis of atrial tachycardia.

1. (a) In cases of wide complex tachycardia in which there appears to be a 1:1 relation between H and V, HH interval change preceding VV interval change suggests supraventricular or BBR tachycardia.

2. **(b)** Cycle length variation may also be helpful when there is **slowing of tachycardia with the development of bundle branch block and acceleration with resolution of the block**. This finding is suggestive of AV reentry using an accessory pathway ipsilateral to the bundle branch block as the retrograde limb. This can be appreciated on the surface ECG. In fact, prolongation in tachycardia cycle length in association with a bundle branch block is caused by prolongation of the VA interval. The activation wavefront must travel down the contralateral bundle and across the intraventricular septum before it reaches the pathway. The change in cycle length is more pronounced with lateral pathways than with septal pathways.
3. **3 HA and VA intervals.** A constant HA or VA relation despite cycle length variation (even in the absence of bundle branch block) is highly suggestive of **AV nodal reentry or accessory pathway–mediated tachycardia.** The change in tachycardia cycle length is caused by varying antegrade conduction time through the AV node. The VA time can also be used to differentiate AV nodal reentry from AV reentry. A VA interval <70 ms is rarely seen with AV reentry and strongly suggests the diagnosis of AV nodal reentry (see Fig. 51.8). VA times in excess of 70 ms are seen with AV reentry and atypical AV nodal reentry (so-called fast–slow AV nodal reentry).
4. **4 Introduction of premature beats during tachycardia.** Premature ventricular beats are typically introduced during tachycardia at intervals when the His bundle is refractory. Because the normal retrograde path (His-AV node) is refractory, preexciting the atrium with a premature ventricular beat at those intervals is diagnostic of the presence of an accessory pathway capable of retrograde conduction. Consistent termination of tachycardia with such premature beats without retrograde conduction to the atrium is also diagnostic of AV reentry and excludes atrial tachycardia.
5. **5 Pacing maneuvers during SVT.** During SVT, ventricular pacing maneuvers can be a useful first step in diagnosing the mechanism of tachycardia. Ventricular pacing at a cycle length slightly faster than the tachycardia cycle length is referred to as ventricular overdrive (VOD) pacing. Successful entrainment occurs when VOD resets the tachycardia such that the atrial rate is accelerated to the paced ventricular cycle length and returns to the tachycardia cycle length when ventricular pacing stops and the tachycardia continues. An atrial–atrial–ventricular response upon cessation of VOD, or V–A–A–V response, is diagnostic of atrial tachycardia. A V–A–V response is most consistent with a reentry tachycardia. The relationship of the postpacing interval to the tachycardia cycle length can then be helpful in differentiating the type of reentry tachycardia.
6. **6 Initiation and termination of tachycardia.** To understand the mechanism of tachycardia, it is important to know the mechanism of initiation. For reentry to occur, block in one limb of the reentrant circuit and slow conduction in the other limb must take place. It is important to review the stimulation sequences that did not induce tachycardia and compare them with those that did. A sudden jump in the AH interval suggests, but is not diagnostic of, AV nodal reentry. Orthodromic AV reentry tachycardia develops during atrial stimulation after antegrade block in the accessory pathway takes place in combination with a critical delay in the AV node. With ventricular stimulation, AV reentry tachycardia develops after block occurs in the AV node or His-Purkinje system. Termination of the tachycardia simultaneous with AV node block (A with no H) suggests AV node dependence and is helpful in excluding AV node–independent tachycardias (atrial tachycardia and flutter).

FIGURE 51.8 Atrioventricular (AV) node reentry tachycardia. Tachycardia is narrow complex and characterized by very short V–A interval and an H–A interval of <70 ms. CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

4. **Significance of induced tachycardia.** With the exception of atrial fibrillation, induced reentrant SVTs signify the presence of an established anatomic circuit. After comparison with the clinical arrhythmia, the induced tachycardia can be considered clinically significant unless clear differences exist. If a wide complex tachycardia with a supraventricular mechanism is induced, the recording is compared with a clinical recording. If the QRS morphology is different from the clinical arrhythmia, a search for a ventricular arrhythmia may be warranted.

5. **Atrial flutter**, a special type of atrial tachycardia that involves a well-defined anatomic circuit, is amenable to curative catheter ablation techniques.

a. In the typical form of atrial flutter, the waveform travels counterclockwise around the tricuspid annulus. The circuit is bounded anteriorly by the tricuspid annulus and posteriorly by the crista terminalis and its inferior medial continuation as the eustachian ridge. The site of functional block appears to be in the isthmus region, which is the narrow corridor between the inferior tricuspid annulus and the inferior vena cava. The site of conduction delay or slowing appears to be caused by transverse conduction block into the crista, forcing the wavefront to enter the crista at its superior end before propagating down the crista into the isthmus region.

b. To induce counterclockwise atrial flutter, progressively more rapid (approximately 250 to 200 ms) burst pacing appears to be most successful and is performed anywhere medial to the isthmus. The impulses block in the isthmus and conduct counterclockwise around the tricuspid ring with sufficient delay to sustain atrial flutter. If burst pacing is used lateral to the isthmus, clockwise atrial flutter may be induced. Successful ablation of typical atrial flutter necessitates generation of bidirectional isthmus block by applying a line of RF lesions that spans the posterior isthmus from the tricuspid valve to the inferior vena cava (the cavotricuspid isthmus).

c. Less commonly, different types of atrial flutter in which the subeustachian isthmus is not part of the circuit are induced. These atypical flutters have many varieties and locations but share a common reentrant circuit that revolves around an area of conduction block or delay, usually scar tissue. Treatment involves creating an ablation line from the area of scar to an anatomic barrier or ablating critically narrowed reentrant paths within a scarred region. The success rates in ablating these atypical forms of atrial flutter are not as high as isthmus-dependent flutters.

6. **Atrial fibrillation.** Although atrial fibrillation is commonly induced during an EPS, routine EPS in patients with atrial fibrillation does not provide much clinical value except in patients with an accessory pathway. EPS in patients with an accessory pathway assists in risk stratification for sudden cardiac death if atrial fibrillation were to occur in the future. Refer to the chapter entitled “Cardiac Ablation” for more details about RF ablation therapies for atrial fibrillation.

C. Evaluation of accessory pathways

1. The **most common locations** for accessory pathways in decreasing order of frequency are left free wall, posterior region, posteroseptal region, right free wall, and the anteroseptal region. Concealed accessory pathways (no evidence of antegrade conduction) with only retrograde conduction are more common than manifest pathways, which have antegrade conduction manifested by delta waves on the surface ECG, the slurred initial deflection of the QRS that suggests preexcitation.

a. **Right-sided accessory pathways** are more likely than left-sided accessory pathways to be associated with **congenital heart disease**. An unusual type of right-sided accessory pathway is the atriofascicular accessory pathways, which originate in the right atrium, traverse the right anterior region of the tricuspid valve annulus, and insert in the region of the right bundle or the right-sided Purkinje network. These accessory pathways have unidirectional antegrade conduction with decremental conduction properties similar to an AV node. These pathways are frequently referred to as Mahaim pathways and typically do not conduct retrogradely.

b. **Multiple accessory pathways** are more frequently encountered on the right side and in survivors of sudden death. In these patients, the most common combination is posteroseptal and right free wall pathways.

c. Both antidromic and orthodromic AV reentrant tachycardias require participation of the accessory pathway. In rare instances, antidromic tachycardia can involve one accessory pathway in the antegrade direction and a second pathway in the retrograde direction.

2. Evidence of preexcitation is supported by the presence of a **short HV interval** (<35 ms) **at rest** or with atrial pacing and the appearance of increasing preexcitation either with atrial pacing or with administration of drugs that cause AV nodal conduction slowing, or with autonomic maneuvers. The electrophysiologic properties of the accessory pathway are examined, including its antegrade and retrograde conduction and refractory periods. If tachycardia is induced during atrial or ventricular stimulation, its mechanism is defined according to the techniques discussed earlier. This depends on whether the tachycardia is narrow or wide complex.

3. **Orthodromic AV reentry tachycardia** is commonly initiated by a ventricular premature stimulus that blocks in the His-Purkinje system or, rarely, in the AV node, but conducts in a retrograde direction over the accessory pathway. It can also be induced by an atrial premature stimulus (echo beat) that blocks the accessory pathway and conducts slowly over the AV conducting system. Induction is facilitated by the presence of a relatively **long antegrade refractory period of the accessory pathway** or a **long retrograde refractory period of the His-Purkinje system**.

4. **Antidromic AV reentry tachycardia** (see Fig. 51.9) can be initiated with burst pacing in the atrium or with a premature atrial stimulus that **blocks in the AV node** and **conducts over the accessory pathway**. Less often, it can be induced with a premature ventricular stimulus that blocks the accessory pathway in a retrograde manner and conducts over the AV node. Induction of antidromic tachycardia necessitates excellent retrograde conduction over the His-Purkinje system and AV node. It almost always involves a free wall accessory pathway as the antegrade limb and is frequently associated with the presence of multiple accessory pathways.

5. **Localizing accessory pathways**

a. **Surface electrocardiographic localization**

1. **1 Delta wave vectors**

1. (a) Left lateral: negative I, aVL; positive II, III, aVF, V_1–V_6

FIGURE 51.9 Antidromic atrioventricular (AV) reentry tachycardia. This tachycardia was induced with atrial burst pacing in a young patient with two right-sided manifest accessory pathways.

The tachycardia is rapid and wide complex, with the earliest retrograde A seen in HBE1–2, consistent with retrograde activation through the AV node. AV node reentry with antegrade activation using the accessory pathway (bystander accessory pathway) was excluded by lack of evidence of dual AV node physiology. CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

2. **(b)** Left posterior wall: positive I, aVL; negative II, III, aVF; positive V_1–V_3/V_4
3. **(c)** Posteroseptal: positive I, aVL; negative II, III, aVF; R/S <1 in V_1
4. **(d)** Right free wall: positive I, aVL, II; negative III; biphasic V_1 and V_2
5. **(e)** Anteroseptal: positive I, aVL; positive II > III; negative V_1–V_6

2. **2 P-wave morphology during orthodromic tachycardia**

1. **(a)** Left lateral: negative I, aVL; positive III > aVF > II; negative V_5 and V_6
2. **(b)** Posteroseptal: positive aVR, > aVL; negative II, III, aVF
3. **(c)** Right free wall: positive I, aVL, II; negative III; biphasic V_1 and V_2

b. Localization during EPS

1. **1** Pacing from multiple atrial sites: shortest A-delta occurs with pacing close to the atrial insertion site of the accessory pathway and results in maximal preexcitation.
2. **2** Retrograde atrial activation during orthodromic tachycardia and V pacing

1. **(a)** Atrial activation sequence

1. **i.** Left and right free wall: eccentric
2. **ii.** Posteroseptal: A_{CSos} earlier than A_{His}
3. **iii.** Anteroseptal: A_{CSos} later than A_{His}

2. **(b)** Atrial activation sequence when a ventricular premature stimulus is delivered during tachycardia at the time when His is refractory
3. **(c)** The earliest site of atrial activation identifies the site of atrial insertion of an accessory pathway

3. **3** Relationship of local ventricular electrogram to delta: earliest V correlates with ventricular insertion site. This may be slightly offset or oblique compared with the atrial insertion site.
4. **4** Effects of bundle branch block

1. **(a)** Bundle branch block increasing the VA interval by >35 ms; ipsilateral free wall accessory pathway
2. **(b)** With bundle branch block ipsilateral to septal accessory pathways, the increase in VA times is <25 ms
3. **(c)** Left anterior fascicular block can increase VA times 15 to 35 ms with left free wall accessory pathway, particularly with an anterolateral left-sided accessory pathway

5. **5** Recording of accessory pathway potential: sharp spike 10 to 30 ms before the onset of the delta wave

6. Identifying the presence of multiple accessory pathways

a. Changing antegrade delta waves during sinus rhythm, atrial pacing, atrial fibrillation, and with antiarrhythmic drugs

b. Evidence of multiple routes of retrograde atrial activation

1. **1** Changing VA time or activation sequence
2. **2** Failure to prolong VA time with ipsilateral bundle branch block

c. Orthodromic tachycardia with antegrade fusion

d. Preexcited tachycardia

1. **1** Antegrade conduction over septal accessory pathway
2. **2** Antidromic tachycardia faster than orthodromic tachycardia

e. Atypical patterns of preexcitation

f. Mismatch of site of antegrade preexcitation and retrograde atrial activation during AV reentry tachycardia

D. Ventricular tachycardia evaluation

1. The most common reason for performing EPS on patients with suspected ventricular arrhythmias is documentation of inducible tachycardia, testing the effect and response to antitachycardia pacing and defibrillation, and endocardial mapping to direct attempts at ablation. Recent trials have stratified patients with ischemic or nonischemic cardiomyopathy, congestive heart failure, and reduced LV ejection fraction at higher risk for sudden cardiac death and thus reduced the usefulness of EPS in determining the need for ICD implantation.
2. An **atrial study** is considered for all patients undergoing evaluation of ventricular tachycardia. This serves three main purposes: diagnosis of the underlying advanced conduction system disease, documentation of coexisting SVT, and induction of rare forms of ventricular tachycardia that may be inducible only with atrial pacing.
3. **Programmed ventricular stimulation** is performed as described earlier. If ventricular tachycardia is not induced despite programmed stimulation from two RV sites (RV apex and RV outflow tract), repeat stimulation can be performed after isoproterenol infusion. However, isoproterenol should not be given to patients with active ischemic heart disease. It is primarily of value to those with exercise-induced or catecholamine-dependent ventricular tachycardia. LV stimulation is not necessary because RV stimulation techniques have adequate sensitivity and specificity, and the risk of left heart catheterization is avoided. If no ventricular tachycardia is induced with any of these techniques, the arrhythmia is deemed noninducible.
4. **Techniques for terminating induced ventricular tachycardia.** Pacing terminates as many as 85% of induced ventricular tachycardias in the laboratory. Success is more likely to be achieved with slower tachycardia rates (<200 beats/min) and in hemodynamically tolerated tachycardias. Other factors predictive of successful pacing include the site of stimulation in relation to the tachycardia zone, ventricular conduction properties, and refractoriness. Pacing can also accelerate tachycardia, an important consideration when antitachycardia pacing is being considered.
5. **Techniques for terminating tachycardia with pacing.** One technique entails the use of one or more **progressively earlier premature ventricular stimuli**. The other technique uses **burst pacing** to overdrive the tachycardia, but there is a greater risk of accelerating the tachycardia into a hemodynamically unstable arrhythmia. Techniques that can be used if pacing fails include delivery of ultrarapid train stimulation and synchronized direct current cardioversion.
6. There are a variety of **responses to programmed stimulation**. What is important is the correlation between these responses in different populations of patients and future risk of adverse outcome. For example, induction of single or double BBR beats has no bearing on long-term outcome among persons with normal LV function and is not considered an abnormal finding. Induction of sustained monomorphic ventricular tachycardia, particularly among persons with reduced LV ejection fraction, identifies a subset of patients at high risk for sudden death.

a. **Sustained monomorphic ventricular tachycardia**

1. **1** Induction of sustained monomorphic ventricular tachycardia is the **most important response** and has the highest predictive value. This is particularly true if the induced tachycardia is similar to the clinical arrhythmia in both rate and structure. Patients with easily induced ventricular tachycardia (e.g., with single premature beats) have worse outcomes than those in whom tachycardia is more difficult to induce. It is important to document reproducibility of ventricular tachycardia during programmed stimulation. Slow, sustained tachycardia, particularly in patients with ischemic substrate, is typically more reproducible than more rapid tachycardias and tachycardias in those with nonischemic cardiomyopathies. Sustained tachycardia has clearly worse prognostic implications than nonsustained tachycardia. There is no agreement on what constitutes an abnormal response among patients with nonsustained tachycardia or whether any therapeutic intervention should be pursued for these patients.
2. **2** Among patients with ischemic substrate, programmed stimulation induces sustained monomorphic ventricular tachycardia in as many as 95% of patients with a history of clinical sustained ventricular tachycardia, approximately 60% of those with nonsustained ventricular tachycardia, and approximately 50% of patients experiencing sudden cardiac death. Induction of sustained monomorphic ventricular tachycardia in any of the above subsets has very high specificity (>90%) for spontaneous clinical ventricular tachycardia and sudden death. Testing at two RV sites increases sensitivity without sacrificing specificity.
3. **3** Patients with **nonischemic substrate** are more challenging to evaluate because EPS are less sensitive and specific. Although inducible sustained monomorphic ventricular tachycardia has a worse prognosis than the noninducible type, the positive predictive value of abnormal results of EPS is at best 70%. Patients with negative results of EPS are still at high risk for sudden death, even if they have no prior clinical events. The prognosis may be more favorable if inducible tachycardia is suppressed by drugs, but the risk of future events continues to be high. One can never be reassured about the outcome among patients with nonischemic cardiomyopathy using results of EPS.
4. **4 BBR tachycardia** is a type of ventricular tachycardia with a well-defined macro reentrant circuit. It occurs most often among patients with dilated cardiomyopathy and is frequently symptomatic.

1. **(a)** In the **typical pattern**, the impulse travels antegrade down the right bundle branch, across the interventricular septum, and retrograde up the left bundle branch. The tachycardia exhibits a left bundle branch block pattern, with a **His deflection preceding every QRS complex**. In sinus rhythm, the **HV interval is abnormally long**, and during tachycardia it is at least equal and frequently longer than the baseline HV.
2. **(b)** In rare instances, it is difficult to differentiate BBR tachycardia from an SVT with aberration or from a myocardial ventricular tachycardia with retrograde His deflections.
3. **(c)** BBR tachycardia is frequently rapid and exhibits AV dissociation. If cycle length variation takes place, it is important to assess the order of changes in the HH and VV intervals. If HH changes take place before VV changes, BBR is likely. A VV change that occurs before HH change and is also associated with a variation in the HV interval suggests myocardial ventricular tachycardia.
4. **(d)** Treatment with **antiarrhythmic agents**, including amiodarone, is not helpful and may lead to stabilization of the reentrant circuit. BBR tachycardia is curable with RF ablation of the right bundle.

b. **Polymorphic ventricular tachycardia** frequently occurs with high-output stimulation. It is also more likely to occur with increasing numbers of extra stimuli.

1. **1 Interpretation** of the induction of polymorphic ventricular tachycardia depends on the clinical situation. For example, inducible polymorphic ventricular tachycardia in a survivor of sudden

cardiac death is considered significant. In a patient with ventricular ectopy and normal ventricular function, inducible polymorphic ventricular tachycardia is a nonspecific response.

2. 2 Similar interpretation applies to **induced ventricular fibrillation**. If the patient has never had clinical ventricular tachycardia or ventricular fibrillation and has no underlying heart disease, the induced ventricular fibrillation is considered a nonspecific finding that does not warrant therapy.

c. Patients with **hypertrophic cardiomyopathy** represent another subset for whom the predictive value of EPS is problematic. Induction of sustained monomorphic ventricular tachycardia, induction of ventricular fibrillation without aggressive stimulation protocols, and induction of ventricular arrhythmias with atrial pacing or as a result of atrial fibrillation are generally considered to be **poor prognostic signs**.

d. **Summary.** It is important to have a thorough understanding of the underlying clinical problem and anatomic substrate to assess the appropriateness of any EPS finding for an individual patient.

1. 1 Repetitive responses caused by BBR are usually physiologic, whereas intramyocardial repetitive ventricular responses are abnormal. However, neither of these responses should be used to guide therapy.

2. 2 Induced polymorphic ventricular tachycardia and ventricular fibrillation can be considered nonspecific findings or clinically significant depending on the clinical circumstances. However, they should not be used to guide drug therapy in any situation.

3. 3 Induced sustained monomorphic ventricular tachycardia identical to the clinical arrhythmia has the highest sensitivity and specificity and has greater importance in predicting outcome.

4. 4 The importance of nonsustained ventricular tachycardia remains controversial. Noninducibility in patients with nonischemic cardiomyopathy or survivors of sudden cardiac death may not provide prediction as accurate as that for patients with underlying ischemic substrate and documented nonsustained ventricular tachycardia. Therapeutic decisions have therefore been individualized.

5. 5 Guidelines derived from studies, including the Multicenter Automatic Defibrillator Implantation Trials (MADIT) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), have obviated the need for performing EPS before deciding to implant ICDs in particular patient populations.

7. **Mapping of ventricular tachycardia.** Mapping of ventricular tachycardia involves identification of the **earliest sites of activation** during tachycardia and detailed outlining of the **tachycardia circuit**. Endocardial mapping has aided in the evaluation of mechanisms of tachycardia. More recently, mapping has been coupled with RF ablation with high rates of success.

a. Mapping can be performed with steerable electrode catheters during EPS or can involve introduction of specialized catheters with various configurations designed to compare several simultaneously acquired endocardial electrograms.

b. Mapping should be performed in the suspected chamber of origin. The surface ECG and clinical features guide in this determination.

c. Activation mapping takes place during the tachycardia. The objective is to identify the site of earliest activation. Because this lengthy process has to take place during tachycardia, it must be hemodynamically tolerable. The earliest activation site should correspond to the exit site of the circuit unless the focus is midmyocardial, epicardial, or in the other ventricle.

d. Sites of origin of tachycardia in patients with ischemic heart disease are usually found in the peri-infarction zone or in the border of an LV aneurysm. To

confirm the site, entrainment from that site is performed. Entrainment involves transient overdrive pacing and resetting of the tachycardia without terminating the tachycardia. When entrainment is achieved within the reentrant circuit inside the slowly conducting scarred regions of the heart, or isthmus, pacing produces QRS morphologic match on all 12 surface ECG leads. The return cycle length of activation at the site of pacing after cessation of pacing equals the tachycardia cycle length (see Fig. 51.10). These two observations imply that depolarization caused by pacing has the same exit from the scar as the tachycardia and that the pacing site is within the circuit.

e. Pace mapping can be used in the evaluation of patients with hemodynamically unstable tachycardia. Ventricular pacing is performed at various sites at rates that do not cause hemodynamic instability. The site where pacing results in QRS match with clinical tachycardia corresponds to the exit sites of the tachycardia circuit. This technique typically requires induction and rapid termination of ventricular tachycardia (VT) with either pace termination or DC cardioversion in order to obtain a 12 lead of the VT because subtle differences in ECG lead placement can alter the surface morphology.

f. **Electroanatomic mapping systems** allow the measurement of tissue voltage, providing accurate delineation of scar tissue and its boundaries. Thus, mapping in sinus rhythm allows for delimitation of the scar and areas of the scar border that are likely sites of tachycardia exit. Pace mapping can be used to identify those sites around the scar that correspond to tachycardia exits. Linear lesions, performed to interrupt these exit sites responsible for reentrant circuits, can be undertaken, allowing successful ablation of tachycardias that would not be otherwise mapped because of patient intolerance of any sustained tachycardia. Another method of mapping a hemodynamically unstable VT is to use a mapping system that can acquire the map of the entire endocardium in a single beat. This requires insertion of an "array" catheter into the left ventricle that acquires the electrograms from 64 points on the balloon and calculates the virtual activation on the endocardial surface. Alternatively, an intra-aortic balloon pump or percutaneous LV assist device may be considered to assist with mapping and ablation during prolonged or hemodynamically unstable VT.

FIGURE 51.10 Entrainment of ventricular tachycardia. Pacing at a rate slightly faster (380 ms) than tachycardia cycle length at a site believed to be the isthmus of the tachycardia resulted in QRS morphology very similar to the native ventricular tachycardia (concealed entrainment) in all 12 leads (only 4 leads shown). In addition, the postpacing interval is very close to the tachycardia cycle length, suggesting that the pacing site is within the tachycardia circuit. Application of radiofrequency energy at this site resulted in successful ablation of this tachycardia. LV, left ventricular; RVA, right ventricular apex.

g. Mapping can also be performed intraoperatively when endocardial resection is considered. Although this approach can still be used, it is infrequently recommended, because other approaches described earlier in combination with implantable defibrillators have yielded good patient survival and excellent success in eliminating problematic VTs.

h. Some patients, including many with nonischemic cardiomyopathy or certain variants such as Chagas disease and hypertrophic cardiomyopathy, may require both endocardial and epicardial approaches to VT mapping and ablation. Percutaneous access into the epicardial space is obtained with a subxiphoid approach under fluoroscopic guidance and small injections of contrast until the parietal pericardium is penetrated. In patients with dense

pericardial adhesions that may limit catheter movement, an intraoperative subxiphoid incision or open sternotomy may be considered to allow for greater exposure and access.

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CHAPTER 52

Cardiac Resynchronization Therapy

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I. INTRODUCTION. The prevalence of heart failure (HF) in the United States has increased considerably in the past two decades as a result of the aging population and better medical management of left ventricular dysfunction (LVD). Unfortunately, medical therapy is not completely effective in preventing or reversing the progression of HF, and as a result, patients with advanced HF have limited options. A subset of patients with systolic LVD who have associated ventricular conduction delay are at highest risk for HF progression and a poor overall outcome. Since the late 1970s, various investigators have shown that left bundle branch block (LBBB), right ventricular (RV) pacing, or intraventricular conduction delay (IVCD) is associated with a less favorable hemodynamic profile in those with LVD and even in normal subjects. **The mechanism for this phenomenon is thought to be due to asynchronous and inefficient contraction of opposing areas of the ventricular myocardium. More importantly, restoring synchronization, either via simultaneous pacing of the RV apex and the left ventricular (LV) free wall or with timed LV free wall activation, can lead to a significant hemodynamic improvement.** Starting in the 1990s, small observational studies suggested benefit from synchronous pacing. Larger randomized clinical trials confirmed these findings. Cardiac resynchronization therapy (CRT) was first approved for maximally medically managed patients with persistent New York Heart Association (NYHA) class III or IV HF symptoms because of severe LVD associated with prolonged QRS duration. Further randomized studies, powered for mortality, showed a significant survival benefit with CRT or the combination of CRT with a defibrillator (CRT-D). More recently, CRT has been shown to be beneficial in less symptomatic patients. Unfortunately, not all patients who are selected for CRT based on current guidelines appear to respond. The terms “responder” or “nonresponder” to CRT have been criticized by many who argue that the natural history of disease progression in any individual patient is not known hence some patients who appear to not have responded may have in fact done even worse if CRT was not employed. Complicating matters further is that there is no uniform definition of response.

II. MECHANISM OF LV DYSSYNCHRONY. The normal pattern of electrical activation of the ventricular myocardium, once the impulse passes through the atrioventricular (AV) node, starts in the His bundle, followed by simultaneous activation of the right and left bundles of the Purkinje system and then by myocardial depolarization. The Purkinje

system is electrically isolated from the rest of the myocardium until it reaches its exit points at the Purkinje–myocardial junctions. As a result, typical LV myocardial activation occurs from the apex to base, simultaneously in the septum and in the LV free wall, and is described as synchronous. Because of tight electromechanical coupling of the myocardium, synchronous ventricular activation is followed by synchronous ventricular contraction.

In the setting of conduction delay, the electromechanical coupling of the heart is disrupted, leading to dyssynchrony. Over time, electromechanical uncoupling leads to impaired stroke volume, worsened mitral insufficiency, prolonged LV isovolumetric events, and impaired diastolic filling. These effects contribute to adverse remodeling in the already impaired heart, creating a vicious cycle that perpetuates this process into more advanced HF. As a result, when comparing patients with similar degrees of LVD, **those with conduction delay have a worse overall prognosis**. CRT has been shown to reverse this deleterious process. Synchronized pacing has been shown to improve LV function without increasing oxygen demand, suggesting that the improvement is related to better efficiency of the LV chamber.

Interestingly, dyssynchronous activation and contraction have an undesirable effect in patients ***without*** LV systolic dysfunction also. When compared with normal controls, patients with LBBB have a lower ejection fraction (EF), are more likely to develop HF, and have a 10-fold greater cardiovascular morbidity and mortality risk. In some patients (patients with chronic LBBB, frequent premature ventricular contractions, or chronic RV pacing), the conduction delay in and of itself may cause deterioration in the EF. In this population, treatment with CRT can have profound effects potentially normalizing the LV function.

III. TYPES OF DYSSYNCHRONY

A. AV dyssynchrony. In the setting of PR or QRS prolongation, the atrial contribution to LV filling is abnormal. Atrial systole can occur too early with respect to ventricular diastole, leading to early truncation of passive LV filling. Early atrial systole also causes an early rise in diastolic ventricular pressure, leading to diastolic mitral regurgitation (MR). Compromised LV filling and MR cause lower cardiac output.

B. Interventricular dyssynchrony. Early RV activation present during LBBB, IVCD, or RV pacing leads to early RV contraction, creating a pressure gradient between the RV and LV that negatively affects LV filling, which translates to a decrease in LV preload and a subsequent decrease in cardiac output. In the early development of CRT, interventricular dyssynchrony was thought to be a major contributor to adverse events in patients with HF and conduction disease and hence the primary target for CRT. Whereas correction of interventricular dyssynchrony with CRT may improve hemodynamics, it is now thought that that correction of intraventricular dyssynchrony is far more important to improved outcomes with CRT.

C. Intraventricular dyssynchrony. In the presence of conduction delay, there is a substantial delay in the activation of certain LV segments compared with others, leading to an inefficient back-and-forth mechanical interaction that results in inefficient myocardial contraction. In the case of a native LBBB, for example, there is a significant delay in activation between the early activated septum and the late activated posterolateral wall, often resulting in profound delays between segments. **Mitigation of intraventricular**

dyssynchrony is currently thought to be the primary mechanism of improved myocardial performance with CRT.

IV.ASSESSMENT OF DYSSYNCHRONY. In addition to the three varieties of dyssynchrony already discussed, dyssynchrony can also be broken into "mechanical" and "electrical." Electrical dyssynchrony refers to delays in depolarization from one segment to another, whereas mechanical dyssynchrony refers to contraction delays from one segment to another. Although the two are presumed to be closely linked, **current measures of electrical and mechanical dyssynchrony have often shown poor agreement**. For example, almost all clinical trials have used prolonged QRS duration, a crude marker of electrical dyssynchrony, as a requisite for inclusion. The relationship, however, between QRS duration and various measures of mechanical dyssynchrony has been poor. Studies have revealed that up to 30% of patients with a prolonged QRS duration do not have mechanical dyssynchrony as assessed by magnetic resonance imaging (MRI) or echocardiography, whereas up to 30% of patients with a normal QRS duration and symptomatic HF have evidence of mechanical dyssynchrony on echo or MRI and could potentially benefit from resynchronization therapy. Currently, the development of new measures of both electrical and mechanical dyssynchrony is an area of intense research. Whereas newer, noninvasive measures of electrical dyssynchrony other than the QRS duration are on the horizon, currently, the bulk of research on dyssynchrony has been dominated by the various metrics of mechanical dyssynchrony, mostly using various echocardiographic techniques. Unfortunately, indices of mechanical dyssynchrony have been disappointing in predicting outcomes to CRT. The main difficulty with all measures of mechanical dyssynchrony has been reproducibility across centers. In the large, multicenter PROSPECT trial, multiple echocardiographic measures of mechanical dyssynchrony were tested. **None, however, were found to be both a sensitive and a specific predictor of subsequent response to CRT.** Technical and interpretative variability across centers was thought to be a major reason behind the only modest predictive ability. More recently, the STARTER and TARGET trials have again promoted the potential applicability of dyssynchrony analyses using strain imaging to predict late activated segments. In these studies, targeting an LV pacing lead to the latest activated site of mechanical activation improved outcomes.

V.ROLE OF CRT. The primary role of CRT is **to improve systolic LV performance via an improvement in chamber efficiency**, thereby leading to symptomatic improvements in patients with medication refractory HF. In clinical trials, the **EF improved by an average of about 5%** with a significant improvement in MR and was accompanied by symptomatic improvement, as evidenced by increased 6-minute walk time and quality of life index score (QOLS). **The remodeling of the LV takes at least 3 or more months.** On average, the LV systolic and diastolic dimensions decrease significantly following prolonged CRT. In studies in which biventricular (Bi-V) pacing was switched off after prolonged synchronized pacing, the systolic benefits disappeared rapidly; however, the LV dimensions were maintained for a longer period of time, suggesting that actual LV remodeling took place during CRT. There is also evidence that CRT may lead to electrical remodeling of the heart although this effect is less well studied. Evidence from randomized clinical trials powered for mortality, in addition to symptomatic improvement, supports the use of CRT alone or in combination with an implantable

cardioverter defibrillator (ICD) in patients with ischemic and nonischemic etiologies of severe LVD.

VI. SUMMARY OF MAJOR CLINICAL TRIALS OF CRT. Most clinical trials evaluating CRT have addressed its role in patients in normal sinus rhythm (NSR) with severe LVD, and indirect evidence of mechanical dyssynchrony represented by prolonged QRS duration (on average, >120 ms). Early studies of CRT compared patients with CRT pacemaker (CRT-P) devices with optimal medical therapy alone and enrolled patients with NYHA class III–IV HF. Over the years, trials progressed to enrolling patients with minimally symptomatic HF and compared patients with CRT-D devices to those with an ICD alone.

A. PATH-CHF. A longitudinal crossover study of 41 patients evaluating CRT-P (Bi-V or LV pacing) versus no therapy. Primary end points of peak VO_2, 6-minute walk, NYHA class, and QOLS significantly improved during CRT.

B. MUSTIC. A small prospective randomized trial powered for symptomatic improvement as measured by hospitalization, 6-minute walk, and QOLS in patients in NSR or with atrial fibrillation at the time of enrollment. The trial showed significant improvements with CRT-P, and the benefit was similar in NSR and atrial fibrillation.

C. MIRACLE. The MIRACLE trial, completed in late 2000, randomized 453 patients with advanced HF and a QRS duration ≥130 ms to CRT versus conventional therapy for HF. The trial revealed significant improvements in peak VO_2 consumption, 6-minute hall walk, QOLSs, EF, NYHA class, and treadmill exercise times with CRT compared with controls. This trial led to the approval of CRT devices by the Food and Drug Administration.

D. MIRACLE-ICD. Very similar to MIRACLE, the MIRACLE-ICD trial was a moderate-sized prospective randomized trial evaluating the safety and efficacy of combining CRT with ICD therapy for a composite end point of mortality, hospitalization, and symptomatic improvement. At 6 months follow-up, the CRT-ICD arm had a significant improvement in the composite end point. Combining CRT with ICD was deemed safe. Of note, CRT-D devices were compared to optimal medical therapy alone in this trial (not to an ICD alone).

E. CARE-HF. The CARE-HF was a large, open-label randomized controlled trial powered to assess mortality comparing CRT-P to optimal medical therapy alone in patients with ischemic and nonischemic etiology of LVD. In addition to the conventional dyssynchrony criteria of QRS duration >150 ms, the trial was the first to implement echocardiographic markers of mechanical dyssynchrony in those patients with QRS duration between 120 and 150 ms. At 3 years of follow-up, the primary end point of all-cause mortality and hospitalization was significantly different in favor of the CRT group. Furthermore, the secondary end point of all-cause mortality reached statistical significance after 3 years of follow-up, and the survival curves continued to separate. The number needed to treat with CRT to save one life was estimated at nine patients.

F. COMPANION. A large, open-label randomized (1:2:2) prospective trial powered for mortality and hospitalization benefit in patients with ischemic and nonischemic etiologies of LVD comparing medical therapy versus CRT-P or CRT-D. In addition to conventional QRS criteria for CRT, patients also had to have had one episode of hospitalization for HF in the year prior to randomization. Both CRT-D and CRT-P were

superior in terms of the primary end point of all-cause mortality and hospitalization compared with optimal medical therapy alone. The secondary end point of all-cause mortality was significantly different in the CRT-D group compared with optimal medical therapy alone. The CRT-P group showed a strong trend toward mortality benefit compared with optimal medical therapy alone that did not reach statistical significance. The trial was not powered to compare mortality benefits between the two device groups. In the CRT-D group, the mortality benefit was noticed shortly after the beginning of the trial, as compared with 6 to 12 months after study initiation in CARE-HF. The early mortality benefit in this trial was thought to be ICD related. The later benefits were attributed to both ICD and CRT therapies. The results of this trial led to approval of combined CRT-D therapy in the above population of patients.

G. ECHO-CRT. A large clinical multicenter trial examining the role of CRT pacing in patients with EF <35%, narrow QRS (<130 ms), and echocardiographic evidence of LV dyssynchrony. Dyssynchrony was defined by means of color-coded tissue Doppler imaging as an opposing-wall delay in the peak systolic velocity of 80 ms or more in apical four-chamber or apical long-axis views or by means of speckle-tracking radial strain as a delay in the anteroseptal-to-posterior wall of 130 ms or more in the mid-LV short-axis view. All patients underwent device implantation but were randomized to have CRT pacing on (404 patients) or off (405 patients in which device settings were set to minimize RV pacing). Mean QRS duration was 105 ms. The study was terminated because of futility where the CRT group had increased mortality (11.1% vs. 6.4%; hazard ratio [HR] 1.81; $p = 0.02$). This study suggested that implanting CRT in patients with a narrow QRS may be harmful.

H. BLOCK-HF. A randomized clinical trial examining the role of CRT pacing in patients with AV block and systolic dysfunction who require significant ventricular pacing. The trial enrolled patients with indications for pacing with AV block; NYHA class I, II, or III HF; and a left ventricular ejection fraction (LVEF) of 50% or less. They all got CRT devices and were randomized to biventricular pacing (349 patients) versus RV pacing (342 patients). Patients got ICD if they had an indication for one. The primary outcome was the time to death from any cause, an urgent care visit for HF that required intravenous therapy, or a 15% or more increase in the LV end-systolic volume (ESV) index. The primary outcome occurred less frequently in the biventricular pacing group (HR 0.74, confidence interval [CI], 0.6 to 0.9).

VII. MAJOR TRIALS OF CRT IN MINIMALLY SYMPTOMATIC HF

A. REVERSE. The REVERSE study, published in 2008, was a large randomized, double-blind trial designed to assess whether CRT in addition to medical therapy could delay progressive myocardial remodeling and/or prevent HF progression. The study enrolled 610 patients with a 2:1 enrollment design such that 419 patients received a CRT-D device and 191 patients received an ICD alone. Inclusion criteria for the study were NYHA class I or II symptoms, an LVEF ≤40%, an LV end-diastolic dimension ≥55 mm, NSR, and a QRS duration ≥120 ms. The primary end point of REVERSE was a novel clinical composite end point developed by Packer and colleagues, which rates patients as "improved," "unchanged," or "worsened" based on the combination of mortality status, hospitalizations because of HF, withdrawal of consent, and worsening NYHA class. The American arm of the study concluded at 12 months, with the European arm proceeding to 24 months. Although there was no difference in the primary end point at 12 months,

patients in the CRT arm derived significantly greater reductions in the LV ESV index and the LV end-diastolic volume (EDV) index, respectively, and improvement in LVEF compared with those without CRT. During the 12-month follow-up period, there was no difference in mortality between the two groups; however, CRT significantly lowered HF hospitalizations. In the European arm of the trial in which follow-up was continued for an additional year, the benefit of CRT in inducing reductions in LV volumes and improvement in LVEF persisted at 24 months.

B. **MADIT-CRT.** MADIT-CRT, published in 2009, sought to determine the impact of CRT on HF hospitalizations and all-cause mortality in patients with NYHA class I or II HF symptoms. This multicenter, unblinded study randomized 1,820 patients in North America and Europe with an LVEF ≤30%, NYHA class I or II symptoms (patients with nonischemic cardiomyopathy and NYHA class I symptoms were excluded), NSR, and a QRS duration ≥130 ms to a CRT-D device or an ICD alone. The primary end point for the study was death from any cause or a nonfatal HF event. At a mean follow-up of 2.4 years, patients in the CRT arm had a significantly lower incidence of the primary end point compared with the ICD-alone arm. Similar to what was shown in REVERSE, patients in the CRT arm of MADIT-CRT realized significantly greater improvements in myocardial structure and function compared with those without CRT.

C. **RAFT.** The RAFT trial which began enrollment in 2003 was a large, double-blinded, randomized controlled trial of 1,798 patients with NYHA class II or III symptoms, an LVEF ≤30%, and a QRS duration ≥120 ms (or a paced QRS >200 ms), which compared therapy with CRT-D versus that with an ICD alone. Originally, the trial sought to determine whether CRT in addition to an ICD would improve survival in patients with class II and III symptoms. After publication of the CARE-HF trial and subsequent guideline changes, however, the protocol was altered in early 2006 to include only patients with NYHA class II symptoms. Of 894 patients receiving a CRT-D device in the RAFT trial, 79.2% had NYHA class II symptoms. For inclusion, patients had to either be in NSR or have rate-controlled permanent atrial fibrillation or flutter. The primary end point of all-cause death or HF hospitalization occurred in 33.2% of the CRT-D group and in 40.3% of the ICD-only group over a follow-up of 40 ± 20 months. In looking at only patients with NYHA class II symptoms, patients in the CRT arm had reductions in the primary end point as well as in both cardiovascular and all-cause mortality and hospitalizations because of HF.

VIII. FACTORS ASSOCIATED WITH IMPROVED OUTCOMES IN CRT.

Several factors have been associated with improved outcomes with CRT.

A. **Women** have continually derived improved outcomes in multiple studies compared with men. Although the reason for this has been debated, it is likely due to a lower LV mass at the same QRS duration (more relative dyssynchrony) compared with men.

B. Patients with **nonischemic cardiomyopathy** appear to be more likely to derive reverse ventricular remodeling than patients with ischemic cardiomyopathy.

C. Patients with **LBBB** either native or paced are far more likely to improve function with CRT compared with patients with a non-LBBB (right bundle branch block [RBBB] or IVCD).

D. Lastly patients with **wide QRS durations (>150 ms)** appear to have improved outcomes compared with patients with narrower QRS durations (120 to 149 ms). There is

debate among experts as to the relative importance of QRS morphology compared to QRS duration. Whereas patients with LBBB have been shown to outperform patients with non-LBBB when it comes to CRT responsiveness, patients with LBBB also inherently have a wider QRS duration for the most part. Taking the literature into account, both QRS duration and morphology likely play a role.

E. Lead position is an important determinant of response. **Apical lead positions are inferior** to mid and basal positions. Septal locations such as pure anterior or posterior locations (in the great cardiac vein which parallels the LAD or the middle cardiac vein which parallels the posterior descending artery) are inferior to lateral locations although the data behind this is less robust.

IX. QLV and RV–LV Timing. Electrical delay or electrical dyssynchrony is a key factor when predicting response to CRT. Electrical delay can be easily measured in the electrophysiology lab at the time of CRT implant. The SMART-AV QLV substudy looked at the relationship between the intrinsic electrical delay of the LV and clinical end points. LV electrical delay was defined by the time interval from the first QRS deflection on surface electrocardiogram (ECG) to the local intrinsic activation at the LV stimulation site (QLV) as measured in the electrophysiology lab. The goal of optimizing CRT is to deliver electrical stimuli in an area that has the latest activation within the LV. The study found that when the observed QLV was >95 ms, HF patients had the best improvements in EF, ESV, EDV, and quality of life measurements at 6 months follow-up. Measuring the time between the RV and LV electrograms is a similar measure to QLV, with the advantage that this time is easily measurable through CRT devices. Whereas the utility of QLV and RV–LV timing in terms of selecting lead location and choosing pacing vectors has been encouraging, neither as of yet have been shown to be sensitive nor specific for predicting long-term outcomes.

X. Current guidelines and recommendations. Based on the inclusion criteria from the available large randomized trials at that time, the American Heart Association/American College of Cardiology 2012 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult gives CRT the following indications (see Table 52.1):

A. Class Ia (level of evidence A): In patients with ischemic or nonischemic etiology of depressed LV function, EF ≤ 35%, and NYHA class II, III, or ambulatory class IV, on guideline-directed medical therapy (GDMT) for ≥3 months or ≥40 days after MI, in sinus rhythm with an LBBB with a QRS complex ≥150 ms.

B. Class IIa: In patients with ischemic or nonischemic etiology of depressed LV function, EF ≤ 35%, and NYHA class II, III, or ambulatory class IV, on GDMT for ≥3 months or ≥40 days after MI who are in sinus rhythm with an LBBB QRS 120 to 149 ms (level of evidence B); sinus rhythm with non-LBBB QRS ≥150 ms (level of evidence A); patients anticipated to require frequent ventricular pacing (>40%) (level of evidence C); or atrial fibrillation if ventricular pacing is required or QRS criteria above are met and rate control (including AV node ablation) will result in nearly 100% ventricular pacing (level of evidence B).

C. Class IIb: Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤ 35%, and NYHA class II, III, or ambulatory class IV, on GDMT for ≥3 months or ≥40 days after MI with non-LBBB QRS 120 to 149 ms and NYHA III/ambulatory IV on GDMT (level of evidence B); in patients with non-LBBB with QRS

>150 ms and NYHA II on GDMT (level of evidence B); in patients with ischemic cardiomyopathy who have an EF <30%, LBBB QRS ≥150 ms (level of evidence C).

TABLE 52.1 Current Recommendations for the Use of CRT in Patients with HF

Recommendation
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, and NYHA c ambulatory class IV, on GDMT, in sinus rhythm with an LBBB with a QRS complex ≥150 ms
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, and NYHA c ambulatory class IV, on GDMT who are in sinus rhythm with an LBBB QRS 120–149 ms
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, and NYHA c ambulatory class IV, on GDMT who are in sinus rhythm with a non-LBBB QRS ≥150 ms
Patients with depressed LV function, EF ≤35% and anticipated to require frequent ventricular pacing
Patients with atrial fibrillation if ventricular pacing is required or QRS criteria above are met and (including AV node ablation) will result in nearly 100% ventricular pacing
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, on GDMT, and ambulatory class IV, with non-LBBB with QRS 120–149 ms
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, on GDMT, and non-LBBB with QRS >150 ms
Patients with ischemic etiology of depressed LV function, EF ≤30%, sinus rhythm, NYHA class I or LBBB QRS ≥150 ms
CRT is not recommended in patients on inotropic support except in special cases when patients transplant or have LV assist device or in patients with less than 1 year survival
CRT is not recommended in patients with NYHA class I or II symptoms and non-LBBB pattern with <150 ms

D. CRT, cardiac resynchronization therapy; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; LBBB, left bundle branch block; LV, left ventricular; NYHA, New York Heart Association.

E. Adapted from the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm; American Heart Association, Inc.

F. CRT is not recommended in patients on inotropic support except in special cases when patients are listed for transplant or have LV assist device or in patients with less than 1 year survival (level of evidence C); patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration <150 ms (level of evidence B).

XI. Implantation Procedure. Unlike conventional transvenous pacemaker or ICD implantation that requires lead placement in the right atrium and/or the right ventricle only, Bi-V pacing requires LV lead implantation. Initially, this was achieved via a thoracotomy; however, currently up to 98% of Bi-V devices are placed via a transvenous

approach. Although now used infrequently, some patients are still referred for a thoracotomy after a failed transvenous approach.

The procedure is performed in an electrophysiology laboratory under sterile conditions. All patients receive preprocedural antibiotics at least 30 minutes before the procedure. A subcutaneous pocket is first prepared, making sure that appropriate hemostasis is achieved. Typically, a cephalic or axillary vein approach to venous access is used. The right atrial and RV leads are implanted in a fashion similar to a pacemaker or ICD implantation. The LV lead is placed through the coronary sinus (CS) into a CS branch on the lateral free wall of the left ventricle. Modern CRT systems have the availability of quadripolar LV pacing leads, which are desirable in terms of adding flexibility to programming options compared with older bipolar leads. Performing an occlusive CS venogram may help identify the appropriate vein. Various sheaths, catheters, and guidewires are available to cannulate the CS and advance the pacing lead into the appropriate vein. Although the optimal site for LV lead placement is controversial, many experts agree that septal positions (straight anterior or posterior) and apical positions are suboptimal. Once the lead is advanced, its location should be confirmed by fluoroscopy, typically in the left anterior oblique (LAO) view. The goal is to document base to mid-posterolateral LV lead placement and maximal LV–RV lead separation in the LAO view. A steep angulation in the LAO view tends to be most accurate. Pacing thresholds are acceptable if <3 V at 0.5 ms. Diaphragmatic capture is excluded by high-voltage pacing. If high pacing threshold or diaphragm capture occurs, the lead should be repositioned. CS trauma is occasionally noted during lead placement, and it may range from dissection to frank perforation. Because the pressure in the venous system is low, serious sequelae are unusual and cardiac tamponade rarely results. After adequate LV lead placement and confirmed appropriate LV lead function, care must be taken during guidewire, CS platform, and stylet removal, so as not to disrupt lead position. Lead dislodgement occurs in as many as 5% of implantations. The time frame for the majority of dislodgements is the first 24 to 48 hours postimplantation, when patients resume activity. For that same reason, patients are encouraged to ambulate while still in-house to prevent any out-of-hospital dislodgement, which may have more serious consequences.

XII. Programming and follow-up. Currently, multiple configurations for Bi-V pacing exist. The available pacing configurations vary by device manufacturer. Changing configurations for pacing can be very useful in cases of poor thresholds or diaphragmatic stimulation.

Ventricular pacing must be **continuous** during CRT in order to obtain maximal benefit. Typically, DDD mode with a short AV delay (80 to 110 ms) to prevent native conduction is typically employed. More recently, fusion pacing algorithms have been developed in which RV pacing is limited or completely omitted and the LV paced wave front fuses with intrinsic conduction.

Follow-up of CRT devices includes a 12-lead ECG to assess for Bi-V capture and device interrogation to assess pacing thresholds. Patents should have a posteroanterior and lateral chest ray to confirm lead position and to rule out pneumothorax. In those patients who are deemed nonresponders, echocardiography may be used to optimally time the AV delay based on Doppler mitral valve inflow patterns or Doppler aortic velocity time integral. Generally speaking, interventricular timing (V–V interval),

although programmable, is not taken into consideration during CRT programming. Limited studies suggest that AV programming may lead to a better acute hemodynamic response to CRT in certain patients. The value of VV optimization is of considerable debate. In addition, specialized CRT clinics may help troubleshoot device issues, treat arrhythmias, maximize congestive heart failure (CHF) medications, and optimize the AV interval. Although such clinics are limited mostly to specialized centers, such clinics have shown improved outcomes in patients receiving CRT.

XIII. Future Directions. Although CRT has emerged as one of the most important advances in the treatment of LVD over the last 15 years, several important questions remain. Despite the myriad of parameters of mechanical dyssynchrony that are available, none has been shown to be a practical and reliable predictor of response. Developing a measure of dyssynchrony that predicts response accurately and can be used across multiple care settings remains a challenge. ECHO-CRT trial has made it clear that CRT does not benefit patients with narrow QRS even if they have echocardiographic evidence of dyssynchrony. Lastly, the role of CRT in patients without a native or RV-paced LBBB morphology is an area of considerable controversy. Patients with RBBB have early activation of the left ventricle and late activation of the right ventricle, calling into question the role of LV pacing for these patients. Still, most patients with RBBB have a wider QRS duration than would be expected from having a "pure" RBBB alone. This implies additional left-sided delay that may be mitigated by CRT. Although retrospective studies have certainly called into question the benefits of CRT in this population, currently, there is no prospective randomized trial to provide a more definitive answer. Patients with nonspecific IVCD are a heterogeneous population, likely with both right- and left-sided delay. In retrospective studies, the response rate of this population is more akin to those with RBBB than LBBB; however, the studies have been small.

XIV. Summary. CRT has emerged as an effective therapy in patients with LVD refractory to CHF medications and a wide QRS duration. Major clinical trials have proven significant morbidity and mortality benefits from CRT first in patients with advanced heart and more recently in those with minimal symptoms. The issue of nonresponse to CRT continues to be a major problem, and much ongoing research continues to be dedicated to predicting which patients will respond to this therapy. Although many studies have shown some predictive ability of various imaging modalities, none to date has been shown to be a reliable predictor of response that could be utilized across multiple centers. Although the response to CRT in patients with a native LBBB or RV-paced rhythm is well documented, the response in patients with RBBB or a nonspecific IVCD continues to be debated.

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CHAPTER 53

Cardiac Pacing

Joseph M. Bumgarner

I. INTRODUCTION. The indications and technology of cardiac pacing continue to evolve, leading to a rapid increase in the number of pacemakers implanted. Pacemaker implantation rates increased from 329 implants per million in 1990 to 612 per million in 2002. In 2011, 400,000 cardiac devices were implanted and over 3 million people in the United States had implantable cardiac rhythm management devices. It is imperative that the physician caring for the pacemaker patient understand the basic physiology and technology of cardiac pacing and be able to apply these principles to effectively manage the unique problems with which these patients may present.

II. BASIC COMPONENTS OF CARDIAC PACEMAKERS

A. Pulse generator

1. **Power source (battery).** Lithium ions are the most common chemical compound used. Lithium batteries deplete over a more predictable time course than other types of compounds, such as zinc mercuric oxide, that were used in prior generations of devices.

2. **Circuitry**

a. **Output circuits.** These circuits control programmable features of the output pulse, including amplitude and pulse width.

b. **Sensing circuits.** These circuits process the intracardiac electrogram, including amplification and filtering of the signal and also provide other functions such as management of external electromagnetic interference (EMI). A bandpass filter allows signals of a certain frequency range to be passed whereas signals of other frequency ranges are blocked or attenuated. Pacemakers use a bandpass filter to distinguish between cardiac depolarization and repolarization signals from extracardiac signals, such as myopotentials from the chest wall musculature. Some appropriate signals that pass through the filter are small in amplitude, and a sense amplifier increases the appropriate signal for the device to process.

c. **Timing circuits.** These circuits control the pacing intervals and sensing/refractory periods. They may be altered by input from the sensing circuits.

d. **Telemetry circuit.** These circuits allow communication between an external programmer and the pulse generator for pacemaker programming or retrieval of information.

e. **Microprocessor.** Most modern pacemakers have computer chips with read-only memory and random access memory and therefore have enhanced capabilities, such as downloading of new features via telemetry and increased storage of diagnostic data.

f. **Sensor circuit for rate-adaptive pacing.** See Section VII.

B. Lead system

1. **Terminal pin.** The male portion of the proximal lead that connects to the pulse generator
2. **Lead body.** Consists of conductor(s) and insulation. The conducting wire connects the stimulating and sensing electrodes to the terminal pin. The lead insulation is most commonly silicone rubber or a polyurethane material.
3. **Stimulating/sensing electrode(s).** The distal end of the lead that connects via a fixation mechanism to atrial or ventricular myocardium
4. **Fixation device.** Passive fixation represents an attachment mechanism (e.g., "fins" or "tines") that anchors electrodes to the endocardial trabeculae. Active fixation leads are secured to the endocardium using a "screw-in" mechanism. Over the past decade, active fixation leads have been implanted much more commonly. These types of leads have a lower rate of early dislodgement and yet higher chronic capture thresholds than passive fixation leads.

C. Polarity. This refers to the electrode configuration of the pacing lead or the configuration of the pulse generator. Polarity may be unipolar or bipolar; however, some pacemakers can be programmed to pace in one polarity and sense in another (only if a bipolar lead is present).

1. **Unipolar.** Configuration in which the cathode (negative) is on the lead, usually the lead tip, and the anode (positive) is the pacemaker can. This results in a large sensing "antenna" and produces large pacemaker artifact (spikes) on the electrocardiogram (ECG) because of proximity of the circuit to ECG electrodes.

a. **Advantages.** Better sensing of premature ventricular contractions (PVCs), low-amplitude signals, and shifted axis

b. **Disadvantages.** Oversensing of extraneous signals, especially pectoralis muscle activity (myopotentials), and inadvertent skeletal muscle stimulation may occur. Moreover, large pacemaker artifacts on the ECG may obscure native electrical activity.

2. **Bipolar.** Both electrodes are at the end of the lead—the cathode (negative) at the distal tip and the anode (positive) at the proximal ring. This results in a smaller sensing "antenna" with smaller pacemaker artifact (spikes) on the ECG. Myocardial stimulation occurs as electrons from the cathode travel through the myocardium and back to the anode. Most modern pacing leads are bipolar leads with the option to program to unipolar sensing. Some coronary sinus leads have four poles with many programming options for bipolar or unipolar pacing from the various poles.

a. **Advantages.** Less myopotential oversensing and skeletal muscle stimulation, and the smaller pacemaker artifact on the ECG does not obscure native wave morphology.

D. Lead–heart interface. This is equivalent to the site of energy transfer (pacing) and sensing functions.

III. PACEMAKER CLASSIFICATION. The North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group initially published a "pacemaker code" in 1983. Guidelines were later revised in 2002 and the five-position code remains the accepted nomenclature for pacemaker therapy (see Table 53.1). The first two positions (chamber paced and chamber sensed) are straightforward.

The third position, however, is often misunderstood. As outlined in Table 53.1, the third position reflects the device response to a sensed event (labeled "I," "T," or "D"). "I" (Inhibited)—the device will pulse the given chamber unless it senses an intrinsic event. Thus when programmed DDI, atrioventricular (AV) synchrony will only exist if the atrial chamber is paced. If the atrial activity is intrinsic and the ventricular response depends only on the sensed activity in that chamber, then AV synchrony will not be provided. "T" (Triggered)—this mode is used during device testing where a sensed event results in the device producing a pulse. "D" (Dual)—atrial and ventricular sensing and pacing with dual-chamber devices. When programmed DDD, a sensed atrial beat inhibits atrial pacing and, after a programmed time interval, triggers ventricular pacing. This mode enables tracking of intrinsic atrial activity and corresponding ventricular pacing to allow AV synchrony.

IV. INDICATIONS FOR PACEMAKER IMPLANTATION. The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) published updated guidelines for indications for pacemaker implantation in device-based therapy of cardiac rhythm abnormalities in 2012 (see Table 53.2).

V. PHYSIOLOGY OF CARDIAC PACING

A. Pulse generator output. This is determined by the output voltage and duration of the stimulating pulse (pulse width). Most implanted cardiac pacemakers use constant-voltage output (as opposed to most temporary cardiac pacemakers, which use constant-current output).

TABLE 53.1 Revised NASPE/BPEG Generic (NBG) Code for Antibradycardia, Adaptive Rate, an

Position	I	II	III	IV
Category	Chamber(s) paced	Chamber(s) sensed	Response to sensing	Programm modula
Letters	0 ≥ none	0 ≥ none	0 ≥ none	0 ≥ none
	A ≥ atrium	A ≥ atrium	T ≥ triggered	R ≥ rate r
	V ≥ ventricle	V ≥ ventricle	I ≥ inhibited	
	D ≥ dual (A + V)	D ≥ dual (A + V)	D ≥ dual (T + I)	
Manufacturers' designation only	>S ≥ single (A or V)	S ≥ single (A or V)		

B. BPEG, British Pacing and Electrophysiology Group; NASPE, North American Society of Pacing and Electrophysiology.

C. From Bernstein AD, Daubert JC, Fletcher RD, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group. *Pacing Clin Electrophysiol*. 2002;25(2):260–264. Copyright © 2002 Futura Publishing Company, Inc. Reprinted by permission of John Wiley & Sons, Inc.

D. Strength–duration relation. There is an exponential relationship between the stimulus amplitude for myocardial stimulation and the pulse width, such that there is a rapidly rising strength–duration curve at pulse widths <0.25 ms and a flatter curve at pulse widths >1.0 ms (see Fig. 53.1).

1. **Rheobase.** The flattened portion of the strength–duration curve indicating the point at which increasing pulse width is no longer associated with a progressive decrease in stimulus amplitude (voltage) required for myocardial stimulation. In general, the rheobase voltage is determined by assessing the threshold stimulus voltage at a pulse width of 2.0 ms.
2. **Chronaxie.** This corresponds to the threshold pulse width at twice the rheobase voltage. The chronaxie pulse duration approximates the point of minimal threshold energy on the strength–duration curve.

E. Safety margins

1. **Voltage.** The voltage output should be programmed to a level that is approximately twice the capture (stimulation) threshold for a 2:1 output safety margin.
2. **Pulse width.** The pulse duration should be programmed to a level approximately three times the pulse width capture threshold for a 3:1 output safety margin. The typical range for pulse width is 0.2 to 1.0 ms.

F. Temporal changes in stimulation threshold. Typically, the stimulation threshold rises within 24 hours following implantation of a permanent pacemaker lead. The threshold peaks at 1 to 2 weeks, then gradually declines and plateaus at approximately 6 weeks at a level less than the acute peak, but greater than that measured at implantation. The absolute value of the temporal changes in stimulation thresholds varies between individuals and also between various types of electrodes.

VI.PACEMAKER TIMING CYCLES AND INTERVALS

A. Timing circuits. A pacemaker can be thought of as a series of timing circuits. An understanding of how these timing circuits interact can facilitate the analysis of pacemaker rhythms. The timing circuit runs until the cycle is completed or until it is reset. Completion of a timing cycle results in the release of a pacing output or the initiation of another timing cycle. Figure 53.2 illustrates the basic timing cycles and intervals for a dual-chamber pacemaker. The basic terms and abbreviations used for the pacemaker timing cycles and refractory periods are defined in the glossary.

TABLE 53.2 Indications for Cardiac Pacing

	Class I	Class II
SND	1. SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms 2. Symptomatic chronotropic incompetence 3. Symptomatic sinus bradycardia that results from required drug therapy for medical conditions	IIa: 1. SND with heart rate <40 beats/min w a clear association between signific symptoms consistent with bradyca and the actual presence of bradyca has not been documented 2. Syncope of unexplained origin w clinically significant abnormalities sinus node function are discovered provoked in electrophysiologic studies

TABLE 53.2 Indications for Cardiac Pacing

		IIb: In minimally symptomatic patients w chronic heart rate <40 beats/min w awake
Acquired AV block	1. Third-degree and advanced second-degree AV block at any anatomic level associated with the following conditions: • Bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be due to AV block • Arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia • Awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 s or any escape rate <40 beats/min, or with an escape rhythm that is below the AV node	IIa: 1. Persistent third-degree AV block with escape rate >40 beats/min asymptomatic adult patients with cardiomegaly 2. For asymptomatic second-degree block at intra- or infra-His levels found electrophysiologic study 3. First- or second-degree AV block in setting of symptoms similar pacemaker syndrome or hemodyna instability 4. Asymptomatic type II second-degree block with a narrow QRS
	• Awake, symptom-free patients with AF and bradycardia with one or more pauses of at least 5 s or longer • After catheter ablation of the AV junction • Postoperative AV block that is not expected to resolve after cardiac surgery • Neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns–Sayre syndrome, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy, with or without symptoms • Second-degree AV block with associated symptomatic bradycardia regardless of type or	IIb: 1. Neuromuscular diseases such myotonic muscular dystrophy, dystrophy (limb-girdle musc dystrophy), and peroneal musc atrophy with any degree of AV bl (including first-degree AV block), with without symptoms, because there r be unpredictable progression of conduction disease 2. AV block in the setting of drug and/or drug toxicity when the block expected to recur even after the dru withdrawn

TABLE 53.2 Indications for Cardiac Pacing

	site of block • Asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of 40 beats/min or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node • Second- or third-degree AV block during exercise in the absence of myocardial ischemia	
HCM	Permanent pacing is indicated for SND or AV block in patients with HCM	IIa: In medically refractory symptom patients with HCM and significant res or provoked LV outflow tract obstruct As for class I indications, when factors for SCD are present, conside DDD ICD
After the acute phase of MI	1. Persistent second-degree AV block in the His-Purkinje system with alternating bundle branch block or third-degree AV block within or below the His-Purkinje system after ST-segment MI 2. Transient advanced second- or third-degree infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiologic study may be necessary 3. Persistent and symptomatic second- or third-degree AV block	IIa: None IIb: Persistent second- or third-degree block at the AV node level, even with symptoms
Chronic bifascicular and trifascicular block	1. Advanced second-degree AV block or intermittent third-degree AV block 2. Type II second-degree AV block 3. Alternating bundle branch block	IIa: 1. Syncope not demonstrated to be du AV block when other likely causes h been excluded, specifically VT 2. Incidental finding at electrophysiol study of a markedly prolonged interval (.100 ms) in asymptom patients

TABLE 53.2 Indications for Cardiac Pacing

		3. Incidental finding at electrophysiolo study of pacing-induced infra-His bl that is not physiologic IIb: 1. Neuromuscular diseases such myotonic muscular dystrophy, dystrophy (limb-girdle musc dystrophy), and peroneal musc atrophy with bifascicular block or fascicular block, with or with symptoms
Hypersensitive carotid sinus syndrome and neurocardiogenic syncope	Recurrent syncope caused by spontaneously occurring carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole of more than 3 s	IIa: Syncope without clear, provoca events and with a hypersensi cardioinhibitory response of 3 s or lon IIb: Significantly symptom neurocardiogenic syncope associa with bradycardia documer spontaneously or at the time of tilt-ta testing
Termination of tachyarrhythmias		IIa: Symptomatic recurrent SVT that reproducibly terminated by pacing w catheter ablation and/or drugs fail control the arrhythmia or prod intolerable side effects
Prevention of tachycardia	Sustained pause-dependent VT, with or without QT prolongation	IIa: High-risk patients with congenital l QT syndrome IIb: Prevention of symptomatic, dr refractory, recurrent AF in patients v coexisting SND
Pacing after cardiac transplantation	Persistent inappropriate or symptomatic bradycardia not expected to resolve and for other class I indications for permanent	IIa: None IIb: 1. Relative bradycardia is prolonged recurrent, which limits rehabilitation

TABLE 53.2 Indications for Cardiac Pacing

	pacing	discharge after postoperative recov from cardiac transplantation 2. Syncope after cardiac transplanta even when bradyarrhythmia has been documented

B. Class I: Conditions for which there is evidence and/or general agreement that pacing is beneficial, useful, and effective.

C. Class IIa: Conditions for which there is evidence and/or general agreement that pacing can be beneficial, useful, and effective.

D. Class IIb: Conditions for which the usefulness/efficacy of pacing is uncertain or not well established.

E. Class III: Conditions for which there is evidence and/or general agreement that pacing is not beneficial and in some cases may be harmful.

F. AF, atrial fibrillation; AV, atrioventricular; DDD, dual pacing for both chambers, dual-chamber activity sensing, and dual response; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter–defibrillator; LV, left ventricular; MI, myocardial infarction; SCD, sudden cardiac death; SND, sinus node dysfunction; SVT, sustained ventricular tachycardia; VT, ventricular tachycardia.

G. Reprinted from Epstein AE, DiMarco JP, Ellenbogen, KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. J Am Coll Cardiol. 2013;61:e6–e75. Copyright © 2013 American College of Cardiology Foundation, the American Heart Association, Inc., and the Heart Rhythm Society. With permission.

H. **FIGURE 53.1** Strength–duration curve. **FIGURE 53.2** Timing cycles and intervals for a dual-chamber pacemaker. DDD, dual pacing for both chambers, dual-chamber activity sensing, and dual response; PVARP, postventricular atrial refractory period.

I. Base rate behavior

1. Single-chamber pacemakers have a timing circuit that either is inhibited (reset) by a sensed native heartbeat or completes its cycle with a stimulus output. Dual-chamber pacemakers are more complex and incorporate more timing circuits. Figure 53.2 illustrates the timing cycles of a dual-chamber pacemaker in DDD mode. In general, base rate (lower rate) pacing for dual-chamber pacemakers involves two timing circuits.

a. The first timing circuit is the interval from a ventricular-sensed or ventricular-paced event to an atrial-paced event (atrial escape interval [AEI]).

b. The second timing circuit is the interval from an atrial-sensed or atrial-paced event to a ventricular-paced event (atrioventricular interval [AVI]). An atrial-sensed event that occurs before the completion of the AEI results in termination of that interval and initiation of the AVI.

2. The response of a dual-chamber pacemaker to a sensed ventricular signal varies among manufacturers. Some pacemakers use a ventricular-based timing system and others use an atrial-based timing system.

a. **Ventricular-based timing.** In this type of pacemaker timing system, the AEI is fixed. A ventricular-sensed event during the AEI will reset the timing circuit. A ventricular-sensed event during the AVI terminates that interval and initiates the AEI.

b. **Atrial-based timing.** In this type of pacemaker timing system, the AA interval is fixed. A ventricular-sensed event during the AEI will reset the AA timing circuit and add the programmed AVI. A ventricular-sensed event during the AVI will inhibit a ventricular output, but will not alter the AA interval.

3. Interpretation of pacemaker rhythm that has ventricular-sensed beats requires knowledge of the type of timing system the pacemaker uses. Both the ventricular-based and atrial-based timing systems should be analyzed by measuring backward from an atrial-paced event. The point of ventricular sensing for a ventricular-based timing system will be found at the point before the atrial-paced event that is equal to the AEI. For an atrial-based timing system, the measurement before the atrial-paced event should be to the point that is equal to the AA interval. Knowledge of these principles allows one to evaluate the ventricular sensing for a given pacemaker. Be aware that some pacemakers have incorporated modifications of these systems that take advantage of features from both timing systems. For example, a pacemaker with an atrial-based timing system may behave as a ventricular-based timing system.

4. **Hysteresis** is a pacing feature that attempts to allow the heart's native conduction system to predominate and therefore modifies base rate behavior. This feature works by using a longer escape interval after a sensed beat than after a paced beat. For example, the device sets the hysteresis rate at 50 beats/min whereas the basal rate is 60 beats/min. Therefore, if the patient's intrinsic rate is >50 beats/min, the device will not pace. However, if the patient's rate falls below 50 beats/min, the pacer will pace at 60 beats/min. As hysteresis can appear as an unusually long delay on the ECG strip, it can be misinterpreted as failure to pace or as inappropriate-sensing.

J. Upper rate behavior

1. As the sinus rate accelerates, the sensed atrial events terminate the AEI and initiate the AVI. The result is P-wave synchronous ventricular pacing (unless the PR interval is shorter than the PV interval, in which case pacing will be fully inhibited).

2. The maximal atrial rate that a dual-chamber pacemaker can sense is determined by the total atrial refractory period (TARP). The TARP is composed of the AVI and the postventricular atrial refractory period (PVARP). The PVARP is an interval during which the atrial channel can see incoming signals, but will not respond to them. However, because signals are seen in PVARP, the pacer can use advanced features to assess whether high atrial rates are occurring. As the sinus rate accelerates, the native atrial intervals become shorter than the TARP, and some atrial events will not be sensed. An abrupt, fixed block occurs as the pacemaker only intermittently senses the P-waves, which may result in symptoms as the rate drops precipitously.

3. Maximal tracking rate interval (MTRI) or upper rate limit is an additional timing circuit designed to avoid abrupt blocks at upper pacing rates. It works in conjunction with the AVI to determine the highest ventricular pacing rate that can be achieved in response to atrial-sensed events. A sensed atrial event initiates the AVI and the MTRI.

a. If the AVI completes its cycle and the MTRI has also completed its cycle, then a ventricular output occurs at the programmed AV interval.

b. If the AVI completes its cycle and the MTRI has not completed its cycle, then the ventricular output is delayed until the MTRI has timed out. This prolongs the PV interval and allows continued tracking of the atrial rate. However, the longer PV interval also places the ventricular output closer to the following P-wave.

c. If the sinus rate accelerates to a sufficient rate, the delayed ventricular output may cause the following P-wave to fall within the PVARP and not be sensed. The result is an intermittent "dropped" beat and a pause similar to Wenckebach behavior. However, abrupt block is less likely. More modern pacemakers may incorporate features designed to limit the degree of fixed block at the upper rate limit, such as rate smoothing (adjustment of the AEI as the PV interval changes) and rate-responsive AV delay. However, fixed block at the upper rate limit may still occur, particularly if the device is suboptimally programmed.

VII. RATE-ADAPTIVE PACING.

The primary purpose of rate-adaptive pacing is to emulate the function of the sinus node for patients with chronotropic incompetence or atrial arrhythmias that preclude reliable sensing of native sinoatrial rhythm. This function is expressed with the letter "R" in the fourth position (AAIR, VVIR, DDDR, and so on).

A. Primary components of a rate-adaptive pacemaker system

1. A sensor located in the pacing lead or pacemaker itself detects a physical or physiologic parameter that is directly or indirectly related to metabolic demand.
2. Rate-modulating circuitry within the pacemaker contains an algorithm that translates a change in the sensed parameter to a change in the pacing rate.
3. Algorithm programmability such that a physician can make adjustments to accommodate the heart rate requirements of the individual patient.
4. Pacemakers can set the sensor to on or off. Some pacemakers can be put in a passive mode in which they store information in order to predict how the pacer would act if set to rate-responsive behavior.

B. Basic technical categories of pacemaker sensors

(see Table 53.3). Motion sensors are the most commonly used due to their simplicity, speed of response, and compatibility with standard unipolar and bipolar pacing leads. Other sensors are more physiologic but may require technically complex pacing leads. Of the physiologic sensors, only the minute ventilation type is widely available. Minute ventilation sensors are prone to interference from electromagnetic sources, coughing, hyperventilation, and arm swinging.

VIII. AUTOMATIC MODE SWITCHING.

Automatic mode switching is a programmable response of a dual-chamber pacemaker during an atrial tachyarrhythmia (atrial tachycardia, atrial fibrillation, or atrial flutter) designed to avoid nonphysiologic ventricular pacing because of atrial tracking. Generally, the device switches from a DDD mode to a VVI mode, usually with a gradual reduction of the pacing rate. The device switches back to the DDD mode after the atrial tachyarrhythmia resolves. Mode switch information can also be helpful in documenting atrial arrhythmia burden in order to help dictate medical therapy for arrhythmias.

IX. BASIC PACING MODES.

The choice of pacemaker generator and the mode of pacing depend mainly on the underlying rhythm disturbance and whether AV synchrony and rate response are desired (see Table 53.4).

A. Ventricular demand pacing (VVI).

This remains the most commonly used pacing mode worldwide. Although VVI pacing protects the patient from lethal

bradycardias, AV synchrony is not restored or maintained nor does it provide rate responsiveness in the patient with chronotropic incompetence. Because AV synchrony is absent, the rate of pacemaker syndrome is high (up to 83% in randomized trials).

TABLE 53.3 Sensors in Rate-Responsive Pacing

Methods	Physiologic Parameters	Mechanism	Advantages
Impedance sensing	Respiratory rate Minute ventilation Stroke volume	Impedance plethysmography	Highly physiolog Highly proporti metabolic dem
Ventricular evoked response	Evoked QT interval (stim-T interval)	Reflects catecholamines	More physiologic
Vibration, acceleration, gravitation, motion sensing	Body movement	Piezoelectric element	Rapid response No special lead r
Special sensors on pacing electrode	Central venous temperature[a] dP/dt[b] Mixed venous oxygen saturation[b]	Thermistor Piezoelectric element Optical sensor	More physiologic

[a] No longer produced, although still in use in Japan.

[b] Presently available only in clinical trials.

From Lau CP. The range of sensors and algorithms used in rate adaptive cardiac pacing. *Pacing Clin Electrophysiol*. 1992;15(8):1177–1190. Adapted by permission of John Wiley & Sons, Inc.

TABLE 53.4 Guidelines for Choice of Pacemaker Generator in Selected Indications for Pacing

	Sinus Node Dysfunction	AV Block
Single-chamber atrial pacemaker	No suspected abnormality of AV conduction and not at increased risk for future AV block Maintenance of AV synchrony during pacing if desired RR if desired	Not appropriate
Single-chamber ventricular pacemaker	Maintenance of AVS during pacing not necessary RR available if desired	Chronic AF or other at tachyarrhythmia or maintenance AVS not necessary RR available if desired
Dual-chamber	AVS during pacing desired	AVS during pacing desired

TABLE 53.4 Guidelines for Choice of Pacemaker Generator in Selected Indications for Pacing

pacemaker	Suspected abnormality of AV conduction or increased risk of AV block	Atrial pacing desired RR available if desired
Single-lead, atrial-sensing ventricular pacemaker	Not appropriate	Normal sinus function and no ne for atrial pacing Desire to limit the number pacemaker leads

E. AF, atrial fibrillation; AV, atrioventricular; AVS, atrioventricular synchrony; RR, rate response.

F. AAI (atrial demand pacing). This mode is appropriate for patients with sinus node dysfunction who have intact AV conduction. A sensed atrial event will inhibit atrial pacing, and expiration of a preset AA interval will pace the atrium at a preset rate. Because there will be no ventricular support if AV block should occur, careful testing of AV conduction is necessary at the time of pacemaker implantation (incremental atrial pacing). This mode is infrequently used in the United States.

G. AV sequential pacing

1. DDI. There are both atrial and ventricular sensing and pacing, but no atrial tracking can occur. The pacemaker rate is therefore fixed, and this mode is rarely used.

2. VDD. In this mode, ventricular stimulation can either be inhibited by a spontaneous ventricular beat or be initiated by an atrially tracked beat, and it can therefore be used in patients with normal sinus function but impaired AV conduction. This modality uses a "floating" sensing electrode on the atrial portion of the ventricular lead, but it is altogether rarely used.

3. DDD. This system provides the most physiologic pacing mode. The pacer can be totally inhibited with normal sinus rhythm, can pace the atrium with spontaneous ventricular depolarization, can pace the ventricle in response to a spontaneous P-wave, and can sequentially pace both the atrium and ventricle. This system is most appropriate in patients who have impaired AV conduction with either an intact or dysfunctional sinus node.

H. Reducing ventricular pacing. Prolonged ventricular pacing has been associated with adverse cardiac outcomes. These adverse outcomes are the result of ventricular dyssynchrony and include left ventricular (LV) remodeling, reduced ejection fraction (EF), and death in patients with an already reduced EF. Pacing algorithms have been developed that combine single-chamber atrial pacing (AAI) with the safety of DDD pacing. Several randomized trials have demonstrated that AAI-DDD pacing can reduce adverse outcomes from ventricular pacing.

X.BIVENTRICULAR PACING. Because patients with systolic LV dysfunction and wide QRS complexes have dyssynergic contractility, the use of multisite atrial, right ventricular (RV), and LV pacing strategies has been proposed. For this purpose, an additional pacemaker lead is placed transvenously into the coronary sinus or epicardially during open chest surgery for simultaneous stimulation of the left and right ventricles.

A. Biventricular cardiac resynchronization pacing for heart failure has been accepted as standard therapy for patients with a depressed EF (< 35%), QRS duration > 120 ms, and

New York Heart Association class III or IV symptoms despite appropriate medical therapy. Several randomized studies, including MUSTIC, MIRACLE, MIRACLE-ICD, PATH-CHF, and VENTAK-CHF/CONTAK-CD, have demonstrated improved functional status, exercise capacity, and quality of life with biventricular pacing. CARE-HF demonstrated a decrease in the primary end point of death and hospitalization with biventricular pacing in heart failure patients with depressed systolic function, class III/IV symptoms, and wide QRS.

B. Consideration for implantation of a biventricular pacemaker should be given for patients with LV dysfunction who will require a high percentage of ventricular pacing. This recommendation is based on the findings from the DAVID trial where high rates of RV pacing caused ventricular dyssynchrony and more hospitalization for congestive heart failure (CHF) or death.

C. Although the overall rate of clinical improvement with biventricular pacing is high in these trials (about 70% of patients), it is not entirely clear how to identify patients who will respond ahead of time. Multiple echocardiographic and electrocardiographic measures have been investigated to help predict an individual patient's likelihood of clinical response, but so far no single modality has proven entirely reliable.

XI.PACEMAKER IMPLANTATION: PERTINENT ISSUES FOR THE PHYSICIAN

A. Preoperative issues. Several issues must be addressed for the patient scheduled for routine pacemaker implantation.

1. History and physical examination. Attention should be given to any findings that may affect the site and approach for pacemaker implantation, such as patient handedness (pacemakers are generally implanted on the contralateral side), history of mastectomy, presence of congenital abnormalities (e.g., anomalous venous drainage), current central venous lines, or tricuspid valve disease or surgery.

2. Informed consent (risks, benefits, and alternatives)

3. Tests

a. Posteroanterior and lateral chest radiograph

b. Twelve-lead ECG should be obtained.

c. Blood tests may include serum electrolytes, complete blood count, creatinine, prothrombin/international normalized ratio (INR), and partial thromboplastin times.

4. Medications

a. Clinical trials suggest that approximately 25% of pacemaker patients receive long-term oral anticoagulation. Most physicians prefer warfarin to be discontinued at least 3 days before the procedure. In some cases, such as primary implants or generator changes, warfarin can be kept close to therapeutic, with INR at approximately 2.0. Apixaban and rivaroxaban should be held at least 24 hours before pacemaker implantation. Dabigatran, whose clearance is dependent upon renal function, should be held at least 24 hours before pacemaker implantation in patients with a creatinine clearance >80 mL/min and at least 48 hours for creatinine clearances <50 mL/min. Consider admission to the hospital for intravenous heparin if the risk of discontinuation of anticoagulation is high. Heparin may be discontinued 4 to 6 hours before the procedure.

b. The dosage of oral hypoglycemics or insulin may have to be adjusted.

5. Patient preparation

a. The patient should have nothing by mouth for at least 6 to 8 hours before the procedure. Intravenous hydration should be initiated upon arrival to the laboratory to prevent hypovolemia, which may make venous cannulation more difficult.

b. An intravenous catheter is particularly helpful if placed in the arm ipsilateral to the proposed pacemaker site. This allows the ability to perform a venogram if there is difficulty in obtaining venous access during pacemaker implantation.

c. The patient should be shaved and cleansed (e.g., with povidone iodine) in the area from above the nipple line to the angle of the jaw and from the sternum to the axillary line on the side of the implantation site.

d. Antibiotic prophylaxis before pacemaker implantation is a controversial issue, and various prospective studies have provided conflicting information. Some centers have advocated antibiotic prophylaxis with an agent active against staphylococci for patients at high risk for endocarditis, such as those with prosthetic valves or complex congenital heart disease, or for redo procedures or for prolonged or potentially contaminating procedures. Other centers use antibiotic prophylaxis routinely (systemically and/or locally).

B. Postoperative issues

1. **General recommendations.** Patients are usually admitted for overnight observation on telemetry after pacemaker implantation.

2. **Postoperative testing.** Posteroanterior and lateral chest radiograph should be obtained to document proper position of the pacemaker leads and connection of the terminal pins to the pulse generator. The radiograph should also be examined for evidence of pneumothorax, pericardial effusion, or pleural effusion.

3. **Resuming anticoagulation.** Anticoagulation should not be aggressive in the early postimplantation period because of the risk of pacemaker pocket hematoma, which has been associated with increased risk of complications such as reoperation and infection. Administration of therapeutic doses of unfractionated or low-molecular-weight heparin in the 48 hours following device implantation will increase the risk of hematoma and should generally be avoided. If warfarin was held prior to device implantation, it may be restarted the day prior to device implantation based on the INR. Data regarding appropriate reinitiation timing of new oral anticoagulant medications are lacking. Expert opinion has suggested a period of interruption varying between 3 and 7 days.

4. **Pacemaker evaluation**

a. Evaluation in the pacemaker clinic before discharge includes assessment of pacing and sensing thresholds and lead impedance in order to optimize patient hemodynamics and minimize battery expenditure.

b. Capture thresholds are expected to rise over the first 2 to 6 weeks after implantation. Therefore, the pacemaker should be programmed with an adequate safety margin to account for these changes.

c. Rate adaptation for activity-sensing pacemakers may be programmed according to informal (e.g., hallway walking) or formal (e.g., treadmill) exercise testing.

5. **Discharge planning**

a. **Discharge instruction.** Usually includes patient education regarding the recognition of pacemaker pocket complications, such as signs of infections,

bleeding, or hematoma. The patient is generally advised to avoid heavy lifting or vigorous activity (especially forceful abduction) with the arm ipsilateral to the implant site.

b. The patient should be provided with information regarding his or her pacemaker, including a wallet card identifying the pacemaker and lead(s) manufacturer, model numbers, and serial numbers.

c. The patient may be provided with and instructed in the use of a transtelephonic monitoring system for remote evaluation of the pacemaker.

d. Endocarditis prophylaxis is generally *not* recommended routinely for patients with pacemakers, according to the updated AHA guidelines.

XII.COMMON PACEMAKER PROBLEMS

A. Acute complications of pacemaker implantation

1. Pneumothorax/hemothorax

a. This complication may be asymptomatic and detected only by chest radiograph. The diagnosis should be considered in a patient with dyspnea and/or pleuritic chest pain after implantation.

b. A small pneumothorax may resolve without intervention. However, the presence of severe symptoms, a pneumothorax >10%, or an expanding or persistent pneumothorax often necessitates placement of a chest tube.

2. Pacemaker pocket hematoma

a. This is one of the most common complications of pacemaker implantation and is often due to small vessel venous bleeding inside the pacemaker pocket. Bleeding may also arise from arterial vessels or retrograde flow of venous blood along the pacemaker leads into the pocket.

b. Signs and symptoms may include pain, swelling, and sometimes bleeding at the pocket site.

c. Small hematomas may be managed conservatively with pressure dressings, elevation (head of bed at least 45°), and analgesics. The patient should be positioned on his or her side contralateral to the pacemaker site. Large hematomas may compromise the integrity of the incision site and result in dehiscence. The patient may require urgent surgical exploration and hematoma evacuation in the electrophysiology laboratory or operating room.

d. Percutaneous insertion of a needle to drain a hematoma increases the risk of infection and should be avoided.

3. Cardiac or central venous perforation.

Perforation may lead to pericardial effusion and cardiac tamponade and should be suspected in the patient with chest pain, pericardial friction rub, or hypotension after pacemaker implantation. A chest radiograph may reveal an enlarged cardiac silhouette or an extracardiac lead tip. A change in the paced ventricular morphology, particularly a right bundle branch pattern, may indicate ventricular lead migration. The hemodynamically unstable patient with tamponade will require urgent pericardiocentesis and drainage of the effusion.

4. Diaphragmatic stimulation.

Stimulation of the left diaphragm may occur with a pacing lead at the RV apex, particularly at high pacing outputs. The possibility of cardiac perforation should be considered. Stimulation of the right diaphragm may occur due to stimulation of the right phrenic nerve by a displaced atrial lead. Reduction in the pacemaker output voltage or lead repositioning may be necessary.

5. Local muscular stimulation

a. This may occur with a unipolar pacemaker configuration, particularly if the pulse generator is positioned upside down within the pocket (whereby a node is directly in contact with the pectoralis muscle).

b. A pacing lead fracture may result in leakage of current into the surrounding tissue, resulting in local muscle stimulation.

6. Pacemaker malfunction

a. The pulse generator may be defective or may have been damaged at the time of implantation (e.g., by electrocautery or direct current [DC] defibrillation).

b. Improper fixation of the terminal pins of the pacing leads into the pulse generator (e.g., loose-set screws) may result in complete or intermittent pacemaker malfunction with high impedance measurements.

7. Lead dislodgement or damage

a. Pacing leads may become dislodged soon after implantation before the lead has become more fixed in place through clotting and fibrosis. Lead dislodgement may be suspected by noncapture, high lead impedance, undersensing, or oversensing on telemetry or ECG and may be confirmed by chest radiography or formal pacemaker testing.

b. The lead may be damaged at the time of implantation by forceful handling or excessively tight retention sutures.

c. Interrogation of a device with a damaged lead may reveal changes in impedance. A break in the insulation of the lead results in low impedance. A contained fracture of the lead conductor, poor terminal pin to device connection, or lead dislodgement all result in high impedance.

B. Chronic complications of pacemaker implantation

1. Pacemaker system infection

a. The reported incidence of pacemaker infection is 1.9 per 1,000 device-years based on a large cohort study spanning 30 years. As noted earlier, the number of pacemakers implanted annually continues to increase, and yet the rate of device-related infections is increasing at a disproportionately higher rate. Recognition of these infections and appropriate treatment is critical for health-care providers managing patients with cardiac implantable devices. The infection may involve only the pacemaker pocket or the entire system, with subsequent life-threatening sepsis. There is a higher incidence with repeat operations (e.g., pulse generator replacement). Causative organisms tend to be skin flora such as *Staphylococcus* species.

b. Treatment should include intravenous antibiotics; however, antibiotic therapy rarely eradicates the infection unless the pacemaker system is removed. Mortality rates for device-related endocarditis range from 31% to 66% without device removal. Mortality improves to 18% or less with a combined approach of medical therapy and complete device removal.

c. The timing of system removal depends on the clinical status of the patient; however, prolonged delays should be avoided.

2. Intravascular thrombosis or obstruction

a. Vascular complications are common with device therapy. They range from asymptomatic venous occlusion to extremity edema. Mortality from vascular complications is rare. Initial treatments may include heat and upper-extremity elevation. Symptomatic thrombosis of the subclavian or axillary veins may require anticoagulation or

systemic thrombolytic therapy. It is recommended that documented deep venous thrombosis be treated with anticoagulation with warfarin for at least 6 months, unless contraindicated.

b. Superior vena cava stenosis or occlusion may require percutaneous balloon dilatation or surgical consultation for consideration of repair.

3. **Twiddler syndrome.** A condition in which the pacemaker is turned, usually unintentionally, upside down within the pacemaker pocket. The leads may become twisted, resulting in excessive traction on the leads and dislodgement.

XIII.PACEMAKER SYSTEM MALFUNCTION

A. In assessing the patient with suspected pacemaker malfunction, it is important to interpret the ECG carefully. Ideally, intracardiac tracings obtained by pacemaker interrogation should be interpreted. Pacing artifacts or spikes are high-frequency signals and are often filtered out by newer digital surface ECG machines. Furthermore, pacing artifacts from bipolar leads are smaller and more difficult to see than artifacts from unipolar leads. It may be necessary to record multiple leads or use an older analogue recorder to clearly visualize the pacing artifact. Pseudomalfunction occurs when recording and digital artifacts are misinterpreted. Approaching the paced patient's ECG systematically will help to determine the appropriateness of pacing.

B. General evaluation for possible pacemaker malfunction

1. If a recent pacemaker interrogation is available, review the programmed parameters for the pacemaker, particularly the mode, base rate, upper rate limit, intervals, and the presence of other features such as automatic mode switching, hysteresis, rate-adaptive features, or managed ventricular pacing.

2. Obtain a 12-lead ECG and evaluate the following:

a. Determine whether pacing stimulus artifacts are present and whether the appropriate chamber is captured.

b. If no pacing stimulus artifact can be seen, native depolarization should be adequate.

c. Evaluate whether native beats are appropriately sensed in relation to paced complexes.

d. Evaluate the timing cycles of a dual-chamber pacemaker by measuring backward from an atrially paced event.

C. Patients with pacemaker system malfunction generally demonstrate absence of a pacing stimulus artifact, failure to capture, or failure to sense.

1. **Failure of pacemaker stimulus output.** A differential diagnosis of the more common causes of pauses during a paced rhythm is listed later in this chapter. Application of a magnet over the pacemaker should result in asynchronous pacing. If the pauses resolve when the magnet is applied, then the diagnosis of oversensing is most likely. If the pauses do not resolve, then one of the other causes should be considered.

a. **Pulse generator failure.** The pulse generator may be at the end of life (EOL), which may easily be detected with a pacemaker check.

b. **Lead failure.** This can be due to loose-set screw or terminal pin disconnection, lead conductor failure, or lead insulation failure. Suspicion of lead malfunction should prompt the clinician to obtain a chest radiograph. This may reveal the terminal pin not situated properly within the header of the pulse generator or it may demonstrate a defect in the lead insulation or conductor coil. A significant increase in the lead impedance suggests lead

conductor failure, and a significant decrease in the lead impedance suggests lead insulation failure.

c. **Oversensing.** EMI, myopotentials, cross talk, or T-wave oversensing can lead to falsely interpreted signals.

d. **Pseudomalfunction.** Pacemaker malfunction can be mistakenly diagnosed if the small spikes from a bipolar system are not appreciated on the surface ECG. Malfunction can also be diagnosed mistakenly if attention is not paid to additional features that allow the heart rate to fall below or above the set base rate. It is important to remember additional features such as hysteresis, sleep settings, rate-adaptive behaviors, or automatic mode switch, each of which can be mistaken for pacemaker malfunction.

2. **Failure to capture**

a. **Elevated capture threshold.** Electrolyte disturbance (e.g., hyperkalemia and acidemia), antiarrhythmic drugs (particularly class Ic agents such as flecainide), and myocardial fibrosis (e.g., cardiomyopathy and myocardial infarction [MI]) can increase the capture threshold.

b. **Lead malfunction**

1. 1 Lead fracture
2. 2 Lead dislodgement or perforation may result in a change in the paced morphology, especially a change from left to right bundle branch morphology.

c. **Exit block.** Exit block is defined as failure of the pacing output at the distal electrode to stimulate adjacent myocardium. This is often caused by the inflammatory reaction that occurs at the pacemaker lead tip at the time of implantation. It occurs in approximately 5% of cases and may be managed with systemic steroids. Most pacing leads have steroid-eluting electrodes designed to minimize the degree of inflammation at the electrode tip and decrease the incidence of exit block.

d. **Latency.** Defined as the delay between the delivery of an output pulse and the onset of electrical systole, such as occurs with severe electrolyte disturbances

e. **Pseudomalfunction.** Artifact with small spikes on the surface ECG, such as occurs when the patient's refractory periods interfere with pacer function

3. **Failure to sense**

a. Lead dislodgement is usually accompanied by failure to capture (see discussion in Section XIII.C.2)

b. Lead insulation failure (see discussion in Section XIII.C.1.b)

c. Inadequate endocardial signal

d. Change in electrogram. Transient changes may occur due to electrolyte or acid–base disturbance, and permanent changes may occur due to MI or cardiomyopathy.

e. Ectopic beats

f. Pulse generator failure (sensing circuits)

g. Functional undersensing. Defined as undersensing that occurs due to normal pacemaker function, such as refractory periods, blanking periods, or safety pacing

D. **Other pacemaker malfunctions**

1. **Pacemaker syndrome.** Pacemaker syndrome is defined as the signs and symptoms that occur in the pacemaker patient because of inadequate timing of atrial and ventricular contractions. Pacemaker syndrome is commonly caused by retrograde

ventriculoatrial (VA) conduction, which causes atrial contraction against closed mitral and tricuspid valves. Pacemaker syndrome may also occur during an exercise-induced atrial arrhythmia because of loss of AV synchrony when a device with an automatic mode-switching feature converts to VVI pacing.

2. **Pacemaker-mediated tachycardia (PMT).** This is defined as a paced tachycardia that is sustained by the continued active participation of the pacemaker in the rhythm. At first glance, the resultant wide-complex (paced) tachycardia may appear to be ventricular tachycardia, especially for pacemakers with bipolar leads where the pacing artifact may be difficult to discern on ECG.

a. One form of PMT is the rapid ventricular pacing that occurs as a dual-chamber pacemaker attempts to track the rapid atrial rate during an atrial tachyarrhythmic episode.

b. Another form of PMT occurs when there is oversensing in the atrial channel, such as myopotentials.

c. **Endless-loop tachycardia (ELT).** PMT in which a repetitive sequence of sensing of retrograde atrial activity results in triggering of a ventricular-paced beat at the end of the MTRI. ELT requires a trigger for initiation, which may be any event that results in AV dissociation and allows retrograde VA conduction to occur after a native or paced ventricular beat. The trigger may be a PVC, atrial undersensing, atrial oversensing, or atrial noncapture. ELT is sustained until there is VA block. Application of a magnet over the pacemaker will terminate ELT. The most reliable way to prevent ELT is to program the PVARP to a value that exceeds the VA conduction interval. Some of the more modern pacemakers have PMT or ELT recognition and termination algorithms designed to prevent and/or terminate PMT and ELT.

XIV.COMMON ISSUES FOR THE PATIENT WITH A PACEMAKER

A. Perioperative patient

1. **Preoperative assessment.** Review of pertinent history and a physical examination should be performed. The patient should undergo a pacemaker evaluation to assess the programmed parameters, pacing and sensing thresholds, and lead impedance.

2. The degree of pacemaker dependence should be determined. A patient who is pacemaker-dependent should have temporary pacing equipment readily available.

3. If the operative field is in the area near the pacemaker, the rate response feature of the pacemaker should be deactivated to avoid inappropriate rapid pacing because of vibrations or pressure transmitted to the pulse generator.

4. Electrocautery may result in temporary inhibition of pacemaker output because of oversensing of the EMI. Electrocautery should be used sparingly and in short bursts, and the cautery electrode should be placed at a distance from the pacemaker site.

5. Postoperatively, the pacemaker should be reevaluated for any sign of malfunction, the presence of a reset mode, and any change in lead threshold or impedance values. A chest radiograph should be obtained after cardiac surgery to evaluate for lead damage or dislodgement.

B. EMI in the hospital environment

1. **Magnetic resonance imaging (MRI).** The magnetic field generated by the electromagnet and the radiofrequency signal produced to modulate the magnetic field for MRI may cause torque forces or malfunction of cardiac pacemakers. More modern pacemakers contain fewer ferromagnetic components than previous pacemakers, so that torque

forces are less common. The magnetic forces may close the pacemaker reed switch and result in asynchronous pacing. The radiofrequency signal may result in inhibition of pacing, rapid pacing, or reversion to reset mode. Unipolar pacemakers are more susceptible to interference from MRI. Whereas a small number of centers have developed specific scanning protocols for patients with cardiac implantable electronic devices (CIEDs), in general, MRI should be avoided in most pacemaker patients unless absolutely necessary.

Recently, MRI conditional pacemaker systems have emerged. As new applications for MRI continue to emerge in clinical practice, recent estimates suggest that as many as 50% to 75% of patients with CIED will have an indication for MRI during their lifetime. MRI conditional technology will undoubtedly continue to evolve.

2. **Extracorporeal shock-wave lithotripsy (ESWL)**

a. ESWL is a treatment for renal calculi that involves the production of focused hydraulic shock waves from an underwater spark gap. Interference or damage to a pacemaker may occur due to the spark gap or the shock waves. Activity-based rate adaptation pacemakers with piezoelectric crystals may be damaged by the shock waves, and the shock waves may cause oversensing and subsequent nonphysiologic rapid pacing rates. Such pacemakers should be reprogrammed with the rate-adaptive feature deactivated before the procedure. If the pacemaker with a piezoelectric crystal is located in the abdomen, then ESWL should not be performed.

b. The shock waves may be misinterpreted as atrial activity; therefore, dual-chamber pacemakers should be programmed to VVI mode to avoid rapid ventricular pacing.

c. A patient with a pacemaker may undergo ESWL; however, the pulse generator should be as far as possible from the focal point of the lithotripsy shock waves, and a cardiologist who is experienced in pacemaker management should be available nearby during the procedure.

3. **Radiation therapy**

a. Diagnostic radiation does not interfere with cardiac pacemakers. Therapeutic radiation therapy to the thorax such as that used for breast or lung malignancies may result in interference and/or cumulative damage. The damage to the integrated circuitry of the pacemaker results from leakage currents between the insulated parts. This damage is directly related to the cumulative radiation dose.

b. The pacemaker should be assessed before and after a treatment session. ECG monitoring is recommended for patients who are pacemaker-dependent. The pulse generator should be shielded from the ionizing radiation or moved to another site if necessary.

4. **Cardiac monitors.** Cardiac monitors that inject current into the patient's body in order to measure minute ventilation may interfere with pacemakers that use minute ventilation for rate adaptation.

5. **Transcutaneous electric nerve stimulation** is considered safe for patients with bipolar pacemakers. Patients with unipolar pacemakers may require a reduction in sensitivity.

6. **Dental equipment.** Some types of dental equipment may cause pacemaker inhibition, particularly for unipolar pacemakers. Vibrations may increase the pacing rate of activity-sensing rate-adaptive pacemakers.

7. **Cardioversion/defibrillation.** The shock from a DC cardioversion or defibrillation may cause damage to the pulse generator or result in the device being reset. If DC cardioversion or defibrillation is necessary, the patch electrodes should be positioned as far as possible from the pulse generator. A pacemaker evaluation should be performed after the procedure.
8. **Electroconvulsive therapy** generally does not interfere with pacemaker function. The patient should have a pacemaker evaluation before and after each session. ECG monitoring during the session is prudent. Seizure activity during the procedure may produce myopotential inhibition of unipolar pacemakers.
9. **Diathermy** may result in pacemaker interference or damage if applied to the region near the pulse generator.
10. **Electrocautery** (discussed in Section **XIV.A.4**)

C. Environmental EMI

1. **Cellular telephones.** These devices are generally safe. Older models were reported to interfere with cardiac pacemakers while transmitting or receiving calls. A pacemaker patient should not carry a cellular telephone near the pacemaker site (i.e., shirt pocket) and should avoid holding the telephone to the ipsilateral ear during use.
2. **Electronic article surveillance (EAS)** is a type of antitheft system consisting of a gate that produces an electromagnetic field through which individuals must walk. The field may result in pacemaker interference, primarily inhibition of pacemaker output. Patients with unipolar dual-chamber pacemakers are particularly susceptible to interference from EAS systems.
3. **Industrial electrical equipment.** This includes devices, such as arc welders, that may generate strong electrical fields. The strength of the electrical field varies among various types of equipment and if sufficiently strong may interfere with unipolar pacemakers. Patients may require individual environmental testing to ensure safety.
4. **Microwave ovens.** Because of better sealing of microwave ovens and improved shielding of pulse generators, interference with pacemakers by microwave ovens is no longer considered a significant problem.
5. **Metal detectors.** Although the metal detectors in public places such as airports may raise an alarm because of detection of a pacemaker, there is generally no significant interference with pacemaker function. Patients should avoid lingering around these devices and pass through them at a normal speed.
6. **High-voltage power lines and electrical substations.** These areas may cause inhibition or asynchronous pacing in unipolar pacemakers if the patient is quite close to the electrical field. At usual public distances from such areas, there should be no pacemaker interference.

D. Pacemaker response to EMI

1. **Pacing inhibition.** For obvious reasons, this may be catastrophic. The majority of pacemakers used today contain protective algorithms that make prolonged inhibition uncommon.
2. **Rapid pacing.** Oversensing of EMI by the atrial channel in a device set to DDD can cause the pacer to trigger ventricular pacing at or near the upper tracking limit. This response is usually well tolerated, but in certain individuals when sustained it may cause

palpitations, hypotension, or angina. Rapid pacing may also occur via activation of minute ventilation sensors.

3. **Reversion to asynchronous pacing.** Most pacers have algorithms that protect against prolonged inhibition from noise. Algorithms are based upon the principle that detected rapid frequency signals are unlikely to represent myocardial activation. The pacemaker is programmed to have a noise sampling window during the ventricular refractory period. In most devices, repetitive signaling detected in the noise sampling window reverts the device to asynchronous pacing. Asynchronous pacing is generally safe, but it is not without the risks of losing AV synchrony. Also, pacing may rarely occur during the ventricular vulnerable period and may initiate ventricular arrhythmias.

XV.CARDIAC PACING: CLINICAL TRIALS

A. Conventional pacing trials

1. Numerous clinical trials, mostly small and nonrandomized, have been performed with regard to exercise capacity and quality of life for various pacemaker modes, chamber(s) paced, rate-adaptive pacing, and types of sensors.
2. Clinical trials have firmly established the superiority of rate-adaptive (VVIR) over fixed-rate ventricular pacing (VVI) with regard to quality of life and exercise performance.
3. Numerous clinical trials have been undertaken to prove the benefit of dual-chamber/atrial-based pacing in patients undergoing postoperative permanent pacemaker implantation for sinus node dysfunction or high-degree AV block.
4. There are conflicting data regarding the benefit of dual-chamber pacing over rate-adaptive ventricular pacing. Early nonrandomized trials demonstrated mortality benefit with DDD pacing over VVI in patients with complete heart block. However, in randomized prospective trials, atrial pacing has not been shown to decrease rates of death or heart failure in patients treated for sinus node dysfunction and high-degree AV block. However, there are several randomized trials demonstrating that atrial-based pacing does, in fact, lead to a reduction in both atrial fibrillation and stroke. However, this benefit may be limited to patients with sinus node dysfunction. The one clear benefit that dual-chamber/atrial-based pacing provides is the avoidance of pacemaker syndrome, which can be seen in up to 10% of patients with VVI pacing.
5. The following paragraphs summarize some of the larger-scale, randomized studies of ventricular- versus atrial-based cardiac pacing modes.

a. **Pacemaker Selection in the Elderly trial.** A single-blind, randomized, controlled trial of ventricular pacing versus dual-chamber pacing in 407 patients older than 65 years. The primary end point was quality of life with up to 30 months follow-up. Quality of life improved with pacemaker implantation. Patients with sinus node dysfunction, but not AV block, had significantly better quality of life with dual-chamber pacing than with ventricular pacing.

b. **Canadian Trial of Physiologic Pacing.** In this trial, 1,474 patients were assigned to ventricular pacing and 1,094 patients to physiologic pacing. During a mean follow-up period of 3 years, there was no significant effect on the risk of death, stroke, or hospitalization for CHF according to the type of pacemaker used. However, the annual rate of atrial fibrillation was significantly lower in the atrial pacing group, although there was a 2-year delay before this beneficial effect emerged. There was a 50% reduction in perioperative

complications with the implant of ventricular pacing systems, but in the ventricular pacing group, there was a 5% incidence of pacemaker syndrome that required upgrade to a dual-chamber device.

c. **Mode Selection Trial in Sinus Node Dysfunction.** A randomized trial that attempted to compare dual-chamber with single-chamber ventricular pacing in 2,010 patients with sinus node dysfunction. There was no advantage for dual-chamber pacing over single-chamber ventricular pacing in terms of the trial's primary end point: Death from any cause or nonfatal stroke over 33.1 months of follow-up. However, some advantages were seen with the dual-chamber modality in secondary end points, including reductions in atrial fibrillation and symptoms of heart failure and improvement in quality of life. There was no difference in heart failure admission rates between the two groups.

d. **Pacemaker Atrial Tachycardia trial.** This was a mode randomization study in 198 patients (median age 72 years), all of whom received dual-chamber rate-adaptive pacemakers programmed to either VVIR or DDDR pacing. Intention-to-treat analysis showed no significant difference in atrial tachyarrhythmia recurrence rates at 1 year (VVIR 43%; DDDR 48%; $p = 0.09$).

e. **UK Pacing and Cardiovascular Events trial.** This was a trial comparing VVI(R) and DDD pacing in 2,021 elderly patients (mean age 80 years) with high-grade AV block. Patients were randomized to DDD (50%), VVI (25%), and VVIR (25%). No difference was detected in rates of stroke, atrial fibrillation, or heart failure hospitalizations.

f. **Meta-analysis of trials comparing atrial- and ventricular-based pacing.** Healey et al. in 2006 completed a large meta-analysis of all randomized controlled trials comparing ventricular- and atrial-based pacing modes. A total of 35,000 patient-years of follow-up were reviewed. There was no significant reduction in mortality or heart failure with atrial-based pacing. However, there was a significant reduction in atrial fibrillation (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.77 to 0.89) and a borderline reduction in stroke (HR 0.81, 95% CI 0.67 to 0.99).

6. The practice of RV apical pacing as the preferred method remains controversial. It provides a reliable and stable position for long-term ventricular pacing. However, RV pacing creates ventricular desynchronization and leads to several adverse effects, including LV systolic and diastolic dysfunction. Retrospective and prospective analysis has linked increased numbers of RV-paced beats with increased incidence of atrial fibrillation and heart failure. Current forms of pacemaker technology that minimize RV pacing are preferred to older pacemaker technologies. The following are landmark trials that have associated RV pacing with deleterious outcomes.

a. **DAVID.** The DAVID trial was the first study of ventricular pacing strategies in implantable cardioverter–defibrillator patients. The trial hypothesized that dual-chamber pacing would result in a lower rate of heart failure in these patients with EF <40%. At 1 year, rates of death and first hospitalization for heart failure were significantly increased in the dual-chamber group. The authors noted an increased rate of RV apex pacing in the DDD-70 group (60%) versus the VVI-40 group (3%). The authors concluded that the greater exposure to the deleterious effects of RV pacing in the DDD group led to worse outcomes.

b. **SAVE PACe.** This trial examined whether the application of newer technologies to limit frequency of ventricular pacing could lead to a decrease in atrial fibrillation in patients with dual-chamber pacemakers. Patients with sinus node disease, intact

AV conduction, and a normal QRS interval were randomly assigned to receive conventional dual-chamber pacing or dual-chamber minimal ventricular pacing with the use of features to promote AV conduction and reduce ventricular dyssynchrony. Persistent atrial fibrillation was found to occur less frequently in the dual-chamber minimal ventricular pacing group (HR 0.60, 95% CI 0.41 to 0.88) than in the conventional dual-chamber group.

c. **PROTECT-PACE.** This trial was a randomized, prospective, international, multicenter study that compared change in LVEF between RV apical and high septal pacing over a 2-year period in 240 patients with high-grade AV block and a preserved baseline EF. At the conclusion of the study, lead position was not associated with a significant difference between LVEF, heart failure hospitalization, mortality, or atrial fibrillation burden. The authors concluded that RV septal pacing provided no protective effect on LV function over RV apical pacing in the first 2 years.

d. **Recommendations.** The most recent recommendations for cardiac pacing and resynchronization released by the AHA/ACC/HRS in 2012 specifically address the implications of apical versus RV outflow tract/septal pacing. The recommendations mention that small trials have demonstrated septal pacing preserved LV function over the mid- to long term and that His bundle pacing also appears to be beneficial. However, the guidelines note that it is too early to propose a recommendation concerning the optimal location of the RV pacing lead and do not include results from the recently published PROTECT-PACE trial.

XVI. EVOLVING INDICATIONS FOR PACEMAKER THERAPY

A. Hypertrophic cardiomyopathy

1. **Presumed mechanism of benefit.** The idea of RV pacing to treat hypertrophic cardiomyopathy is based on the effective increase in left ventricular outflow tract (LVOT) diameter caused by altered septal activation.

2. **Recommendations.** Pacing is a class IIa recommendation in the 2012 ACCF/AHA/HRS guidelines and is reserved for symptomatic drug-refractory patients with significant LVOT gradients who have contraindications for septal ablation or myectomy (see Table 53.2).

B. Long QT syndrome

1. **Presumed mechanism of benefit.** In patients with long QT syndrome, life-threatening episodes of polymorphic ventricular tachycardia and torsades are typically preceded by pauses or severe bradycardia. By preventing these episodes, pacing may decrease the likelihood of events.

2. **Recommendations.** The 2012 ACCF/AHA/HRS guidelines state that permanent pacing is reasonable for high-risk patients with congenital long QT syndrome.

XVII. FUTURE DIRECTIONS

A. **Leadless pacemakers.** Despite considerable technologic advances in the design and implantation of cardiac pacemakers, approximately 1 in 10 patients ultimately experience a pacemaker-related adverse event. These events are typically related to the pulse generator, surgical pocket, or transvenous lead. Recently, a fully self-contained, leadless cardiac pacemaker has been developed that combines the battery, electronics, and electrodes in a small casing which can be delivered transcutaneously through the femoral vein. A coiled spring affixes the device to the endocardium in the RV apex. A docking interface on the proximal portion of the device provides both delivery and retrieval capabilities. Several small nonrandomized studies have demonstrated leadless pacemaker

systems can be safely implanted and provide durable single-chamber pacing from the right ventricle.

B. Sensor technology. Advances in physiologic sensors and rate adaptation algorithms include the following.

1. **Multiple sensors for more physiologic pacing.** For example, a desirable sensor combination is an activity sensor, which typically has a more rapid response, and another sensor such as minute ventilation, which typically has a more delayed but workload-proportional response.
2. **Sensor blending** refers to the relative contribution of each sensor during each phase of activity and may be programmable.
3. **Sensor "cross-checking"** is done to determine if an increase in the intrinsic atrial rate is appropriate. If the sensor does not confirm activity while the pacemaker senses an increased atrial rate, the pacemaker will use the sensor to dictate the appropriate heart rate. Also, pacemakers with multiple sensors are able to detect intersensor disagreement and thereby avoid inappropriately rapid pacing because of a false-positive response of one sensor.

XVIII. GLOSSARY

A. Cardiac pacing: basic terminology

1. **"60,000 rule."** Converts rate (beats/min) to interval (milliseconds) and vice versa, as there are 60,000 ms in 1 minute. Note the formula: 60,000/interval (milliseconds) = rate (beats/min).
2. **Anode.** Refers to the positive pole. The anode of a unipolar pacing system is the pulse generator case. The anode of a bipolar pacing system is the proximal ring electrode of the pacing lead.
3. **Capture.** The effective cardiac depolarization resulting from a pacing stimulus
4. **Cardiac stimulation threshold (mA).** The minimal electrical energy required to consistently depolarize cardiac tissue through a given electrode. This threshold changes with time after implantation (acute, subacute, and chronic).
5. **Cathode.** Refers to the negative pole. The cathode of a unipolar pacing system is the electrode at the distal portion of the pacing lead. The cathode of a bipolar pacing system is the distal tip electrode of the pacing lead.
6. **Cross talk.** In dual-chamber pacing systems, the inappropriate detection (sensing) of an event or signal in one chamber by the sense amplifier of the other chamber (usually inhibition of a ventricular output pulse because of ventricular channel detection of an atrial output pulse)
7. **Current (*I*).** The rate of transfer or the flow of electricity, measured in milliamperes (mA)
8. **Elective replacement interval (ERI), also known as elective replacement time (ERT) or recommended replacement time.** Terms indicating the pulse generator have reached a point in its service life where system failure will likely occur within 3 to 6 months. The ERI indicator for a pacemaker varies between models and manufacturers, but is usually indicated by a change in pacing rate, mode, or function. Pacemaker manufacturers generally recommend pulse generator replacement when the ERI is identified.

ERI/ERT indicators for various pacemaker models are published in a handbook that should be available in the pacemaker clinic.

9. **External EMI.** Electrical signals from noncardiac or nonphysiologic sources that may affect pacemaker function. Sources of EMI are discussed below.
10. **End of life.** Term indicating the depletion of battery power for the pulse generator. The EOL indicator for a pacemaker varies between models and manufacturers, but is usually indicated by a decrease in the magnet-related pacing rate to a certain percentage of the beginning-of-life rate. There may also be a change in pacemaker mode (e.g., from DDD to VVI). Telemetry of the cell impedance of the pulse generator also provides information regarding the status of battery power for those pacemakers with such a feature. Pacemaker manufacturers generally recommend urgent pulse generator replacement if EOL of a device is identified. EOL indicators for various pacemaker models are published in a handbook that should be available in the pacemaker clinic.
11. **Fusion.** Results when the pacemaker output occurs at the same time as an intrinsic event, and both contribute to cardiac depolarization. The morphology of the fused beat has characteristics of both the paced and intrinsic events.
12. **Impedance (*Z*).** Total resistance to the flow of current through a conductor. For pacemaker systems, this includes resistance produced by electronic components and body tissues. Temporal changes in pacing impedance usually include a decreasing impedance over the first 1 to 2 weeks following implantation, then increasing impedance to a level that is somewhat higher than the impedance at the time of implantation. Serial measurements of pacing impedance may be useful for assessing lead integrity, as discussed later in this chapter.
13. **Magnet mode.** The response of a pacemaker when a magnetic field of sufficient strength is applied and closes the pulse generator's reed switch. The pulse generator paces at a predetermined rate and mode, which vary among pacemaker models and manufacturers. Generally, the mode is asynchronous pacing. Magnet mode can be used to assess pacemaker function and battery status (see discussion on ERI in Section **XVIII.A.8** and on EOL in Section **XVIII.A.10**).
14. **Noncapture.** The absence of cardiac depolarization following a pacing stimulus
15. **Ohm's law.** $V = I \times R$ (*voltage* = *current* × *resistance*)
16. **Output.** The output of a pacemaker is determined by the voltage and pulse width.
17. **Oversensing.** The sensing of inappropriate cardiac or extracardiac signals and responding to them as if they were appropriate native sensed events. "Oversensing results in underpacing."
18. **Pacemaker-mediated tachycardia.** Sudden onset of a sustained ventricular-paced rhythm at the maximum tracking rate of the pacemaker. PMT is sustained by continued active participation of the pacemaker in the tachycardia circuit. PMT is discussed in more detail in Section **XIII.D.2**.
19. **Pacing interval (milliseconds).** The interval between two consecutive paced events
20. **Pseudofusion.** Results when an intrinsic event occurs before the pacemaker output is delivered. When this happens, the pacemaker output does not contribute

to cardiac depolarization. The morphology of the pseudofusion beat resembles the intrinsic event.

21. **Pseudo-pseudofusion.** Results when a PVC that resembles the ventricular-paced complex follows an atrial output spike
22. **Pulse width.** The measurement in milliseconds of the pacemaker output spike (also known as pulse duration)
23. **Reed switch.** A switch within the pulse generator that closes when a magnetic field of sufficient strength is applied to it (such as a ring or donut magnet, or a programming head). The pacemaker will convert to magnet mode.
24. **Resistance** (***R***). The opposition to the flow of electrical current through a material, measured in ohms
25. **Sensing.** The ability of a pacemaker to recognize native cardiac signals. Refers to the amplitude of the signal (mV) required for the pacemaker to detect the signal. Higher numbers reflect less sensitivity; lower numbers reflect more sensitivity.
26. **Undersensing.** The failure to recognize and respond appropriately to cardiac signals. "Undersensing results in overpacing."
27. **Voltage** (***V***). The difference in potential energy between two points, measured in mV

B. Cardiac pacing: timing cycles and refractory periods

1. A = atrial-paced event
2. Absolute refractory period: The period following a sensed or paced event during which the sense amplifier is unresponsive to incoming signals
3. AEI = atrial escape interval: For atrial single-chamber pacing systems, the period from a sensed atrial event to the next atrial-paced event. For dual-chamber pacing systems, the period initiated by a ventricular-sensed or ventricular-paced event and ending with the next atrial-paced event
4. ARP = atrial refractory period, which is the atrial timing cycle during which the atrial sense amplifier is unresponsive to incoming signals. For single-chamber atrial pacing modes, the atrial refractory period is initiated by an atrial-sensed or atrial-paced event. For dual-chamber pacing modes, the AV interval and the PVARP determine the TARP. TARP = AVI + PVARP.
5. AV = atrioventricular sequential pacing
6. AVI = atrioventricular pacing interval (also known as AV delay): In dual-chamber pacing, the period between an atrial-sensed or atrial-paced event and a ventricular-paced event (usually programmable)
7. Blanking period: An interval (usually 12 to 125 ms) initiated by an output pulse during which the sense amplifier is temporarily disabled. In dual-chamber pacing, the blanking period is designed to prevent the inappropriate detection of signals from the other chamber (cross talk). For example, an atrial-sensed or atrial-paced event initiates a ventricular blanking period during which the ventricular sense amplifier is temporarily disabled.
8. CDW = cross-talk detection window: In dual-chamber pacing, a timing cycle (usually 51 to 150 ms) immediately following the ventricular blanking period during which a ventricular-sensed event is considered to be cross talk but results in a triggered ventricular output at the end of an abbreviated AV interval (safety pacing)

9. LRL = lower rate limit (also known as base rate or minimum rate): The rate at which the pacemaker paces in the absence of sensed intrinsic events (generally programmable in most pacemakers)
10. MSR = maximal sensor rate: A programmable value in rate-adaptive pacemaker systems that designates the highest pacing rate that can be achieved in response to a sensor input. The MSR may be programmed independently of the MTR.
11. MTR = maximal tracking rate (also known as upper rate limit [URL]): A programmable value for dual-chamber pacemaker sensing and tracking modes that designates the highest ventricular pacing rate that can be achieved in response to atrial-sensed events with 1:1 AV synchrony at the programmed AV delay
12. P = native atrial depolarization
13. R = native ventricular depolarization
14. Relative refractory period: A "noise sampling" period following the absolute refractory period during which some incoming signals (generally those signals in the frequency range of interference) are monitored by the sense amplifier. Sensed signals during this period may result in the initiation of a new refractory period but do not reset the timing circuit.
15. RRAVD = rate-responsive atrioventricular delay. A programmable feature of some dual-chamber pacing systems that progressively shortens the PV or AV interval as the sinus or sensor-driven atrial rate increases. This is designed to provide a more physiologic AVI at higher heart rates and to allow tracking of higher atrial rates (a shorter AVI decreases the TARP), thereby lessening the chance of a fixed-block upper rate response.
16. V = ventricular-paced event
17. VRP = ventricular refractory period. The timing cycle initiated by a ventricular-sensed or ventricular-paced event during which the ventricular sense amplifier is unresponsive to incoming signals. This is not the same as the ventricular blanking period (see information regarding this in Section **XVIII.B.7**).

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CHAPTER 54

Antitachycardia Devices

Joseph M. Bumgarner

I. INTRODUCTION

A. The modern implantable cardioverter–defibrillator (ICD) is a multifunctional, multiprogrammable electronic device designed to abort life-threatening arrhythmias. It is programmed to automatically detect and manage episodes of ventricular tachycardia (VT), ventricular fibrillation (VF), or bradycardia. Current ICDs are able to deliver multitiered therapies, which may include a combination of antitachycardia pacing (ATP), cardioversion, and defibrillation. The devices also offer bradycardic support, which may include rate-responsive single- or dual-chamber pacing and automatic mode switch function. Modern ICDs are able to deliver resynchronization therapy, a significant advancement in the management of heart failure. The devices are also able to store electrograms (EGMs), which can be easily retrieved. This function can be of immense use for follow-up management of the patient and programming of the device.

Multiple clinical trials have demonstrated the efficacy of ICDs to accurately detect and manage sudden cardiac death (SCD). ICDs are superior to conventional medical therapy in both primary and secondary prophylaxis of SCD. The majority of patients who have indications for an ICD implant are those with left ventricular (LV) dysfunction, both ischemic and nonischemic.

B. Mirowski first introduced the concept of an ICD in the 1960s, with the first human implant reported in 1980. Early ICD implantations required a thoracotomy for placement of an epicardial lead system. Subsequent advancements in device and lead technology over the last 35 years have significantly reduced the size of the pulse generator, while improving programmability and diagnostic data stored within the device. An improved understanding of VF, defibrillation, and cardiac pacing has resulted in the development of biphasic shock waveforms and transvenous pace/defibrillation lead systems that preclude the need for epicardial patches. As a result, modern ICDs are increasingly more compact, provide expansive programming capability, and offer convenience with added features such as remote interrogation.

C. To avoid complications associated with vascular access in patients who have an indication for ICD therapy but who do not require pacing, a new generation of ICD systems can be placed without transvenous access. The **subcutaneous ICD** (S-ICD) was developed over the last decade and allows for defibrillation therapy without venous access. The pulse generator is implanted under the skin on the lateral chest wall and connected to a defibrillation lead that is tunneled along the left lateral margin of the breastbone. In 2012,

the United States Food and Drug Administration (FDA) approved the use of S-ICDs after several initial studies demonstrated comparable efficacy in cardioversion of induced and spontaneous VT and VF when compared to conventional transvenous systems. These initial studies also showed that inappropriate shocks occurred in a similar percentage of patients compared to conventional ICDs. The long-term efficacy of S-ICDs is currently being investigated in a randomized trial and prospective registries.

II. ICD COMPONENTS

A. The current-day ICD is a sophisticated and intelligent computer. It consists of a generator and leads. The ICD generator consists of a battery, capacitors, DC–DC converter using an oscillator rectifier mechanism, a microprocessor, and telemetry communication coils and their connections. The generator serves as an active electrode within the shocking configuration in most of the modern ICDs and is thus called the "hot can." The newest generation of ICDs utilize a lithium manganese dioxide battery. These can generate approximately 3.2 V at full charge. Because most ICDs use two batteries connected in series, the full initial voltage is approximately 6.4 V. The generator has capacitors that can charge within 7 to 30 seconds to store up to 30 to 40 J of energy. This can be delivered to the heart within a 10- to 20-ms interval when therapy is required.

B. The three essential functions of the ICD—**tachycardia detection, tachycardia therapy, and bradycardia pacing**—are delivered through the active electrodes, which are the noninsulated segments of the leads. Most of the current-day leads have sensing and pacing electrodes at the tip and distal (right ventricle) and proximal (superior vena cava [SVC]) shocking coils. The function of ventricular sensing and pacing is achieved by a technology similar to that in pacemakers. This is done through two "dedicated bipolar" electrodes at the distal end of the right ventricular (RV) lead (tip/ring). Sometimes, it may be achieved by "integrated bipolar" electrodes, wherein the bipole is formed by the tip of the ventricular lead and the distal shocking coil (tip/coil). Ventricular pacing in biventricular ICDs is from the tip of the RV and LV leads, respectively, to either the ring (true bipolar) or the distal shocking coil (integrated bipolar). To avoid the problem of "double counting," most newer devices restrict the ventricular sensing function to the RV lead alone.

C. For the delivery of shock therapy, most systems now incorporate either the RV coil, SVC coil, and pulse generator can or the RV coil and can without an SVC coil.

III. INDICATIONS AND CONTRAINDICATIONS

A. **ACCF/AHA/HRS 2012 focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities.** These are the most current guidelines for the implantation of ICDs. The guidelines stratify the various indications as class I, class II (a and b), and class III on the basis of the data from clinical trials and opinion of a panel of experts.

B. **Class I indications.** These are conditions for which there is evidence and/or general agreement that ICD therapy is beneficial, useful, and effective.

1. Survivors of SCD secondary to VF or hemodynamically unstable VT after evaluation to define the cause of the arrhythmia and to exclude completely reversible causes
2. Syncope of unknown etiology with inducible VF or hemodynamically significant VT during electrophysiology study
3. Structural heart disease and spontaneous hemodynamically unstable or stable VT

4. Ischemic cardiomyopathy, New York Heart Association (NYHA) class I, and a left ventricular ejection fraction (LVEF) ≤30% who are at least 40 days post–myocardial infarction (MI)
5. Ischemic cardiomyopathy, NYHA class II or III with an LVEF ≤35% who are at least 40 days post-MI
6. Ischemic cardiomyopathy, ejection fraction (EF) ≤ 40%, nonsustained VT, and inducible VF or sustained VT at electrophysiology study
7. Nonischemic dilated cardiomyopathy, NYHA class II or III, and LVEF ≤ 35%

C. **Class IIa indications.** These are conditions for which there is evidence and/or general agreement that ICD therapy can be beneficial, useful, and effective.

1. Unexplained syncope with significant LV dysfunction and nonischemic cardiomyopathy
2. Normal or nearly normal LVEF with sustained VT
3. Patients with hypertrophic cardiomyopathy and at least one risk factor for SCD
4. Patients with arrhythmogenic RV dysplasia with at least one risk factor for SCD
5. Patients with long QT with syncope or VT while taking β-blockers
6. Patients waiting heart transplantation (nonhospitalized)
7. Patients with Brugada with a history of syncope or VT but no episodes of cardiac arrest
8. Patients with catecholaminergic polymorphic VT with syncope or sustained VT while taking β-blockers
9. Patients with cardiac sarcoid, giant cell myocarditis, or Chagas disease

D. **Class IIb.** These are conditions for which the usefulness/efficacy of ICD therapy is uncertain or not well established.

1. Nonischemic cardiomyopathy with an EF ≤35% and NYHA class I
2. Long QT and risk factors for SCD
3. LV noncompaction
4. Patients with familial cardiomyopathy and a predisposition to SCD
5. Patients with structural heart disease and syncope but with no identifiable etiology

E. **Class III indications/contraindications.** These are conditions for which there is general agreement that ICDs are not useful and possibly harmful. These include patients with a structurally normal heart and syncope without any inducible ventricular arrhythmias. ICDs should also be avoided in patients with VT and a treatable or ablatable cause (Wolff–Parkinson–White syndrome, outflow tract VTs, fascicular VTs, etc.) or a reversible cause (acute MI, myocardial ischemia, electrolyte imbalance, drug toxicity, or trauma). It is also important to avoid using ICDs in patients with severe psychiatric illnesses or in patients with terminal illnesses, where the expected life span is less than 12 months. ICDs could do more harm than good in patients with incessant ventricular arrhythmias, where it is important to control the arrhythmia before ICD implantation to avoid recurrent painful shocks. ICDs are also contraindicated in patients with NYHA class IV heart failure who are drug refractory and are not candidates for heart transplantation or cardiac resynchronization therapy (CRT).

IV. IMPLANTATION

A. **Device implantation.** Currently, available devices are small enough to allow implantation in the left pectoral region. Animal studies have shown that the defibrillation efficacy of the hot-can ICDs is superior in the left pectoral or axillary regions followed by the right pectoral and then the abdominal sites. A right pectoral system may be necessary in patients who have vascular access problems on the left side or who have undergone pectoral surgery

(e.g., mastectomy). For patients with high defibrillation thresholds (DFTs), additional lead placement, such as a subcutaneous array or coil, an azygous coil, a coronary sinus coil, or an epicardial patch, may be necessary. Epicardial patch placement is usually reserved for patients who have failed to meet implantation criteria with a transvenous lead system or if there has been previous bilateral pectoral or tricuspid valve replacement surgery.

For pectoral implants, a single 2″ to 3″ incision is made transversely below the clavicle, about 1 cm below and parallel to the deltopectoral groove. Transvenous lead placement is achieved through a subclavian vein puncture or by cephalic vein cutdown. An "extrathoracic" subclavian vein puncture or cephalic vein cutdown for access minimizes the risk of pneumothorax and also the risk of lead failure caused by subclavian crush injury.

B. **Lead placement.** The lead is advanced to the RV apex under fluoroscopic guidance, where the tip is secured via an active fixation screw or embedded in the trabeculae with passive fixation tines. It is important to assess the quality of signals at the time of implant, because it is the best guide to the adequacy of long-term sensing of the lead. The DFT is optimized with the lead placed at the RV apex; therefore, this position is often preferred even if there is compromise of the sensing thresholds. If there is already a pacemaker lead in the RV apex, then septal placement of the lead tip is chosen so that the lead tips are at maximal distance from each other to avoid device–device interactions. On occasion, placing an additional pacing–sensing lead in the right ventricle may be necessary when the defibrillation efficacy and pace–sense function of the leads are optimized at different locations.

C. **Threshold studies.** The lead is tested for pace–sense thresholds using an external high-voltage system analyzer or pacing system analyzer. In general, an acute pacing threshold of 2 V or less, R-wave amplitude of 5 mV or more, and lead impedance within the accepted range of the manufacturer (typically 300 to 1,200 Ω) are necessary to meet the implant criteria. The lead is secured within the pocket with a suture sleeve tie-down. If the device uses an atrial and/or an LV lead, then these are implanted at this time. The leads are attached to the pulse generator, and the system is placed in either a submuscular or a subcutaneous pocket. The pulse generator should be placed with excess lead coiled posteriorly to reduce the risk of damaging the leads at the time of generator change and to maximize the ability to communicate with an external programming wand. The device is then interrogated to ensure appropriate communication. Pace–sense thresholds are again tested by telemetry to demonstrate consistency.

D. Defibrillation testing is best assessed by **evaluating the DFT**, which is defined as the lowest delivered shock strength required for successful defibrillation. A synchronized sinus test shock may be performed by delivery of a low-energy (<2 J) synchronized shock on the QRS complex. This low-energy test allows the assessment of sensing as well as shock impedance (typically 35 to 90 Ω). For the purpose of defibrillation testing, VF is typically induced with a shock on T wave. Alternatively, or if shock on the T wave is unsuccessful, ultrafast burst pacing (30-ms intervals) or application of an alternating current may be used. Appropriate ICD detection and effective therapy are verified. In our lab, we typically start with a 10 to 15 J therapy, with subsequent therapies escalating in steps of 5 to 15 J. Usually, a maximum of three device-based therapies are attempted before rescue with external defibrillation at maximum energy. Two successful therapies that are at least 10 J less than the maximal output of the device are generally required. In general, this approach identifies

the level of energy required to achieve a 50% to 75% success rate of defibrillation. Defibrillation therapy is then programmed at a level at least 10 J over the DFT. Rarely, a patient may require the addition of a shocking coil in the SVC, azygous vein, or subcutaneous coil to achieve an adequate safety margin.

Recent studies have revealed a trend toward ICD implantation without DFT testing. Although the risk of failing defibrillation is very low, patients receiving ICDs in the current era may have more severe heart failure, comorbidities, and a higher risk of failing defibrillation. In the absence of prospective randomized trials, DFT testing is currently recommended for most patients undergoing initial ICD implantation. ***Reasons to avoid DFT testing*** include left atrial or ventricular thrombus, atrial fibrillation without therapeutic anticoagulation, hemodynamic instability, severe aortic stenosis, severe unrevascularized multivessel or left main coronary artery disease, active ischemia, recent stroke, or significant respiratory comorbidity that would inhibit the use of adequate sedation.

E. Risks and complications. The risks involved with implantation are similar to those of pacemaker insertion. Operative risks include bleeding, pneumothorax, hemothorax, infection, myocardial damage, vascular/cardiac perforation, tamponade, thromboemboli, deep venous thrombosis, acceleration of arrhythmias, air embolism, and death. A rare but dangerous complication is the occurrence of electromechanical dissociation or refractory VF during DFT testing. Because of the nature of the procedure, a separate standby external pacemaker–defibrillator should be immediately available for rescue therapy should the implanted device fail to appropriately treat an arrhythmia. The overall mortality rate is much less than 1%. Late complications include chronic nerve damage, erosion, extrusion, fluid accumulation, infection, formation of hematomas/cysts, keloids, lead migration, lead dislodgment, and venous occlusion.

V. DEVICE REPLACEMENT

A. Battery status is determined by the measured voltage, and this is retrieved with device interrogation. Generator replacement is generally recommended when the device reaches a battery voltage of around 2.6 V, termed elective replacement indicator. In such situations, the generator should be replaced within a few months. With continued depletion of the battery voltage, the generator reaches end of life, a situation that indicates a more urgent need for generator replacement as the battery voltage drops below 2.2 V. This may lead to longer charge times and incomplete or inappropriate function of the device.

B. Pulse generator replacement represents a vulnerable period for the ICD/lead system. A four fold increased risk of infection has been reported with ICD pulse generator replacement. In the past, manufacturers have had multiple-lead models of variable pin lengths and diameters. Beginning in 1991, they adopted the 3.2-mm international pace–sense standard (IS-1) and the 3.2-mm defibrillation standard (DF-1). Prior to an attempted device replacement, assessment of the lead model should be done to verify that the appropriate replacement header or adapters are available at the time of surgery.

C. Leads may be inadvertently damaged during exploration of the pocket or during the exchange of pulse generators. Intraoperative assessment of lead function is imperative prior to introducing the replacement generator to the operative field. Replacement of a pace–sense or defibrillation lead may be necessary and requires the use of a different device header.

VI. TACHYCARDIA DETECTION AND THERAPY

A. **EGM and tachycardia sensing.** The ICD senses the intracardiac EGM signal via the implanted ventricular sensing electrodes. Recognition of a ventricular arrhythmia depends mainly on the analysis of the R-R intervals (heart rate is determined similarly). Accuracy of the EGM depends on the health of the adjacent myocardium and appropriate contact. Accuracy also depends on far-field signals from the muscles, atrium, or other sources of electromagnetic interference. The sensed signals are passed through a band-pass filter that consists of high- and low-frequency cutoffs to represent true signal events. The accuracy of signals in newer devices has been further improved by analysis of the signal frequency, slew rate, amplitude, EGM width, autogain, and autothreshold. These variables are important in helping the device differentiate VT and VF from other events like atrial fibrillation, sinus tachycardia, and other supraventricular tachycardias (SVTs), thus reducing the incidence of spurious shocks.

   Each EGM event and R-R interval is marked and detected, and there are various algorithms that attempt to identify events as either normal or abnormal. "Abnormal" events include bradycardia that requires pacing, VT requiring ATP or low-energy synchronized shocks, or VF requiring defibrillation. Most algorithms depend on the ventricular rate criterion. Other variables, such as the suddenness of onset, variation in cycle length, and change in EGM morphology, help to increase the specificity for diagnosis but at a cost of reduced sensitivity. These should be adjusted and programmed on the basis of individual requirement and clinical scenario of each patient.

B. **Event detection** occurs if the device reaches a specified number of intervals programmed by the physician to detect VT or VF, at which point the ICD delivers the prescribed therapy. Most devices reconfirm the ongoing episode to avoid therapy for nonsustained events. After delivery of therapy, the device either confirms termination of the episode or meets criteria for redetection, and the next programmed therapy is delivered. The ICD automatically adjusts its sensitivity thresholds following sensed and paced events through an autogain mechanism. This allows the device to automatically adjust its sensitivity during a tachycardia episode in response to the changing amplitude of the ventricular signal.

C. **Atrioventricular (AV) sequential devices** incorporate programmable dual-chamber supraventricular criteria that may help to exclude inappropriate management of supraventricular tachyarrhythmias.

D. **Tachycardia therapy.** Most devices allow for programming of several tachycardia zones. The VT zone is programmed with a lower detection cutoff that would include any clinical VT events. Ideally, the cutoff rate for the detection of tachycardia should be above the patient's maximal heart rate to avoid therapy for sinus tachycardia. ATP schemes include burst pacing and ramp pacing. Burst pacing sequences deliver a set of ventricular pulses at a fixed rate faster than that of the VT in an attempt to terminate the reentry VT by overdriving the circuit. Ramp pacing consists of a set of ventricular pulses in which each subsequent paced interval is incrementally shorter than the preceding one. Although this is a more aggressive protocol, there is also a higher chance of the VT degenerating into VF with this therapy. Overall, some studies have shown about 90% success in termination of VT with ATP.

   Following a failed ATP attempt, interburst decrement allows a more aggressive shortening of the intervals during either a burst or a ramp attempt. The first pulse of a burst or ramp sequence (S_1) is delivered at a calculated percentage of the tachycardia cycle length. The

S_1percentage cycle lengths, number of pulses, interburst decrement, and number of ATP attempts are all programmable features. In addition, cardioversion therapy (1 to 36 J) can be programmed in a VT zone. All VT zones have a programmable time limit on episode duration, at which point the device defaults to the next zone. Also, if a tachycardia is accelerated to a faster arrhythmia, then the ICD will deliver the therapy appropriate for the rate of the accelerated tachycardia.

E. Defibrillation therapy. Successful ICD management of VF can occur only with rapid defibrillation therapy. To avoid any delay to defibrillation, ICDs can now deliver ATP during the time needed for capacitor charging before shock delivery. When this ATP therapy is successful, the device will abort charging prior to shock delivery. All devices are programmed with a VF zone because of the risk of acceleration with ATP or cardioversion. Because of the hemodynamic instability seen with fast VT or VF, most devices are typically programmed to manage any sustained episode with rates higher than 180 to 200 beats/min with defibrillation therapy. The device should be programmed with at least a 10-J safety margin over the DFT observed either at implant or during follow-up testing. Up to six additional shocks may be programmed, with maximal outputs programmed at the second or third shock and onward. Several ICD programming trials have demonstrated that a longer detection delay before ICD shock delivery reduces inappropriate shocks. The Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) trial was a large, randomized study that demonstrated using a rate cutoff of 200 beats/min with a 2.5-second delay before device therapy initiation is associated with a significant reduction in unnecessary ICD therapy and all-cause mortality in patients with primary prevention ICDs.

VII. BRADYCARDIA DETECTION AND THERAPY

A. All currently available ICDs provide basic VVI pacing with separate programmable postshock lower rate limit and output. Some dual-chamber devices have been introduced with an atrial lead for diagnostic use only or for AV-synchronized pacing. These devices allow multiple programmable pacing modes, including single- and dual-chamber, fixed-rate, or rate-responsive pacing with automatic mode switch. These expanded pacing modes have obviated the need for a separate dual-chamber pacemaker. In addition, they may reduce the inappropriate shocks attributed to SVT. Such devices may also have capabilities to detect and treat atrial arrhythmias in a manner similar to that for the ventricular arrhythmias. However, in patients without any pacing indications, it may actually be detrimental to pace the right ventricle, especially in patients with preexisting LV dysfunction. This has been well demonstrated in the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. Such patients should either be given a single-chamber ICD or, if there are indications for a dual-chamber ICD for tachycardia discrimination or atrial arrhythmias, be programmed for backup pacing in the VVI mode.

B. In AV-synchronized devices, the ICD can continue to sense tachyarrhythmias in both chambers regardless of the programmed bradycardic pacing mode. To maintain proper sensing, both atrial and ventricular sensing thresholds are adjusted with autogain. The ICD has multiple blanking periods to avoid postpacing polarization, T-wave oversensing, and cross talk between chambers. To avoid undersensing of tachyarrhythmias, short cross-chamber blanking periods after paced events and no cross-chamber blanking after sensed events are necessary. The AV synchronous devices have programmable refractory periods

available for bradycardia functions, but these refractory periods do not affect tachyarrhythmia detection.

VIII. MAGNET FUNCTION

A. Confusion abounds concerning the function of a magnet with ICDs. The pulse generator contains a reed switch that is closed when a magnet is placed over the device. Closure of the reed switch prevents delivery of tachyarrhythmia therapy. Unlike pacemakers, bradycardia pacing is not affected by the use of a magnet in ICDs. Normal device therapy resumes when the magnet is removed and the reed switch opens.

IX. MANAGING AND FOLLOWING PATIENTS

A. In the United States, the government mandates patient registration and tracking. Once registered, a patient receives a permanent identification card to carry at all times. A MedicAlert is strongly encouraged. Manufacturer guidelines suggest that patients should follow up every 3 to 6 months depending on clinical status. Even if remote follow-up is available, it should be supplemented by clinic visits. Patients should be informed that they are likely to receive therapies. At the follow-up visit, a history of symptoms that might suggest tachyarrhythmias should be obtained. The diagnostic and episode data should be reviewed. Current devices also include stored-episode EGMs to allow review of aborted shocks as well as delivered therapies. Device pacing and sensing thresholds should be obtained. There are no specific guidelines for follow-up testing of ICD defibrillation function. In general, patients experiencing device activation should be evaluated shortly after an event to assess for safe and appropriate device function. When device function or concomitant antiarrhythmic therapy is modified, an evaluation of the sensing, pacing, and DFTs is often necessary. Practice patterns vary widely regarding empirical device programming and electrophysiologic testing of modified ICD programming. Some sources recommend that operating a motor vehicle should be avoided for 6 months following a symptomatic arrhythmic event.

B. In general, ICD pulse generators have a 5 to 10 year longevity depending on usage. The programmer allows evaluation of battery status. As the device approaches the elective replacement interval, follow-up visits should be intensified. In general, once the device reaches the elective replacement interval, it operates normally for at least 3 months, depending on the frequency of therapy. Capacitor deformation occurs during periods when no shocks are delivered and results in longer charge times as well as decreased battery longevity. Current ICDs perform an automatic capacitor reformation that charges the capacitors and delivers the energy to an internal test load. This function improves subsequent charge times and battery longevity.

C. Typically, 40% of patients receive a therapy within the first year after implantation and 10% per year thereafter. If multiple ICD discharges are experienced, medical attention should be sought emergently.

D. Inappropriate shocks have been estimated to occur in 10% to 15% of patients with ICDs. These inappropriate therapies contribute to significant morbidity and distress for the patient. Early studies including MADIT II and SCD HeFT demonstrated an association between inappropriate shocks and greater all-cause mortality. Importantly, these studies did not use SVT-VT discrimination algorithms. The MADIT-RIT study found that reprogramming ICD therapy to reduce inappropriate shocks brought about a reduction in all-cause mortality during an average follow-up of 1.4 years. Recently, a single-center cohort study, involving

nearly 1,700 patients, investigated the association between inappropriate ICD shocks and adverse outcomes. Over a 10-year period, this study found no association between inappropriate ICD therapy and increased mortality. **Failure to discriminate between ventricular and supraventricular rhythms is the most common reason for inappropriate shocks.** It is important to evaluate the patients for appropriateness of therapy. The most common cause of inappropriate shocks is atrial fibrillation with a fast ventricular rate. Shocks delivered during physical exertion noted to have gradually increasing heart rates and gradually decreasing V-V intervals suggest sinus tachycardia. Therapy is likely to be inappropriate in this setting also. Ideally, the cutoff rate for the detection of tachyarrhythmias should be greater than the patient's maximal heart rate. In many cases, the VT rate falls within the patient's achievable sinus rate. Programmable enhancements, such as sudden onset and sustained high rate, can allow sinus tachycardia overlap into the VT zone without delivery of an inappropriate shock. Additional enhancements such as morphology discrimination of the ventricular EGM as well as the introduction of dual-chamber devices with timing intervals, marker channels, and mode-switching capabilities have improved the specificity of device therapy. The annual rate of inappropriate shocks has fallen from as high as 50% for SVT alone in early studies to as low as 1% in modern clinical trials with the use of these sophisticated SVT-VT discrimination algorithms. Patients who are likely to benefit most from these algorithms are those with slower monomorphic VT, those at risk for atrial fibrillation with rapid ventricular rates, or those capable of exercising to sinus rates in the VT zone.

E. In the event of multiple ICD discharges, a magnet can be used to inhibit ICD therapy so that the underlying rhythm can be appropriately assessed and managed. The device should be interrogated as soon as possible to assess ICD function and facilitate diagnosis. If a SVT is present, then it should be managed as medically appropriate. For patient comfort, the magnet should be left in place to inhibit ICD therapy until the device can be reprogrammed or the SVT is terminated. If VF is present, the device is assumed inoperable and cardiopulmonary resuscitation with external defibrillation should be applied.

F. Patients receiving ICDs may suffer from significant psychological and emotional disturbances. Education and psychological support are beneficial in improving these patients' quality of life.

X. ELECTROMAGNETIC INTERFERENCE.

Patients should be counseled to avoid sources of electromagnetic interference because such interference may cause the pulse generator to become inhibited and either fail to deliver appropriate therapy or deliver inappropriate therapy. Potential sources of electromagnetic interference include industrial transformers, radiofrequency transmitters such as radar, therapeutic diathermy equipment, arc welding equipment, toy radio transmitters, antitheft devices, and magnetic security wands. The safe use of medical technologies such as electrosurgery, lithotripsy, external defibrillation, and ionizing irradiation can be accomplished by deactivating the device before the event. Shielding of the device is also appropriate when possible. The device should be evaluated for appropriate operation following exposure. Magnetic resonance imaging (MRI) is contraindicated for most devices; however, some newer generation ICDs have been deemed MRI compatible by the FDA. Reports of interference created by cellular phones may be related to either a magnetic field from within the phone or the radiofrequency signal generated by the phone. It is suggested that if a patient

with ICD wishes to use a cellular phone, it should be held to the ear opposite the device and should not be carried in a pocket close to the device.

XI. FUTURE. ICD implantation rates have risen tremendously over the last two decades. Multiple clinical studies have demonstrated the role of ICDs in the primary and secondary prevention of SCD. Multiple trials have also demonstrated the role of an ICD in combination with CRT in reducing mortality and hospital admissions in patients with heart failure. Improvements in electronic technology will continue to expand the programming capabilities of these devices while reducing their size. S-ICDs are now available and provide a less invasive approach for patients who have an indication for ICD therapy but do not require pacing. ICD lead technology is also expected to improve, thereby decreasing the number of lead-related complications. Leadless systems are in clinical trials and may be an option for select patients in the future.

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CHAPTER 55

Catheter Ablation

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I. INTRODUCTION AND HISTORICAL BACKGROUND

A. Ablation of cardiac arrhythmias forms the cornerstone of the modern practice of cardiac electrophysiology. Cardiac surgeons and cardiac electrophysiologists worked together to develop surgical management of refractory arrhythmias in the 1960s and 1970s. In the 1980s, the serendipitous discovery that direct current could be applied to intracardiac structures through percutaneously placed intracardiac electrode catheters to achieve focused ablation moved the nonpharmacologic management of cardiac arrhythmias out of the operating room and into the electrophysiology laboratory. The advent of catheters that could channel alternating current at radiofrequency (RF) levels in the 1990s to safely and strategically target arrhythmogenic myocardial tissue led to the exponential growth of the practice of catheter ablation.

II. GENERAL OVERVIEW

A. Patient selection/indications

1. Catheter ablation of cardiac arrhythmias is a very effective tool for properly selected patients. Both efficacy and safety weigh heavily in the risk/benefit profile of the procedure.

2. Ablation can be considered as primary therapy in arrhythmias where success rates are typically high. Examples include typical right atrial (RA) flutter, atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), atrial tachycardia (AT), paroxysmal atrial fibrillation (AF) with a structurally normal heart, and ventricular tachycardia (VT) in structurally normal hearts. Ablation for arrhythmias such as persistent AF, atypical atrial flutter, and scar-related VT tends to have a lower success rate and tends to be reserved for patients refractory to standard medical therapy or patients who strongly prefer to avoid antiarrhythmic drug therapy.

B. Contraindications

1. Patients should be hemodynamically stable and any heart failure should be well compensated prior to beginning a catheter ablation procedure.

2. Active infections should be appropriately managed.

3. Ongoing bleeding issues should be addressed as well.

4. Patients with breathing difficulty, airway problems, or difficulty lying flat must have these problems addressed because some procedures can be lengthy and several hours of bedrest is required after any catheter ablation procedure.

5. Often consultation and assistance from an anesthesiologist is required to safely conduct the procedure—many ablations are performed under general anesthesia because it improves patient comfort and may improve outcomes in arrhythmias such as AF.

C. Vascular access

1. Catheter ablation builds on the concepts of cardiac catheterization as well as catheter-based electrophysiology studies. As such, percutaneous vascular access is critical for a successful procedure. Femoral venous and arterial access are the primary sites utilized for catheter ablation. Ablation in the right atrium and right ventricle are performed via the femoral venous access site. Left atrial (LA) ablation is typically performed via the femoral venous site using a transseptal puncture to cross from the right atrium to the left atrium. Left ventricular (LV) ablation can be performed via venous access and transseptal puncture or a femoral arterial access site then crossing retrograde across the aortic valve.
2. Ultrasound-guided percutaneous access has proven effective for reducing vascular access complication rates to less than 1% and should be considered standard of care to maintain appropriate patient safety especially when procedures are performed with minimal interruption of chronic oral anticoagulation.
3. For certain arrhythmias, epicardial ablation is required. Percutaneous access to the pericardial space can be accomplished using fluoroscopic guidance with subxiphoid approach and a standard Tuohy needle. A wire is then introduced into the pericardial space and a sheath is placed over the wire. Ablation catheters can then be placed into the pericardial space through the sheath and carefully manipulated to the appropriate ablation targets. When performed by operators with appropriate experience and skill level with this approach, the overall rate of complications is reasonably low. This approach is sometimes not feasible in patients with prior open heart surgery secondary to the presence of adhesions.

D. Anticoagulation

1. In patients with arrhythmias that require chronic oral anticoagulation, multiple studies have demonstrated the safety of minimal or no interruption of anticoagulation.
2. Any ablation requiring the presence of catheters in the left ventricle or left atrium should be performed with heparin infusion initiated after vascular access is established and with a goal activated clotting time (ACT) in the range of 300 to 450 seconds depending on the type and length of the procedure.
3. If arterial access is required, the international normalized ratio (INR) should be at least 1.5 to 2.0 (or less) in patients taking warfarin. For patients taking a novel oral anticoagulant (NOAC, i.e., oral factor Xa inhibitor or oral thrombin inhibitor) undergoing arterial access, the agent should be held 24 to 48 hours prior to the procedure. Decisions regarding a specific INR target or timing for holding an NOAC should be based on an individual patient's risk/benefit ratio with regard to bleeding and risk for thromboembolic complications.

E. Equipment

1. Catheter ablation requires all the standard equipment typically found in any electrophysiology laboratory including cinefluoroscopy, hemodynamic monitoring, high-fidelity recording systems, electrical stimulator for pacing, cardioverter/defibrillator, an RF generator, and electro-anatomic mapping (EAM) equipment. If specialized ablation techniques are employed (i.e., cryoablation, laser, high-intensity focused ultrasound, microwave, robot-assisted procedures), then the appropriate equipment for these techniques would also be

needed but these are not considered standard to every interventional electrophysiology laboratory.

2. Three-dimensional EAM systems. The development of these systems has enabled a significant increase in the efficacy of catheter ablation. The basic principle of EAM is to identify the location of one or more catheters with high spatial resolution. A three-dimensional anatomic model of the chamber or chambers of interest can be created using a roving catheter to define the borders of the chamber. Additionally, electrical information such as voltage and activation timing can be visually superimposed upon the three-dimensional anatomic map. These systems also catalog locations paired with electrograms as well as locations of ablation lesions. Two primary modalities currently exist in clinical practice. The systems have very similar output but significantly different mechanisms to identify and track catheter location.

a. ***Magnetic-based mapping***

1. 1 This system utilizes low-intensity magnetic fields to triangulate the position of catheter tips within the body. An electromagnetic location pad is attached to the fluoroscopy table beneath the patient and sensors within the catheters detect the low-intensity magnetic fields generated by the location pad. The system is able to detect both the real-time position and orientation of the catheter.
2. 2 Pitfalls: The map is created in reference to a fixed magnetic array. Movement of the patient can shift the cardiac structures relative to the map and can necessitate remapping.

b. ***Impedance-based mapping***

1. 1 Impedance-based mapping systems rely on locator patches applied to the patient's skin. An electrical signal is emitted from the patches creating a voltage gradient along three different axes. The degree of voltage detected by the catheter electrodes determines their three-dimensional position. This reliance primarily on electrical impedance leads to more versatile catheter compatibility, because of the nonrequirement of a special sensor in the catheter, as well as slightly faster signal acquisition. Impedance-based systems can also give an estimate of a catheter's proximity to the endocardium.
2. 2 Pitfalls: Impedance-based systems may be slightly less accurate compared to magnetic systems because stable and consistent measurements rely on a stable volume status. Using an irrigated tip ablation catheter can lead to significant changes in volume status throughout the course of a procedure, thereby hindering the reliability of stable and consistent electrical impedance measurements throughout the course of a procedure.

c. The newest generations of EAM systems combine magnetic and impedance-based data with the goal of providing the best of both technologies.

3. **Ablation energy/catheters**

a. ***Radiofrequency ablation***. RF energy accomplishes tissue destruction by conductive heating of the underlying tissue because the tissue resists conduction of the energy. Once the tissue is heated to a temperature over 50°C, irreversible tissue injury occurs. Heating occurs in direct proportion to the amount of power delivered and degree of tissue resistance to energy conduction. Blood passing over the surface of the catheter–tissue interface serves to cool the area by means of convection. This balance of conductive heating and convective cooling helps maintain a balance in the temperature generation. This balance is critical for safe and effective lesion formation. As the temperature reaches and exceeds 100°C, blood boils and extensive char and coagulum forms on the catheter tip. This can lead to

excessive tissue destruction (so-called “steam pops”) and to increased risk of embolism of char and coagulum.

b. ***Irrigated tip catheters***

1. 1 Ablation of arrhythmias such as AF and scar-mediated VT requires a significantly larger area of ablation, and thus longer time of active ablation, than ablation for arrhythmias with a more focal mechanism (i.e., AT, AVNRT, or AVRT). Using standard RF ablation catheters requires a delicate titration of power to avoid excessive tissue heating, steam pops, and embolism of char and coagulum which could lead to an excessive risk of stroke.
2. 2 To address this problem, catheters with irrigated tips were developed to augment convective cooling of the catheter–blood pool interface. Irrigated tip catheters are now considered standard of care for AF ablation as well as any other ablation procedures that require more extensive ablation, such as ischemic-scar–related VT ablation. Using an irrigated tip catheter actually improves lesion size and significantly reduces the risk of steam pops and embolism.

c. ***Contact force catheters***

1. 1 Force-sensing catheters incorporate specially designed sensors into the tip of an irrigated RF ablation catheter to provide the operator with feedback regarding the amount and direction of force at the catheter tip.
2. 2 There are primarily two different designs for contact force-sensing catheters. One utilizes feedback from the mechanical deformation of springs whereas the other takes advantage of the physical properties of light waves reflected in a small chamber that can change in size based on the degree of force applied (based on the Fabry–Perot interferometer).
3. 3 Both catheters work in conjunction with 3D EAM systems to relay the information back to the operator. Specific force and force-over-time criteria can be defined to give the operator credit for a “good” ablation lesion. Studies have shown that utilizing this approach for AF catheter ablation has led to more effective ablation procedures.

d. ***Phased array catheters***

1. 1 Multielectrode phased array RF ablation catheters have been developed with the goal of delivering a pattern of ablation lesions (both circular and linear) in a more efficient and timely manner. These catheters are not irrigated. In theory, these catheters should lead to more efficient and shorter ablation; however, in practice they have shown a higher rate of embolic phenomena than the rate seen with irrigated tip RF ablation catheters.

e. **Cryoablation**

1. 1 Cryoablation accomplishes tissue destruction by cooling tissues to very low temperatures. Cryoablation catheters deliver cryorefrigerant to the targeted tissue to rapidly lower the tissue temperature. As temperatures within the tissue fall below –40°C, ice crystals form in both the extracellular and intracellular compartments leading to mechanical destruction. Additionally, ice crystals form first in the extracellular compartment causing an acute change in the osmotic gradient, leading to movement of water out of cells subsequently leading to their desiccation. After the cryorefrigerant is stopped, the tissue is passively rewarmed by the surrounding blood. This process leads to additional cellular damage and death because circulatory function is restored and a hyperemic process causes hemorrhage and coagulation necrosis. Further ischemia occurs as the tissue becomes edematous because of the malfunctioning and porous microcirculation. With time, inflammation leads to fibrosis and scar tissue formation within the damaged area.
2. 2 ***Cryoballoon catheters***

1. (a) Special cryoablation catheters are available to accomplish pulmonary vein isolation (PVI). An expandable balloon is mounted on the tip of the catheter and this balloon is expanded by filling it with

cryorefrigerant. The catheter is positioned within the os of each pulmonary vein (PV) and the balloon delivers the hypothermic injury to a circumscribed area within the PV antrum. A central lumen within the catheter allows for a circular mapping catheter to be placed in the PV distal to the balloon to monitor for electrical isolation.

2. **(b)** Randomized trials examining RF versus cryoablation to achieve PVI have shown equal efficacy and equal overall safety. There is a significantly higher rate of phrenic nerve injury with cryoballoon ablation, but the large majority of these injuries lead to only temporary diaphragmatic paralysis. This is counterbalanced by a lower rate of cardiac perforation/tamponade. Procedural time with cryoballoon PVI is also slightly shorter on average than procedural time for RF PVI. Cryoballoon PVI has only been studied in patients with paroxysmal AF. Food and Drug Administration labeling is restricted to use for this indication and does not cover patients with persistent AF.

F. Mapping

1. Successful ablation relies heavily on careful mapping of the targeted arrhythmia. Various mapping techniques exist to help localize arrhythmias and determine the best ablation sites.

2. Activation mapping (Fig. 55.1)

a. This technique is commonly used in mapping focal and reentrant arrhythmias. Multiple electrodes placed in various anatomic locations can help elucidate the timing and path of activation of an arrhythmia. To perform activation mapping, the arrhythmia of interest must be sustained and hemodynamically tolerated by the patient. A stable reference electrogram is also needed—for ventricular arrhythmias this can be a surface QRS complex but p-waves can often be difficult to discern in atrial arrhythmias necessitating an intracardiac electrogram for reference purposes. Once electrodes are placed and a stable reference is determined, then a roving mapping catheter records local activation from various positions in relationship to the reference. For focal arrhythmias, the earliest site of activation in relationship to the reference is typically the target for ablation. For reentrant arrhythmias, the operator seeks to define the circuit. An area of slowed or constrained conduction that is critical to the arrhythmia circuit is the target for ablation.

FIGURE 55.1 Activation mapping of focal arrhythmia: Activation mapping of the right atrium displayed in right lateral projection. The earliest activation is displayed in white in this image (arrow) and is located at the high crista terminalis.

b. Pitfalls

1. 1 This technique only provides the earliest site in the chamber being mapped.
2. 2 Creating a high-density map becomes quite difficult if the arrhythmia of interest is not frequent and/or sustained.
3. 3 Ectopic beats, whether spontaneous or catheter induced, can distort the map if these beats are included in the map.

3. Entrainment mapping (Figs. 55.2 and 55.3)

a. Entrainment is typically used for reentrant arrhythmias to define the arrhythmia circuit. Overdrive pacing is performed from various locations at a slightly faster cycle length than the arrhythmia. When performed at a location within the arrhythmia circuit, the return cycle length after cessation of pacing should be equivalent to the arrhythmia cycle length. Conversely, when pacing outside the circuit, the return cycle length will be significantly longer than the arrhythmia cycle length.

b. Pitfalls

1. 1 Overdrive pacing may break or accelerate the arrhythmia.
2. 2 Local capture may not be possible in areas of diseased/scarred myocardium.

4. Pace mapping

a. Pace mapping is typically used to confirm or localize focal arrhythmias or the exit site from the zone of slow conduction in reentrant arrhythmias. When pacing from the site of origin of arrhythmias with a focal mechanism, the paced morphology of the surface electrograms should exactly match that of the arrhythmia—this is most useful for ventricular arrhythmias because subtle morphology changes are difficult to discern in surface p-waves. For scar-related reentrant ventricular arrhythmia, pacing at the location where the arrhythmia circuit exits the scar should produce a QRS morphology identical to the clinical arrhythmia.

FIGURE 55.2 Entrainment mapping within the circuit: The return cycle length after the last paced beat is measured and in this case is almost identical to the tachycardia cycle length

suggesting the site being paced is within the critical circuit. **FIGURE 55.3** Entrainment mapping outside the circuit: The return cycle length after the last paced beat is measured and in this case is more than 100 ms longer than the tachycardia cycle length suggesting the site being paced is outside of the critical circuit.

b. Pitfalls

1. 1 Local capture may not be possible in areas of diseased/scarred myocardium.
2. 2 Pacing from a blind loop connected to the critical circuit may yield a perfect pace match for a site that is not truly part of a reentrant circuit.

G. Ablation targets

1. Anatomic

a. *Atrial fibrillation*

1. 1 The large majority of AF triggers arise in the area where the PVs connect to the left atrium. Approximately 15% to 30% of patients undergoing AF ablation will have non-PV triggers.

1. (a) Pulmonary vein isolation

1. i. Given that the majority of triggers arise in the area where the PVs join the left atrium, the majority of patients respond well to PVI alone.
2. ii. The most efficacious and safest method for achieving PVI is ablation of the PV antral areas (located just outside the PV ostia) using a circular mapping catheter to confirm elimination of electrograms at the PV ostia.

2. (b) Ablation of nonpulmonary vein triggers

1. i. Non-PV triggers of AF typically arise from specific anatomic areas commonly including the superior vena cava (SVC)–RA junction, left atrial posterior wall, crista terminalis, coronary sinus ostium, ligament of Marshall area, and the interatrial septum. An empiric stepwise approach to ablation of AF would target these areas for ablation in patients with nonparoxysmal AF or possibly in patients presenting for a redo catheter ablation after failing PVI.

3. (c) Focal impulse and rotor modification

1. i. Animal models of AF suggest that non-PV triggers of AF occur due to the development of a persistent electrical rotor that develops at a focal site within atrial tissue.

2. ii. A relatively new mapping system utilizing a basket catheter with 64 electrodes has been developed to map rotors within the atria so that they can be targeted for ablation rather than simply performing empiric ablation of non-PV triggers. The mapping software utilizes complex algorithms to process the atrial electrograms during AF to localize areas where the electrical activity demonstrates focal rotational activity. This is displayed visually on a grid and the coordinates of the rotor are localized to the electrode locations as displayed on the 3D EAM system. Guided by this, *the operator can ablate the anatomic site supporting the rotor.*

b. ***AVNRT***

1. 1 Rapidly conducting and more slowly conducting (fast and slow pathways) inputs into the compact atrioventricular (AV) node are key components of the circuit that supports AVNRT. The fast and slow pathway inputs have typical anatomic locations lending themselves to therapy with ablation using an anatomic approach.
2. 2 The anatomic triangle of Koch outlines the components of the AV node. The triangle's borders are the septal aspect of the tricuspid annulus anteriorly, the tendon of Todaro (septal continuation of the eustachian ridge) posteriorly, and the anterior aspect of the coronary sinus ostium inferiorly. The compact AV node lies at the apex of this triangle. Just superior and anterior to the apex of the triangle is the bundle of His. Fast pathway inputs to the compact AV node lie posterior and superior to the tendon of Todaro. Slow pathway inputs lie anterior to the coronary sinus and inferior to the location of the compact AV node. In some individuals, slow pathway fibers also lie in the proximal coronary sinus and/or on the left atrial side of the septum at the level of the mitral annulus.
3. 3 Consistent with their respective names, fast pathway fibers demonstrate more rapid conduction velocity and slow pathway fibers demonstrate slower conduction velocity. However, the fast pathway typically has a longer refractory period than the slow pathway. Initiation of AVNRT relies on critical prolongation of the conduction time through the slow pathway such that when the impulse reaches the fast pathway region it finds the area repolarized thereby acting as an excitable gap and setting up a reentrant circuit involving the AV node and its inputs. Typical AVNRT conducts antegrade along the slow pathway and retrograde along the fast pathway, whereas atypical AVNRT conducts in the opposite directions. Rare atypical variants can be isolated to slow pathway fibers with slightly different conduction properties—so-called "slow–slow" or "intermediate–slow" variants.
4. 4 During ablation of AVNRT, the catheter is positioned at the tricuspid annulus anterior to the coronary sinus ostium. Ablation of the isthmus between the tricuspid annulus and the coronary sinus ostium eliminates AVNRT in approximately 95% of cases by eliminating the ability of the slow pathway to conduct in a 1:1 ratio. A long sheath with a slight septal curve is helpful to reach the target area. Electrograms at the tip of the ablation catheter should show a small atrial signal with a larger ventricular signal in a ratio of 1:10 to 1:3. Use of smaller and nonirrigated RF catheters and starting with a low level of energy all lead to the lowest risk possible of damaging the compact AV node. A stable catheter position within the more inferior region of the triangle of Koch is essential for a safe ablation because the more superior the catheter moves the risk of damage to the compact AV node increases.
5. 5 Ablation with RF energy should elicit a junctional rhythm when the catheter is positioned at an effective location. These junctional beats may subside as ablation continues but the presence of junctional beats during application of RF energy is strongly associated with a successful ablation. During junctional rhythm, retrograde conduction to the atrium over the fast pathway can be observed and RF energy is stopped immediately if this retrograde conduction is interrupted because it is an early warning sign of impending damage to the compact AV node.

6. 6 A 6-mm tip cryoablation catheter can also be used to ablate AVNRT. Ablation is carried out in a similar location. Compared to RF ablation, cryoablation of AVNRT has a lower rate of damage to the AV node; however, this comes at the cost of a higher rate of arrhythmia recurrence.
7. 7 Variant forms of AVNRT are also typically treated by ablation along the anatomic slow pathway to eliminate 1:1 conduction over the slow pathway. The most efficacious strategy maps the earliest retrograde atrial activity either during tachycardia or during ventricular pacing. This area of early retrograde atrial activation is targeted for ablation. In "slow–slow" variants, this often corresponds to the anterior aspect of the proximal coronary sinus, and in "fast–slow" variants, this often corresponds to a location between the tricuspid annulus and the coronary sinus ostium.

c. *AV junction ablation*

1. 1 Ablation of the AV junction in combination with a pacemaker is an extremely effective method for controlling symptomatic AF. This management approach is typically reserved for patients who continue to have symptomatic AF despite aggressive medical management and/or ablation of AF. The primary drawback of this management approach is that the patient becomes pacemaker dependent.
2. 2 Ablation targets the compact AV node region with the goal of leaving the patient with a junctional escape rhythm. To accomplish this, an ablation catheter locates the His position, usually located at about 1 o'clock on the tricuspid valve (TV) annulus in the LAO fluoroscopic view. The catheter is then moved inferiorly and toward the atrium around the atrial mid-septal region. An ideal electrogram shows a 1:1 to 1:2 atrial to ventricular ratio with a very small His. Alternatively, a unipolar electrogram should show a completely negative His electrogram when the catheter is in the ideal position.
3. 3 When the catheter is in the correct position application of RF energy should result in an accelerated junctional rhythm within a few seconds followed by complete AV nodal block within 30 seconds. If AV nodal block does not occur, then a new position should be sought as further ablation at a nonoptimal site will result in edema and significantly decrease the likelihood of success. A left-sided approach targeting left-sided His electrograms can be utilized in the small minority of cases in which a right-sided approach fails.

d. *Sinus node modification*

1. 1 When the sinus node develops an inappropriately elevated baseline rate that leads to symptoms, medications typically serve as first-line therapy to bring the sinus rate back into normal range and relieve symptoms. However, many patients do not respond to medical management and an ablation approach can be utilized to manage these patients.
2. 2 The anatomic location of the sinus node is targeted for modification with the aim of slowing the sinus rate. The sinus node typically underlies the crista terminalis in the area of the lateral RA wall. The more cranial portions near the SVC–RA junction typically demonstrate faster rates and the more caudal portions demonstrate slower rates. Ablation targeting the cranial portion of the sinus node can help control the rapid rates found in patients with inappropriate sinus tachycardia. Activation mapping during tachycardia can help confirm that this anatomic location is indeed the location of the earliest atrial activation during tachycardia.

2. **Focal**

a. *Atrial tachycardia*

1. 1 AT arises from an automatic focus that activates independently of other atrial tissues and does not depend upon macro-reentry to sustain the arrhythmia.
2. 2 Activation mapping is critical to identify the site of origin for AT. A stable reference is chosen and with guidance from a 3D EAM system, local activation timing during the tachycardia

compared with the reference is plotted onto a 3D anatomic model of the chamber(s) of interest. Once the site of earliest activation is identified, ablation is carried out in this region.

3. 3 Noninducibility of the arrhythmia after ablation using programmed atrial stimulation and isoproterenol infusion is an acceptable end point for ablation.

b. ***Premature depolarizations***

1. 1 Premature atrial depolarizations (PADs) or ventricular depolarizations (PVDs) can lead to significant symptom burden for some patients. PADs can trigger AF. Additionally, a high burden of PVDs can lead to a nonischemic cardiomyopathy and heart failure. All of these are typically managed with medications as first-line therapy. However, in patients who fail to respond to medical therapy, management with catheter ablation can be quite effective.
2. 2 Surface electrocardiogram (ECG) morphology can be used to estimate the location of premature depolarizations, but the most efficacious and precise approach involves activation mapping to locate the earliest focal site of activation. A 3D EAM system provides an excellent display of the activation map to assist with localization of the site of easiest activation.
3. 3 A stable and readily identifiable reference from the chamber of interest (atrial for PADs, ventricle for PVDs—can be surface QRS) is required in order to have an accurate activation map. Ablation targeting the earliest activation site should eliminate the premature beats.

c. ***Outflow tract ventricular tachycardia***

1. 1 VT arising from the RV or LV outflow tract areas typically occurs in patients without underlying structural heart disease. The mechanism is usually triggered activity leading to a focal site of origin. These arrhythmias will often terminate with verapamil or adenosine.
2. 2 Ablation is often the first-line management for these types of ventricular arrhythmias because they have a high rate of success.
3. 3 Surface ECG morphology can provide a very close estimate of the site of origin. Activation mapping is critical to identifying the appropriate ablation target. Ablation with an irrigated catheter at the site of earliest activation leads to a high rate of success.
4. 4 The actual focus causing the arrhythmia may be endocardial or epicardial. In most cases, an endocardial approach is effective because the distance between the two surfaces is relatively small in many of the outflow tract areas. However, in a small subset of patients, the arrhythmia may arise from an area known as the LV summit—this is an epicardial site bounded by the proximal left anterior descending and proximal left circumflex arteries and the great cardiac vein as it branches into the anterior interventricular vein. An endocardial approach is often attempted but the success rate is lower given the distance that the ablation energy must travel to the epicardial site in this area. A catheter-based epicardial approach is often problematic and ineffective given the amount of epicardial fat in this area and the proximity to the major coronary arterial branches. If an endocardial approach at the LV summit area fails, the next alternative is to place the ablation catheter through the coronary sinus and out to the greater cardiac vein targeting the earliest area of activation in this region. If both approaches fail and ablation remains strongly indicated, then the only alternative may be an open surgical approach.

3. Reentrant

a. ***Atrial flutter***

1. 1 **Typical atrial flutter** is dependent upon a macro reentrant circuit involving the cavo-tricuspid isthmus (CTI) within the right atrium. This form of atrial flutter typically presents a much more straightforward and uncomplicated ablation and therefore the threshold for ablation of this type of atrial flutter is lower than for atypical atrial flutter. Typical atrial flutter has a characteristic appearance on surface ECG. The flutter waves in leads II, III, and aVF deflect in the same direction

as each other but opposite the direction of the flutter wave in lead V_1. If the flutter waves in II, III, and aVF are negative and in V_1 are positive, this is termed **counter-clockwise typical atrial flutter**. On the other hand, positive flutter waves in the inferior leads with negative flutter waves in V_1 signifies **clockwise typical atrial flutter**. Clockwise and counter-clockwise refer to the expected direction of propagation through the right atrium with respect to the tricuspid annulus when viewed from the RV apex.

2. **2** Atrial flutter demonstrating flutter waves with any other pattern that does not fit with that defined for typical atrial flutter is termed **atypical atrial flutter**. Atypical atrial flutter also has a reentrant mechanism but the location and size of the circuit can vary widely. These arrhythmias often occur in patients with prior open heart surgery or ablation of atrial arrhythmias. Any process leading to focal scarring within atrial tissue can predispose a patient to these arrhythmias. The ablation of atypical atrial flutter can present a greater challenge. However, with careful mapping techniques, the critical circuit for maintenance of the arrhythmia can often be successfully delineated and targeted for ablation. Therefore, patients with atrial flutter refractory to medical therapy should be offered therapy with catheter ablation.

3. **3 Typical cavo-tricuspid isthmus–dependent flutter**

1. **(a)** The CTI is an anatomically constrained area that is critical to the maintenance of typical RA flutter. An effective line of ablation that transects this structure will terminate the arrhythmia. The line of ablation stretches from the TV annulus back to the inferior vena cava–RA junction. Lesions should be delivered to the central portion of the CTI (6 o'clock position on the tricuspid annulus in the LAO radiographic view) because more septal positions can potentially affect inputs to the AV node and the more lateral region is thicker and can be trabeculated making ablation significantly more difficult and less effective.

2. **(b)** After completion of ablation, block is confirmed with differential pacing. The mapping/ablation catheter is positioned lateral to the ablation line and pacing is performed from the mapping catheter and the conduction time from the pacing stimulus to local activation in the coronary sinus is recorded. Pacing is then performed from the coronary sinus, and time to local activation at the mapping catheter is measured. These two times should be similar and typically 150 ms or greater if bidirectional block across the line has been achieved. Similar maneuvers can be carried out with the mapping catheter just medial to the ablation line and conduction times should be very short at that location. Measuring conduction times prior to ablation can be helpful to use as a comparison especially in patients with delayed interatrial conduction at baseline.

3. **(c)** Additional ablation end points also include noninducibility and a change in the RA activation sequence. When the atrial flutter does not recur during programmed stimulation with rapid atrial pacing and extra-stimulus pacing with the patient at rest and on isopreternol infusion, the end point of noninducibility is said to have been reached. If a multielectrode catheter is properly positioned within the right atrium, then the RA activation sequence can be visualized with RA pacing from sites lateral and medial to the ablation line. If bidirectional block is present, the wavefront should move sequentially across the catheter electrodes rather than spreading out in both directions from the pacing impulse and colliding somewhere within the right atrium creating a chevron pattern of activation rather than a sequential pattern.

4. **4 Atypical flutter**

1. **(a)** Atypical atrial flutter usually arises in patients who have areas ***of scar tissue within one or both atria.*** Often these patients have had prior ablation or open heart surgery. Pathologic processes that produce atrial scar formation—such as long-standing AF, cardiac amyloidosis, congenital heart

disease, or other structural heart disease—can also lead to atrial scar formation. The atypical atrial flutter reentrant circuit depends upon these areas of scar to create conduction block and slowed conduction so that reentry can occur. Often patients do not have one area of scar and once one circuit that can support atrial flutter is ablated then others are identified either during the procedure or at some time after the procedure, making ablation of these arrhythmias more difficult and leading to a higher recurrence rate than that of typical atrial flutter.

2. **(b)** Careful mapping is critical to successful ablation of atypical atrial flutter. The techniques of activation mapping and entrainment previously described in combination with visualization by 3D EAM are essential. Once a circuit is identified, ablation is carried out to eliminate areas of slowed conduction, identified by fractionated electrograms, and to connect areas of nonconduction.

3. **(c)** For example, **patients with prior PVI** can present with an atypical atrial flutter that conducts along a circuit around the mitral valve annulus—so-called perimitral flutter. Perimitral flutter is typically treated by ablating from the mitral annulus to another left atrial structure that shows no conduction; often one of the PVs after PVI has been confirmed.

b. ***Scar-related ventricular tachycardia***

1. **1** Scar-related VT is a reentrant tachyarrhythmia; therefore, the critical circuit can be identified using the principles of entrainment. The circuit relies on a narrow isthmus of myocardium capable of conduction through the scar. The conduction through this circuit is typically slow and delayed and is represented by local mid-diastolic potentials.

2. **2** To perform entrainment of VT the arrhythmia must be sustained, monomorphic with a stable cycle length, and hemodynamically tolerated by the patient long enough for entrainment pacing to be performed. The goal is to locate a site within the VT circuit that is located within the narrow, constrained diastolic isthmus that can be targeted with ablation. The mapping catheter is used to search for areas within the scar demonstrating mid-diastolic potentials starting at the edges and working deeper into the scar. Once mid-diastolic potentials are located entrainment pacing is performed at a cycle length slightly faster than the tachycardia cycle length (TCL)—entrainment is confirmed by acceleration to the paced cycle length with constant fusion. Once entrainment is confirmed then pacing is terminated.

1. **(a)** **Manifest fusion** suggests that the pacing site is outside of a protected isthmus whereas **concealed fusion** suggests that the pacing is within a protected isthmus.

2. **(b)** The post-pacing interval (PPI) is examined on the mapping catheter—measured from the final pacing stimulus to the return of the local electrogram. If pacing from a site within the protected isthmus then the PPI will be the same as the TCL (PPI − TCL = 0).

3. **(c)** When the above findings confirm that the mapping catheter is located within the protected isthmus, the timing from the pacing stimulus to the surface QRS reveals whether the location is near the entrance to the isthmus, somewhere in the middle, or near the exit. **The exit site is the ideal site for ablation.** A stimulus to QRS time that is very near the TCL (generally less than 30%) is consistent with a location near the exit. As the stimulation to QRS time increases to a duration nearer the TCL the location of the catheter becomes closer to the entrance site.

3. **3** Using all of these criteria for VT entrainment mapping in scar-related VT avoids ineffective ablation within bystander sites and blind loops/cul-de-sacs.

c. ***AVRT***

1. **1** AVRT is a **reentrant arrhythmia dependent upon an abnormal connection between the atrium and ventricle termed a bypass tract.** The tachyarrhythmia travels along a circuit involving the atrium, the AV node, the ventricle, and the accessory pathway. The accessory

pathway is targeted for ablation to treat these arrhythmias given that it is typically a small, focal connection between the atrium and ventricle that is not an essential part of the normal conduction system.

2. 2 AVRT can be antidromic (traveling retrograde across the AV node and atrial tissue and antegrade through the bypass tract) or orthodromic (traveling antegrade across the AV node and retrograde across the accessory pathway). Activation mapping during antidromic AVRT will show the earliest ventricular activation at the site of the accessory pathway. Conversely, activation mapping during orthodromic AVRT will show the earliest atrial activation at the site of the accessory pathway.

3. 3 Ideal ablation targets should show a fused A and V electrogram and can sometimes show a small, high-frequency signal known as a pathway potential.

4. Substrate

a. ***Atrial fibrillation***

1. 1 Atrial tissue that exhibits complex fractionated atrial electrograms (CFAEs) possibly represents substrate that sustains AF because it represents tissue with slowed conduction thereby slowing and/or disrupting the propagation of atrial depolarization wavefronts.

2. 2 Utilizing 3D EAM systems CFAEs can be mapped, marked, and then targeted for ablation.

b. ***Scar-related ventricular tachycardia***

1. 1 Not all patients requiring catheter ablation for control of ventricular arrhythmias will be ideal candidates for entrainment mapping. In these circumstances a substrate modification approach can be useful to decrease the burden of ventricular arrhythmias.

1. (a) Substrate modification combines pace mapping with voltage mapping of the ventricular endocardium. Using a 3D EAM system the endocardial voltage within the chamber of interest is displayed along with an anatomic shell of the ventricular endocardium. Voltage data are projected onto the anatomic shell in color-coded fashion so that scarred myocardium can be visualized.

2. (b) Detailed mapping is performed in the area of scar suspected to be involved in the VT circuit. Locations with diastolic potentials are noted and targeted for ablation. Additionally, pacing is performed at various sites within the scar and compared to the clinical arrhythmia. Areas within the scar which demonstrate an excellent pace map match are also targeted for ablation.

H. Post-procedural management

1. Major complications

a. The overall rate of major **complications is on the order of 3% to 6%** depending on the procedure type and patient comorbidities.

b. Vascular access

1. 1 Major vascular access complication rates are on the order of 1% to 2%.

2. 2 As stated previously, when ultrasound-guided access is performed these rates have been shown to be as low as 1% or less.

3. 3 Possible complications include hematoma, retroperitoneal bleeding, pseudoaneurysm, and AV fistula.

c. Cardiac perforation and tamponade

1. 1 The rate of this complication is also 1% to 2%, with lower rates for supraventricular tachycardia ablations.

d. Thromboembolism

1. 1 With appropriate anticoagulation for procedures involving instrumentation in the left atrium and/or left ventricle the overall rate of stroke, transient ischemic attack, or systemic embolization is 1% or less.

e. Death

1. 1 The estimated rate of death as a complication is exceedingly low at about 0.1%.

f. Other

1. 1 The rate of other major complications is overall about 0.5% to 1.0% or less.

2. 2 **Atrial esophageal fistula**

1. (a) This is a potentially devastating but avoidable complication of ablation along the posterior wall of the left atrium where it overlies the esophagus. Utilizing an esophageal temperature probe to monitor esophageal temperatures within the esophagus during ablation, ablation energy is titrated to maintain temperatures below 38°C. With this technique, the rate of atrial esophageal fistula is approximately 0.1%.

3. 3 **Injury to conduction system**

1. (a) The overall rate of injury to the conduction system is approximately 0.5%. However, when the target for ablation lies in close proximity to the AV node or His Purkinje system, the risk of this complication increases.

4. 4 **Genitourinary trauma**

1. (a) For procedures requiring placement of an indwelling bladder catheter because of either use of general anesthesia or length of the procedure the risk of damage to the genitourinary system is approximately 0.5%.

5. 5 **Pulmonary edema**

1. (a) The use of irrigated tip RF ablation catheters can lead to a significant amount of intravascular fluids over the course of an ablation procedure. Careful attention should be paid to the balance of fluid input and output throughout the procedure and diuretics utilized as needed. With this in mind, pulmonary edema still occurs in approximately 0.5% of cases.

g. Complications unique to VT ablation

1. 1 Catheter ablation of VT carries all the typical risks noted above. However, there are unique complications peculiar to VT ablation that should be kept in mind.

2. 2 **Hemodynamic instability**

1. (a) Induction of VT can lead to hemodynamic instability from the tachyarrhythmia and/or because of the fact that many patients with medically refractory VT have significant structural heart disease with reduced ventricular systolic function. Hence it is vital to ensure that a patient's heart failure is well treated and well compensated prior to proceeding with VT ablation. In order to ablate hemodynamically unstable ventricular arrhythmias hemodynamic support in the form of inotropes, intra-aortic balloon pump, LV assist device, extracorporeal membrane oxygenation, or an Impella device may be required.

3. 3 **Coronary artery injury**

1. (a) Injury to coronary arteries can occur with either endocardial or epicardial approaches but it is more common with epicardial approaches. A coronary angiogram prior to mapping and ablation can help identify coronary artery locations and courses thereby lowering the risk of coronary artery injury. The ostium of each coronary artery may be injured during ablation of outflow tract VT arising from either the right or left coronary cusp. An angiogram can be performed to mark the ostia or intracardiac echocardiography can visualize the level of the coronary artery and ensure that the ablation catheter remains well below that level.

2. (b) **Epicardial ablation of VT raises the overall risk of the procedure to a rate as high as 14%.** The higher risk is due in large part to higher incidence of pericardial bleeding complications, coronary artery injury, and phrenic nerve injury.

2. Management of anticoagulation

a. Appropriate management of anticoagulation before, during, and after AF or atrial flutter ablation leads to very low rates of thromboembolic events.

b. **An oral anticoagulant must be started prior to the procedure.** Ideally the patient should be anticoagulated for a period of 3 to 4 weeks prior to the procedure. If this is not possible a TEE can be performed prior to starting the procedure and if no intracardiac thrombus is detected the procedure can be performed with initiation of therapeutic anticoagulation immediately following the procedure. Using anticoagulation in the weeks preceding the procedure allows a clinician to be sure that the patient will tolerate anticoagulation well and also eliminates the need for bridging anticoagulation if warfarin is utilized.

c. The procedure can be safely performed **with limited interruption of therapeutic oral anticoagulation.** Warfarin can be continued without interruption as long as the INR remains within the typical therapeutic window in the periprocedural period. NOACs taken twice daily (dabigatran and apixaban) should be held the morning of the procedure and restarted immediately following the procedure. The last dose of rivaroxaban prior to the procedure should be taken about 18 hours before the estimated start time of the procedure, and it should also be resumed immediately following the procedure.

d. During procedures involving **instrumentation in the left atrium or left ventricle, intravenous heparin bolus and infusion should be initiated after vascular access is achieved**. The infusion should be adjusted and additional boluses given to maintain a target ACT of approximately 350 to 400 seconds. After completion of the procedure heparin should be partially reversed with protamine prior to removal of vascular sheaths (target ACT less than 200 to 250 seconds for venous sheaths). Once the patient is tolerating oral intake they should be given a dose of their oral anticoagulant which will subsequently be resumed on its routine schedule. At our institution we also administer a single dose of aspirin 324 mg at the completion of the procedure.

3. Other post-procedural considerations

a. Patients are typically monitored overnight after the procedure to assure there are no obvious early complications. The patient remains on bedrest with pressure dressings in place at the vascular access sites for a period of about 6 hours after the procedure. Telemetry monitoring of the cardiac rhythm should be performed. If a patient has a permanent pacemaker or defibrillator in place it should be interrogated to ensure that there have been no changes with regard to the pacing and sensing parameters of the individual leads.

b. After AF ablation, monitoring for recurrences varies widely between providers and institutions. At our institution careful monitoring is implemented to accurately determine success rates and to help guide post-procedural management. The patient is supplied with a trans-telephonic heart rhythm monitor and instructed to transmit the heart rhythm at least once weekly and anytime they have symptoms that raise their suspicion for recurrence. This is done for a period of at least 12 weeks post-procedure. This allows the provider to have a reasonable idea of the patient's response to the procedure at the time they return for a 3-month follow-up visit. The monitoring period can be extended on a case-by-case basis. This also allows the provider to make plans with the patient regarding management of antiarrhythmic medications and need for repeat ablation procedures.

c. Therapeutic anticoagulation should be continued for at least 4 to 6 weeks following ablation of AF or atrial flutter, similar to patients undergoing cardioversion. Guidance for anticoagulation beyond this time should be based on individual patient risk for

thromboembolic complications related to AF. At our institution, anticoagulation is typically continued until the 3-month follow-up when a cardiac computed tomography is performed to rule out PV stenosis. Ablation procedures for AF should never be performed with the sole goal of obviating a patient's need for anticoagulation as there is no evidence to suggest that AF ablation reduces a patient's long-term risk for thromboembolic complications.

III.SUMMARY

A. Catheter ablation has grown to become the standard of care for definitive management of tachyarrhythmias both as first-line therapy for certain arrhythmias and when medical management fails for other types. Catheter ablation is minimally invasive and often quite effective. As with any procedure the risks and benefits for an individual patient must always be weighed to determine if a catheter ablation procedure is the appropriate management strategy.

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CHAPTER 57

Temporary Cardiac Pacing

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I. INDICATIONS

A. Acute hemodynamically significant bradycardia or asystole. Temporary pacing is indicated in patients with acute hemodynamically significant bradycardias, including sinus arrest, advanced atrioventricular (AV) blocks, and asystole. Reversible causes such as AV nodal blocker or digoxin toxicity and electrolyte disturbances such as hyperkalemia should be identified and reversed prior to implantation of a permanent pacemaker.

B. Termination of tachycardias. Overdrive pacing can be used to terminate tachyarrhythmias in both the atria and ventricles. When a re-entrant circuit is present (atrial flutter, supraventricular tachycardia, monomorphic ventricular tachycardia), the affected cardiac chamber can be paced starting at a rate of 10 to 15 beats/min faster than the tachycardia. This ***burst* pacing** technique (akin to the antitachycardia pacing feature on implantable defibrillators) is typically initiated for 8 to 12 beats and then abruptly stopped. If the tachycardia persists, the pacing rate is increased by 10 beats/min incrementally. An alternative pacing maneuver, ***ramp* pacing**, involves decreasing the interval between successive pacing impulses, but is technically challenging to perform using temporary cardiac pacing equipment and has been shown to be less efficacious in terminating tachycardias compared with burst pacing. **The advantage of overdrive pacing is avoidance of direct current cardioversion**, but the **major complication is potential conversion to a faster, more unstable rhythm** (atrial or ventricular fibrillation), particularly with faster and longer pacing sequences. Temporary pacing is also indicated in patients with bradycardia-dependent or long-QT–triggered ventricular tachycardias (torsades de pointes) to suppress further arrhythmia occurrences.

C. Condition where there is a chance of recovery. In certain conditions where there is a reasonable chance of conduction recovery (e.g., Lyme disease, myocarditis, postcardiac surgery or inferoposterior myocardial infarction), temporary pacing may be used while performing regular surveillance (pacing turn-down) of the underlying rhythm.

D. Bridge to permanent pacing. Temporary pacing may be used as a bridge to permanent pacing in patients with complete heart block, high-grade second-degree block (Mobitz II), severe sinus node dysfunction, and asystole where **conduction recovery is *not* expected**. Generally, temporary pacing in this setting is for patients with an acute illness (endocarditis or systemic infection elsewhere) that delays permanent pacemaker placement.

E. **Acute myocardial infarction.** Indications for temporary pacing in this setting include development of a new bifascicular block (right bundle branch block [RBBB] with either left-axis [left anterior hemiblock] or right-axis deviation [left posterior hemiblock]), new left bundle branch block (LBBB) with first-degree AV block, alternating LBBB and RBBB, Mobitz type II block, and complete heart block. Patients with right ventricular infarction and loss of AV synchrony may benefit from AV sequential pacing.

F. **Acute aortic regurgitation.** Pacing to increase heart rate in patients with acute severe aortic regurgitation can reduce diastolic filling time and improve hemodynamics by increasing cardiac output and decreasing left ventricular end-diastolic pressure.

G. **Prophylactic.** Prophylactic temporary pacing *may be* considered in the following settings: (a) in patients undergoing right heart catheterization and/or myocardial biopsy with a preexisting LBBB, (b) patients with complex intervention to the right coronary artery because this supplies the AV nodal artery in 90% of individuals, (c) cardioversion in patients with sick sinus syndrome, although generally the use of transcutaneous pacing backup is preferred, (d) or patients with new first-degree AV block with acute endocarditis (especially of the aortic valve). Patients who are undergoing alcohol septal ablation for hypertrophic cardiomyopathy typically receive prophylactic transvenous pacers, given the significant risk of complete heart block during the procedure. Patients who are undergoing balloon aortic valvuloplasty and percutaneous aortic valve replacement have a temporary pacemaker placed for overdrive pacing during balloon inflation and valve implantation.

H. **Electrophysiologic studies.** Temporary atrial, ventricular, His, and coronary sinus pacemakers are frequently used in electrophysiologic studies.

I. **Ischemic evaluation.** Ischemic evaluation is occasionally performed via rapid atrial pacing.

II. PACING MODES

A. **Transcutaneous pacing.** Transcutaneous ventricular pacing involves placement of large-surface-area, high-impedance electrodes on the anterior (over lead V_3 or the palpable cardiac apex) and posterior chest walls (inferior aspect of the scapula, to the left or right of the spine). It usually requires long pulse widths (20 to 40 ms) and high outputs of up to 100 to 200 mA. Transcutaneous pacing is most useful in code situations and may also be useful when transvenous pacing is contraindicated. It avoids the complications associated with transvenous pacing such as pneumothorax, right ventricular perforation, infection, bleeding, and venous thrombosis. Failure to capture and severe patient discomfort necessitating sedation are common.

B. **Transesophageal or transgastric pacing.** This technique uses a flexible electrode on the tip of a catheter that is advanced down the esophagus to a position just behind the left atrium and is usually successful in achieving atrial pacing. The electrode can also be advanced to the fundus of the stomach to pace the ventricle through the diaphragm. However, ventricular pacing is difficult to achieve consistently and without intolerable pain to the patient, and for this reason, it is rarely used.

C. **Epicardial pacing.** Temporary epicardial pacing wires are typically placed at the time of valve surgery, given there is a 6% rate of permanent pacemaker implantation prior to discharge in this population, as compared with 0.8% after coronary artery bypass grafting. Longer cross-clamp times, multiple valve surgical procedures, absence of preoperative sinus rhythm, and reoperation are all predictors of the need for pacemaker implantation in the

valvular surgery population. The electrodes are typically removed with gentle traction when they are no longer needed or no longer functional.

D. Transvenous pacing

1. Relative contraindications

a. Poor vascular access

b. Bleeding disorders or anticoagulant therapy. If the international normalized ratio is >1.8 and platelets are <50,000, then these conditions should be corrected prior to placement of a transvenous pacer if possible.

2. Patient preparation

a. Informed consent should be obtained for the procedure. However, if the patient is hemodynamically unstable because of a cardiac arrhythmia that could be improved with a pacemaker, this procedure is indicated emergently without need for consent.

b. If the procedure is elective, peripheral intravenous access should be obtained before the start of the procedure.

c. The procedure should be performed in a monitored setting that is equipped for cardiopulmonary resuscitation and has fluoroscopy available.

3. Technique

a. **Lead choice.** Multiple varieties of active and passive fixation leads exist. There is evidence that active fixation leads allow for greater pacemaker stability and fewer complications than passive fixation leads. However, active fixation leads can be technically more challenging to place.

b. **Sites.** The preferred site for pacemaker insertion is the right internal jugular vein. The femoral, subclavian, and external jugular veins can also be used. However, if a permanent pacemaker will eventually be inserted, the subclavian vein site ipsilateral to the planned permanent pacemaker site should be avoided, if possible.

c. **Position.** The patient should be placed supine in bed, but may be moved to the Trendelenburg position for internal jugular and subclavian vein cannulation.

d. **Placement**

1. **1 Ventricular pacing.** A venous sheath is inserted into one of the central veins, through which pacing leads are passed. For certain active fixation leads, the lead is loaded first with an inner curved stylet. The pacing lead is advanced through the venous sheath under fluoroscopic guidance (usually 20° to 30° left anterior oblique projection). The lead is advanced to the tricuspid valve and turned clockwise or counterclockwise to direct the tip anteriorly. An attempt is made to cross the valve directly. If unsuccessful, gentle pressure is applied and the lead is torqued, allowing the middle portion to prolapse across the valve into the right ventricle. If the tricuspid valve is difficult to traverse, it may be possible to enter the right ventricle by looping the tip of the lead against the lateral atrial wall and then rotating the loop medially (counterclockwise) toward the septum. Another option is to reshape the lead manually (stylet if using certain active fixation leads), increasing the tip bend before attempting to traverse the tricuspid valve. Once the lead has entered

the right ventricle, the lead can be advanced into the right ventricular outflow tract (RVOT), then slowly pulled back until it drops, and then subsequently advanced into the apex as it drops. When placing certain active fixation leads, after advancing the lead to the RVOT, the inner curved stylet should be removed and replaced with a straight stylet prior to pulling the lead back to the apex. Some degree of buckling is acceptable; however, excessive buckling increases the risk of perforation. Ideally, the pacemaker tip should be near the apex of the right ventricle. **The ideal placement site is on the diaphragmatic surface or "floor" of the right ventricle anywhere between its midpoint and its apex.** The floor of the more proximal ventricle is a second choice; the true apex is not a good choice for placement of the catheter tip. The paced electrocardiogram from this location usually shows an LBBB pattern with left-axis deviation. Ventricular pacing can also be done with the tip in the RVOT if the catheter cannot be placed on the floor of the right ventricle in a stable position. The pacer tip is considerably less stable at this site compared with the right ventricle floor and is more likely to be displaced; however, this is an acceptable position for a screw-in temporary pacing wire. Pacing from this location will show an LBBB pattern with an inferior axis. Use of a balloon-tipped temporary pacing electrode can aid in the advancement of the electrode into the proper position. To ensure maximum lead stability with certain active fixation leads, it is imperative that adequate slack be seen following stylet removal (a heel should be seen fluoroscopically in the inferior right atrium) *and* that suture sleeves are tied down tightly to the skin.

2. **2 Atrial pacing.** The right atrium is the easiest chamber to reach, but locating a stable position can prove difficult (the right atrial appendage is preferred). For passive atrial pacing, a J-tipped atrial pacing catheter is used. Alternatively, an active fixation lead can be screwed in. The atrial appendage is directed anteriorly above the tricuspid annulus, and multiple planes are frequently helpful in verifying the location. (The catheter appears as a "J" in the left anterior oblique projection or as an "L" in the right anterior oblique projection.)
3. **3** Both atrial and ventricular pacing may be performed by placing the catheter in the coronary sinus. The coronary sinus in its proximal portion courses along the left atrium. Ventricular pacing may be achieved by positioning the catheter in a cardiac vein off the coronary sinus. The threshold in the coronary sinus is frequently high, but sometimes it may be a more stable location for atrial pacing than the atrial appendage. Steerable electrophysiologic pacing catheters may be useful in such patients.
4. **Testing.** Once a pacing lead is in a stable position, threshold testing should be performed. The distal electrode of the pacing lead is used as the cathode and connects with the negative terminal of the generator, whereas the ring is used as the anode and connects with the positive terminal. The pacing lead is attached via cable to the pacemaker generator.
    a. **Pacing capture threshold.** Pacing should be started at a rate of 10 to 20 beats/min faster than the intrinsic rate with 5 mA output. If capture is not seen at this point, the catheter needs to be repositioned. Once capture is seen, the output is slowly decreased until loss of capture is seen. The **lowest capturing current is the pacing *stimulation threshold***. If the catheter is in good position, the threshold typically should be <1 mA. Pacing output should be programmed three times the threshold, but pacing is usually performed at a minimum of 5 mA (even if three times the threshold is <5 mA). This is because minor dislodgment can cause major changes in threshold and adds a safety margin.

b. **Sensing threshold.** This is the degree to which the pacemaker sees native cardiac signals (in millivolts). Set the pacing rate to at least 10 beats/min below the patient's intrinsic rate. The sensing setting is then gradually decreased until asynchronous pacing is seen. The pacer should be set at one-half the sensing threshold.

c. **AV interval.** For dual-chamber pacing, the AV interval will need to be programmed. A default of 150 ms is frequently used, but the optimal AV delay may be different in individual patients. Patients with diastolic ventricular dysfunction may need longer AV delay for ventricular filling. In patients with marginal cardiac reserve, obtaining cardiac output measurements at various AV intervals and heart rates may help determine the optimal AV interval and heart rate.

5. **Postplacement chest radiography.** A postprocedure chest radiograph should be obtained to look for pneumothorax. For right ventricular apical pacing, in the posteroanterior view, the electrode tip should be located to the left of the spine. In the lateral view, the electrode tip should be directed inferiorly and anteriorly. For pacing through the coronary sinus, the tip should be to the left of the spine, directed posteriorly and superiorly.

6. **Pacer care**

a. Check the catheter insertion site daily for signs of infection and apply a new sterile dressing at regular intervals.

b. Obtain a daily 12-lead surface electrocardiogram, ideally with and without pacing, to assess changes in native conduction.

c. Check pacemaker function daily by determining the sensing and pacing threshold, and check the underlying rhythm daily by decreasing the pacing rate gradually to "off." Abrupt termination in pacing may increase the risk of long pauses.

7. **Complications**

a. Related to central venous access, including hematoma at the puncture site, inadvertent arterial puncture, arteriovenous fistula, subcutaneous emphysema, brachial plexus injury, pneumothorax, hemothorax, thoracic duct injury, air embolism, venous thrombosis, and infection

b. Cardiac arrhythmias such as premature atrial or ventricular contractions, nonsustained ventricular tachycardia, and new RBBB. These are usually of no consequence (although the latter can result in complete heart block in the setting of a preexisting LBBB).

c. Myocardial perforation with cardiac tamponade. The unipolar recording from the tip normally shows pronounced ST-elevation in comparison with the proximal electrode. ST-depression from the tip is associated with perforation. If perforation is suspected, an echocardiogram should be obtained immediately to assess for pericardial effusion. Even a very small pericardial effusion can cause hemodynamic collapse. If tamponade is suspected,

emergency pericardiocentesis should be performed. If perforation is suspected and the patient is hemodynamically stable, the temporary pacemaker should be withdrawn only when the physician has all equipment available and is prepared to perform an elective pericardiocentesis.

d. Lead dislodgment, particularly with passive fixation leads, leading to failure of capture

e. Pacemaker dysfunction including generator failure and lead over-/undersensing

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CHAPTER 58

Electrical Cardioversion

Corey M. Coleman

I. INTRODUCTION. Delivery of electrical countershock to terminate cardiac arrhythmias is a safe and effective technique that is routinely performed in most hospitals. ***Cardioversion*** is defined as the delivery of energy synchronized to the QRS complex, whereas random delivery of shock during the cardiac cycle (usually done for terminating ventricular fibrillation) is termed ***defibrillation***.

II. MECHANISM. Although it has long been recognized that application of an electrical shock to the myocardium can restore a normal rhythm, knowledge of the fundamental mechanism underlying defibrillation remains incomplete. A rapidly delivered electric shock depolarizes the myocardial cells and creates a zone of myocardium with an extended refractory period. Activation fronts encountering tissue with a prolonged refractory period will not be able to propagate, thus terminating both macro- and micro-reentrant circuits. **Atrial fibrillation and ventricular fibrillation are generally agreed to be more electrically stable rhythms and thus require higher current delivery** for termination. This is likely because in less stable arrhythmias only regional depolarization in the path of an advancing wave front is required. The most common waveform shapes used in external defibrillation are the **monophasic** and **biphasic** waveforms. In biphasic waveforms, the polarity at each electrode reverses partway through the defibrillation waveform. The use of a biphasic waveform in cardioversion and defibrillation has been shown to be associated with an increased efficacy and may reduce the development of postshock arrhythmias.

III. Indications and Contraindications. The indications and contraindications of cardioversion are listed in Tables 58.1 and 58.2, respectively. **Cardioversion should not be performed in patients in whom the rhythm is sinus or the abnormal rhythm is secondary to increased automaticity (e.g., multifocal atrial tachycardia and junctional tachycardia). If the presenting rhythm is ventricular fibrillation or ventricular tachycardia with hemodynamic compromise, the only clear contraindication to defibrillation is clear expression of the patient's (or patient's surrogate's) informed wish not to be resuscitated.**

IV. PROCEDURE

A. Patient preparation

1. **Informed consent** should be obtained from the patient or surrogate (if the patient is unable to comprehend and give meaningful informed consent).
2. In elective cases, patient should **fast for a minimum of 6 to 8 hours**.

3. A review of the patient's medical **history and a focused physical examination** should be performed. **Special attention should be paid to the airway**. Inability to visualize the uvula, inability to open the mouth with at least 2 cm between the teeth, and difficulty in extending the neck are factors that may make potential intubation difficult and may suggest the need for the presence of an anesthesiologist during the procedure.

TABLE 58.1 Indications and Contraindications of Cardioversion

INDICATIONS

Cardioversion

1. Atrial fibrillation/atrial flutter
- **a.** Patient with atrial fibrillation/atrial flutter >48 h (or unknown) duration and a (INR 2–3)
- **b.** Acute-onset atrial fibrillation/flutter with associated hemodynamic compromise
  - **1.** Angina pectoris
  - **2.** Myocardial infarction
  - **3.** Pulmonary edema
  - **4.** Hypotension
  - **5.** Heart failure
- **c.** Atrial fibrillation/flutter of unknown duration and absence of thrombus in left atrium or left atrial appe echocardiogram
- **d.** Atrial fibrillation/flutter <48 h duration → anticoagulation optional—depending on risk

2. Atrial tachycardia
3. Atrioventricular nodal reentrant tachycardia
4. Reentry tachycardias associated with Wolf–Parkinson–White syndrome
5. Ventricular tachycardia

Defibrillation

1. Ventricular fibrillation
2. Ventricular tachycardia with hemodynamic instability

CONTRAINDICATIONS

Cardioversion

1. Known atrial thrombus and no emergent indication
2. Sinus rhythm/tachycardia
3. Tachycardias associated with increased automaticity
- **a.** Multifocal atrial tachycardia
- **b.** Junctional tachycardia

4. Digitalis toxicity
5. Severe electrolyte imbalance and nonemergent indication
6. Unknown duration of atrial fibrillation or atrial flutter in a nonanticoagulated patient in the absence of t
7. Patient who cannot be safely sedated

Defibrillation

1. Prior expression of patients who wish not to be resuscitated

4. INR, international normalized ratio.

5. The patient's **medication and anticoagulation status** (for patients in atrial fibrillation or flutter) should be confirmed. Because patients may not always have symptoms with arrhythmias such as atrial fibrillation and atrial flutter, convincing historical or electrocardiographic evidence of the tachycardia initiating within 48 hours of cardioversion should be documented before cardioverting a patient with atrial fibrillation or atrial flutter without adequate anticoagulation because of the risk of thromboembolism.

TABLE 58.2 Indications for Cardioversion in Patients with Atrial Fibrillation

Class I

1. Immediate electrical cardioversion in patients with paroxysmal AF and a rapid ventricular respon evidence of acute MI or symptomatic hypotension, angina, or HF that does not respond promptly to p
2. Cardioversion in patients without hemodynamic instability when symptoms of AF are unacceptable

Class IIa

1. Electrical cardioversion to accelerate restoration of sinus rhythm in patients with a first-detected episc
2. Electrical cardioversion in patients with persistent AF when early recurrence is unlikely
3. Repeated cardioversion followed by prophylactic drug therapy in patients who relapse to AF witho successful cardioversion

Class III

1. Electrical cardioversion in patients who display spontaneous alteration between AF and sinus rhythm
2. Additional cardioversion in patients with short periods of sinus rhythm who relapse to AF despite mul prophylactic antiarrhythmic drug treatment

6. AF, atrial fibrillation; HF, heart failure; MI, myocardial infarction.

7. Adapted from ACC/AHA/ESC 2001 guidelines. Reprinted with permission from Fuster V, Rydén LE, Asinger RW et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. *Circulation*. 2001;104(17):2118–2150. Copyright © 2001 American Heart Association, Inc.

8. **Anticoagulation** is a key factor for patients in atrial fibrillation or flutter (Table 58.3) to prevent thromboembolism. Three classes of oral anticoagulants are now available for thromboembolic prophylaxis. The oral vitamin K antagonist warfarin has a long history of providing excellent protection against thromboembolic events with a good safety profile as long as the international normalized ratio (INR) is closely monitored and the dose adjusted to keep the INR between 2 and 3. The direct thrombin inhibitor dabigatran was the first of several novel oral anticoagulants approved for thromboembolic prophylaxis in recent years. There are three factor Xa inhibitors approved for use in patients with nonvalvular atrial fibrillation. These are rivaroxaban, apixaban, and edoxaban. All four of these novel oral anticoagulants have been compared to warfarin in randomized trials of long-term management of atrial fibrillation and they provide equal efficacy with lower rates of bleeding. Subanalysis of patients undergoing cardioversion in these large trials suggests similar findings.

9. A 12-lead electrocardiogram (ECG) should be obtained to **confirm the presenting rhythm**, as well as to discern any suggestion of electrolyte abnormality (hypo- or

hyperkalemia) or drug toxicity (digitalis). If any of these is suspected, appropriate blood levels should be checked. Routine measurement of digoxin levels is not recommended.

10. **Peripheral venous access** should be obtained for elective cases.

11. A good-quality **continuous ECG** should be obtained. Good contact of the skin and electrodes is essential, and proper skin preparation, including shaving of the chest hair (if present), is recommended.

12. **Oxygen and airway management** equipment (including suction with suction catheters, bag valve mask, laryngoscope, endotracheal tubes, and pulse oximeter) is required and should be checked prior to the procedure.

B. Technique

1. Once the patient is adequately prepared and an appropriately trained physician is present, **cardioversion patches are placed and the patient is sedated**.

TABLE 58.3 Anticoagulation Status and Cardioversion for Atrial Fibrillation/Flutter

Anticoagulation before Cardioversion

1. Administer oral anticoagulation with Coumadin and ensure therapeutic INR (>2) or NOAC[a] (no n
nonvalvular atrial fibrillation/flutter for a minimum of 3–4 wk prior to cardioversion (target INR 2–3)

or

2. Anticoagulate with heparin[b] to achieve a PTT 1.5–2 times control OR start NOAC. Screen for th
appendage by transesophageal echocardiography

a. If no thrombus, cardiovert and continue heparin while loading Coumadin or continue NOAC. W
heparin until INR is therapeutic (≥2). If NOAC is used, it would be reasonable to continue hep
therapeutic, which is about 8–12 h

or

b. If thrombus is visualized, anticoagulate for 3–4 wk with either Coumadin (target INR 2–3) or NO
echocardiogram to confirm thrombus is resolved prior to cardioversion

3. If emergent indication

Administer heparin (unless contraindicated) to achieve PTT 1.5–2 times control OR, if tolerating o
immediately after cardioversion

Anticoagulation after Cardioversion

Oral anticoagulation for at least 4 wk with Coumadin for a target INR 2–3 or NOAC if no contraindicatio

2. [a] NOAC, novel oral anticoagulant, includes dabigatran, rivaroxaban, apixaban, and edoxaban.

3. [b] Limited data support the use of low-molecular-weight heparin (LMWH) before or after cardioversion (level of evidence: C). Use of LMWH in such clinical situations must be individualized after careful determination of the risks and benefits involved.

4. INR, international normalized ratio; PTT, partial thromboplastin time.

5. **Electrode placement.** Electrode placement on the chest is important to maximize current flow through the heart, which is what actually terminates the arrhythmia. Patches or paddles may be placed in the anteroapical or the anteroposterior position.

a. Although the anteroapical position is easy to use in an emergency, it is associated with a lower delivery of current to the myocardium.

b. The left anteroposterior position is commonly used for cardioversion of atrial arrhythmias because it is associated with a smaller interelectrode distance and a lesser interposition of lung parenchyma. This enhances delivery of current to the atria and improves the success of cardioversion.

c. The right parasternal–left paravertebral electrode patch position is associated with better current delivery to both atria and is particularly useful in patients with atrial abnormalities (e.g., atrial septal defect and rheumatic valve disease). This electrode position is favored in our laboratory for cardioversion of atrial fibrillation (Fig. 58.1).

d. Although internal cardioversion (using a right atrial catheter and a coronary sinus catheter as electrodes or using a right atrial and a posteriorly placed external electrode) has been used in the past for cardioverting morbidly obese patients or patients who are resistant to external cardioversion, it is now rarely necessary, given the widespread availability of biphasic cardioversion.

6. **Sedation.** Short-acting sedatives should be administered before all elective cardioversions, because the procedure is uncomfortable. Commonly used agents include methohexital (0.5 to 0.6 mg/kg body weight), etomidate (0.2 to 0.6 mg/kg body weight over 30 to 60 seconds), propofol (0.7 to 1.2 mg/kg, followed by 0.5 mg/kg every 3 to 5 minutes as needed), and midazolam (0.5 to 2 mg over 2 minutes, repeated every 2 to 3 minutes if necessary). Adequate sedation is confirmed by lack of response to verbal and pressure stimuli and loss of eyelash reflex. Airway, breathing, and oxygenation should be monitored until the patient makes a complete recovery, and appropriate support is provided as needed.

FIGURE 58.1 Right parasternal–left paravertebral electrode patch position.

7. **Energy selection.** Success of cardioversion is dependent on adequate energy delivery to the heart. This, in turn, is dependent on the energy output, current vector, and the transthoracic impedance.

a. The commonly used energy selection for various arrhythmias is outlined in Table 58.4. The energy selected differs between monophasic and biphasic devices.

b. Impedance is defined as opposition to electrical flow or current. Higher impedance results in a reduction in current delivery to the myocardium. Therefore, initial energy selection should be individually tailored after consideration of important patient factors such as body habitus and the presence of lung disease, which may affect impedance. In addition, all efforts must be made to reduce impedance. A key factor that modulates impedance is electrode size, with optimal size approximating the size of the heart. Although smaller electrodes increase impedance, larger ones are associated with current wastage. The optimal diameter of an electrode for an adult patient is approximately 12 cm. Other measures to reduce impedance include application of pressure on the electrodes (approximately 12 kg) during shock delivery, shock during end-expiration, better skin–electrode interface and use of conducting gels, and repeat administration of shocks. Conversely, increasing interelectrode distance and interposition of soft tissue or pulmonary parenchyma increases impedance.

TABLE 58.4 Initial Energy Selection for Commonly Encountered Arrhythmias

TABLE 58.4 Initial Energy Selection for Commonly Encountered Arrhythmias

Arrhythmia	Mo
Ventricular fibrillation (or unstable ventricular tachycardia)	200
Atrial fibrillation	200
Atrial flutter	50
Supraventricular tachycardia	150
Ventricular tachycardia (stable)	100

8. **Synchronization.** Once the underlying rhythm is confirmed and a good-quality ECG is obtained, the synchronize mode is switched on (except for defibrillation, where mode must be asynchronous). **Synchronization is essential to prevent delivery of shock during the vulnerable period** (from 80 ms before to 30 ms after the apex of T-wave), with resultant ventricular fibrillation. Defibrillators are designed to time the shock to the R-wave during synchronization mode. The position of the timing artifact on the R-wave is confirmed on the monitor and on a printout, because the defibrillator may rarely synchronize to the T-wave. Conversely, when defibrillating, the mode must be asynchronous because lack of identifiable QRS complex prevents a defibrillator in the synchronous mode from discharging.

9. **Delivery of shock.** Once the patient is adequately prepared, the electrodes are adequately positioned, and the appropriate output and mode are selected, the adequacy of sedation should be reconfirmed. The defibrillator capacitors are charged, the ancillary staff are warned to stay clear of the patient, proper synchronization is reconfirmed, and the appropriate shock is delivered. The patient is immediately assessed for adequacy of airway, breathing, and circulation. The ECG is inspected to confirm rhythm, and if sedation is still adequate, the procedure is repeated if necessary. The patient is monitored until complete recovery (generally 1 hour). Anticoagulation and antiarrhythmic medications (if any) must be addressed before discharge.

V. COMPLICATIONS OF CARDIOVERSION.

Complications after cardioversion are uncommon but include the following.

A. **Thromboembolism.** About 1% to 7% of patients in atrial fibrillation not anticoagulated before cardioversion develop arterial embolization after the procedure. In appropriately anticoagulated patients, the incidence of embolism is extremely low. In the Assessment of Cardioversion Using Transesophageal Echocardiography trial, comparing anticoagulation for 3 weeks before cardioversion with transesophageal echocardiography (TEE)-guided therapy, the incidence of embolism was 0.5% in the conventional arm and 0.8% in the TEE-guided arm. TEE-guided cardioversion is now widely used in patients who require cardioversion urgently but who have not been adequately anticoagulated for 3 weeks.

B. **Arrhythmias.** It is common for patients to have premature atrial contractions or premature ventricular contractions after cardioversion. Although some patients exhibit transient sinus arrest or atrioventricular block, this is usually self-limited. However, the

ability to provide emergent temporary transthoracic pacing should be available for the rare patient who needs it. Malignant ventricular tachyarrhythmias are rare but may occur if the shock is delivered during the vulnerable period. The risk of malignant tachyarrhythmias is increased in the setting of hypokalemia or digoxin toxicity.

C. **Injuries.** The incidence and severity of chest wall burns can be reduced by the use of conductive gel, good skin and electrode contact, and use of lowest effective energy output.

D. **Airway compromise.** Excessive sedation may be associated with respiratory depression. This is more likely in the elderly or in those with hepatic or renal dysfunction. Appropriate adjustment of dose and monitoring of airway and oxygenation until complete recovery will minimize any undue effects of excessive sedation.

E. **Myocardial depression.** Cardioversion is a safe procedure with a wide margin of safety. Transient ST-segment elevation without apparent myocardial damage and minor elevations in creatine kinase myocardial band isoenzyme or in troponin I have been reported in rare instances. Rarely, patients have developed pulmonary edema after direct current cardioversion.

F. **Injuries to the operator.** Injuries to the operator are rare, with an incidence <1 in 1,700 in one series. Most are minor electrical injuries and manifest as extremity paresthesias. Major electrocution is extremely rare, and the reported cases have all been associated with equipment malfunction. Cardioversion in the presence of wet skin or nitroglycerin ointment can lead to arcing and may present a fire hazard.

VI.TROUBLESHOOTING

A. **Monitor does not work.** This is usually related to a mechanical problem. The power source, lead connections, and monitor lead electrode patches should be checked.

B. **Timing artifact falls on T-wave.** Monitoring lead should be changed and the correct position of the timing artifact confirmed prior to cardioversion.

C. **Capacitor does not discharge.** When operating in the synchronized mode, the capacitor will not discharge until it recognizes a synchronized QRS. The switch should be pressed until the capacitor discharges. If this method fails, the monitoring lead should be changed and cardioversion attempted again.

D. **Cardioversion unsuccessful**

1. The first step should be to repeat the ECG to check the underlying rhythm to confirm diagnosis and to differentiate between failure to cardiovert and successful cardioversion that is followed by recurrence of the presenting arrhythmia.
2. For patients who truly fail to cardiovert, a higher energy level may be considered for a repeat attempt. A biphasic device should be used if available and all possible measures to reduce impedance applied (see Section **IV.B.4.b**).
3. Another option for patients who truly fail to cardiovert is to reposition the patches to better capture the myocardium between the patches and, if not done initially, application of pressure on the electrodes (approximately 12 kg) during shock delivery to improve contact and decrease impedance.
4. Unsuccessful cardioversion may be secondary to a deranged metabolic milieu, and reversible causes (such as electrolyte imbalance or thyrotoxicosis) should be corrected.

5. Patients who are on long-term amiodarone therapy may present with atrial fibrillation as the first manifestation of amiodarone-induced hyperthyroidism, which may in turn make cardioversion more difficult.
6. In resistant cases where a biphasic device is unavailable, reversing the polarity of the electrodes with cardioversion at maximal energy, using two defibrillators to increase current, or internal cardioversion may be an option.
7. Use of appropriate antiarrhythmic drugs may facilitate cardioversion and maintenance of sinus rhythm, and the procedure may be repeated after loading with appropriate drugs. Pretreatment with 1 mg ibutilide has been shown to increase the likelihood of successful cardioversion. Ibutilide administration has been associated with the development of torsade de pointes. At our institution, patients pretreated with ibutilide are also given 1 g of intravenous magnesium sulfate in order to minimize this risk.
8. Predictors of unsuccessful cardioversion in chronic atrial fibrillation include long duration of atrial fibrillation, underlying structural heart disease, left atrial enlargement, and cardiomegaly.

VII. SPECIAL SITUATIONS

A. Preexisting permanent pacemaker or implantable cardioverter–defibrillator. Electric current can conduct along the implanted electrode lead and cause myocardial injury. This may manifest as a temporary or permanent increase in stimulation threshold, and, when pronounced, this may manifest as failure of capture-exit block. This can be avoided by **positioning electrodes away from the device**; therefore, the anteroposterior position is preferred. The device should be interrogated before and after cardioversion.

B. Pregnancy. Successful cardioversion has been carried out in all trimesters of pregnancy without ill effects to the mother or the fetus.

VIII. SUMMARY.

Electrical cardioversion is a safe and effective method for terminating tachyarrhythmias. It is a procedure that has changed very little over the past several years primarily because of this fact. Therapeutic anticoagulation is paramount to maintain the safety profile of cardioversion. Lowering the energy threshold for successful cardioversion/defibrillation would be a significant development in regard to this procedure, and efforts to discover a method to do this remain a focus for investigation.

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CHAPTER 59

Right Heart Catheterization

Grant W. Reed
Venugopal Menon

I. INTRODUCTION. In 1947, Dexter et al. observed that the pressure recorded by a catheter wedged in the pulmonary artery (PA) was similar to the filling pressure in the left ventricle (LV). In 1970, Swan and colleagues reported that PA catheterization could be performed by using a specially designed balloon-tipped catheter. Refinements in catheter technology have allowed right heart catheterization (RHC; also known as PA catheterization, or Swan-Ganz catheterization) to assume its role as an integral diagnostic tool to cardiologists and intensivists. RHC remains the gold standard for hemodynamic monitoring and assessment of cardiac output (CO), and it can be helpful in diagnosing and treating critically ill patients with cardiovascular disease.

Although hemodynamic data obtained from RHC is useful in select patients (see Section II), the routine use of RHC in the broader medical or surgical intensive care unit (ICU) populations has not been shown to be helpful. Large observational studies, small randomized studies, and meta-analyses have demonstrated no benefit in length of hospital stay or survival when RHC is used routinely in any clinical circumstance, including severe heart failure (HF). Illustrating this, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial randomized 433 patients with New York Heart Association (NYHA) class IV HF to therapy guided by either clinical assessment or clinical assessment plus PA catheterization, and found there was no difference in the primary end point of survival during the first 6 months after hospitalization.

There was a slight increase in in-hospital adverse events in the PA catheter group; however, there were no deaths related to PA catheter use and no difference in in-hospital or 30-day mortality. Thus, while most studies of RHC have been limited by selection bias and confounding, the routine use of RHC is discouraged. However, there is consensus that utilization in carefully selected patients may be an essential component of patient care.

II. INDICATIONS AND COMMON USES. See Table 59.1 for American College of Cardiology (ACC) recommendations for using PA catheterization.

A. Acute myocardial infarction (MI) complicated by hypotension, congestive HF, sinus tachycardia, right ventricular (RV) infarction, or mechanical complications (such as ventricular septal defect [VSD], pericardial tamponade, or acute mitral regurgitation [MR]).

TABLE 59.1 Common Indications for the Use of Right Heart Catheterization

TABLE 59.1 Common Indications for the Use of Right Heart Catheterization

Heart Failure (HF)

1. To differentiate between cardiogenic and noncardiogenic pulmonary edema.
2. To differentiate between cardiogenic and noncardiogenic shock and to guide its pharmacologic or
3. To guide therapy in patients with biventricular HF.
4. To diagnose pericardial tamponade when echocardiography is unavailable or nondiagnostic.
5. Perioperative management of patients with decompensated HF undergoing high-risk surgery.
6. To identify reversible PH in patients undergoing heart transplant evaluation.

Acute Myocardial Infarction

1. To differentiate between cardiogenic and hypovolemic shock.
2. To guide pharmacologic and/or mechanical support of cardiogenic shock in patients with or withou
3. Short-term guidance of pharmacologic and/or mechanical support in acute mitral regurgitation (MR
4. To establish severity and for short-term guidance of pharmacologic and/or mechanical support surgery.
5. To guide management of right ventricular infarction that does not respond to intravascular volum drugs, and/or restoration of heart rate and atrioventricular synchrony.
6. To manage acute pulmonary edema that does not respond to treatment with diuretics, nitrogly doses of inotropic drugs.

Perioperative Use in Cardiac Surgery

1. To determine the etiology of low cardiac output (hypovolemia vs. ventricular dysfunction) wh inconclusive.
2. To differentiate between right and left ventricular dysfunction and pericardial tamponade whe inconclusive.
3. To guide management of severe low cardiac output syndrome.
4. To diagnose and guide management of PH in patients with systemic hypotension and evidence of

Pulmonary Arterial Hypertension

1. To exclude postcapillary (elevated pulmonary capillary wedge pressure) causes of PH.
2. To diagnose and establish the severity of precapillary (normal pulmonary capillary wedge pressure
3. To select and establish the safety and efficacy of long-term vasodilator therapy based on acute he
4. For hemodynamic assessment before lung transplantation.

B. Adapted from Mueller HS, Chatterjee K, Davis KB, et al. ACC expert consensus document: present use of bedside right heart catheterization in patients with cardiac disease. *J Am Coll Cardiol*. 1998;32(3):840–864. Copyright © 1998 American College of Cardiology. With permission.

C. Assessment of volume status in patients in whom physical signs may be unreliable (e.g., morbidly obese or ventilated patients).

D. Severe LV failure to guide inotropic, diuretic, and afterload reduction management.

E. Differentiation between various shock states (e.g., cardiogenic, distributive, or hypovolemic) and guidance of therapies.

F. Risk stratification for patients during heart transplant evaluation.

G. Cardiac tamponade. Although echocardiography is the diagnostic test of choice, PA catheterization may be used when echocardiography is not readily available or nondiagnostic and the risk or difficulty of pericardiocentesis is high.

H. Assessment of the level and magnitude of an intracardiac shunt, especially if echocardiography is nondiagnostic.

I. Differentiation between constrictive and restrictive cardiac physiology.

J. Severe pulmonary hypertension (PH), and assessment of pulmonary vasculature response to vasodilatory agents.

K. High-risk cardiac patients during preoperative, intraoperative, and postoperative periods to monitor volume status and CO.

L. Severe adult respiratory distress syndrome (noncardiogenic pulmonary edema) during positive end-expiratory pressure trials to assess CO.

III. CONTRAINDICATIONS.

The absolute contraindications to PA catheter placement are right-sided endocarditis, a mechanical tricuspid or pulmonic valve prosthesis, thrombus or tumor in a right heart chamber, uncooperative patient, and terminal illness for which invasive management is considered futile. Relative contraindications are profound coagulopathy (international normalized ratio > 2 or platelet count < 20,000 to 50,000), bioprosthetic tricuspid or pulmonic valve prosthesis, newly implanted pacemaker or defibrillator (unless fluoroscopic guidance is used), and left bundle branch block (LBBB). The latter is a relative contraindication because local trauma to the functioning right bundle while introducing the PA catheter may result in complete heart block and hemodynamic instability. **Consequently, temporary pacing should be immediately available when inserting a PA catheter in patients with preexisting LBBB**. If RHC is essential in patients with thrombocytopenia, coagulopathy, or active anticoagulation, then use of a micropuncture needle should be considered. Finally, it is advisable to treat pneumothorax/hemothorax of the contralateral lung before proceeding, in the event of an ipsilateral pulmonary injury.

IV. TECHNIQUE

A. Venous introducer/sheath insertion. It is important to obtain informed consent in plain language from the patient before the procedure, addressing the utility and major complications of PA catheterization (Table 59.2). Once the procedure is ready to commence, a checklist system should be utilized to ensure safety and success, including a time-out process that confirms “right patient, right procedure, and right site of access.” The

use of a central line kit is a convenient way to streamline the procedure. The patient should be prepped and draped in a sterile fashion from head to toe during the catheter insertion, regardless of the insertion site chosen. Multiple sites can be used for introducer placement; however, **a site that can be readily compressed, such as the internal jugular (IJ) vein, is preferred. Localization and entry into the vein is best performed under ultrasound guidance because an imaging-guided approach decreases procedural complications.** Cannulation of the vein utilizing anatomic landmarks should be considered only when ultrasound guidance is unavailable.

TABLE 59.2 Complications of Right Heart Catheterization

Related to the Introducer	Related to the Catheter Passage	Related to th
Arterial puncture	Arrhythmia (PVC, NSVT, VF)	Thrombosis
Bleeding from insertion site	Complete heart block or RBBB	Thrombophle
Pneumothorax	Coiling	
Nerve injury/Horner syndrome	Valve trauma PA/RV perforation	PA infection b
Air embolism		Balloon ruptu

B. NSVT, nonsustained ventricular tachycardia; PA, pulmonary artery; PVC, premature ventricular contraction; RBBB, right bundle branch block; RV, right ventricular; VF, ventricular fibrillation.

1. The **IJ vein** (see Fig. 59.1) has multiple advantages, including easy compressibility and reduced risk of pneumothorax compared to the subclavian site. The right side is preferred because the venous course from the right IJ, brachiocephalic, and superior vena cava is a direct path to the right atrium (RA). The disadvantages of the IJ vein are the potential for accidental carotid artery puncture and limited neck mobility for patients.

a. The patient should be placed Trendelenburg (or flat if unable to recline), as the IJ will enlarge from venous pooling, and access is often easier in this position.

b. The IJ vein can be entered via an anterior or posterior approach. The anterior approach uses the triangle created by the two heads of the sternocleidomastoid muscle and the clavicle.

1. 1 A finger should be placed on the carotid artery to identify its position and to retract it medially. Approximately 3 to 5 mL of local anesthetic (i.e., 1% lidocaine) should be given in the tissue overlying the vein.
2. 2 The needle should be inserted at the apex of the triangle and advanced in the direction of the ipsilateral nipple at a 45° angle. The vein will usually be entered 3 to 5 cm from the skin surface (this may vary, and ultrasound should be used to guide access).
3. 3 In cases of difficult access or predisposition to bleeding, a micropuncture needle should be considered. Conversely, the vein may be located with a finder needle (20G) before using the large-bore catheter (16G) needle.
4. 4 Once the IJ vein is cannulated, the Seldinger catheter-over-guidewire approach should be used to place the introducer. The guidewire minimizes damage to the vessel and should pass smoothly. Never force the guidewire. If difficulty in threading the wire is encountered, reattach the syringe and attempt to aspirate venous blood to ensure that the needle tip is still located in the vessel.

FIGURE 59.1 Neck anatomy.

5. 5 An instructional video on ultrasound-guided IJ vein access is available from the *New England Journal of Medicine* Web site (see reference) and is a helpful tool for clinicians and students alike.

c. An alternative IJ vein access is the posterior approach.

1. 1 The advantage of the posterior approach is that it minimizes the risk of carotid artery puncture. First, the external jugular vein is located, and the IJ vein is cannulated 1 cm superior to the point where the external jugular vein crosses the lateral edge of the sternocleidomastoid muscle.
2. 2 Another posterior approach is to puncture along the posterior edge of the sternocleidomastoid muscle, two finger widths above the clavicle. The needle should be pointing toward the posterior aspect of the upper portion of the manubrium sterni.
3. 3 Use of ultrasound allows the provider to find the optimal angle for access approach in which the carotid artery is as much to the side of the IJ as possible and not directly beneath.

2. **Cannulation of the subclavian vein** (see Fig. 59.1) is associated with greater patient comfort. However, there is an increased risk of pneumothorax and inadvertent subclavian artery cannulation, especially in patients on mechanical ventilation or with chronic obstructive pulmonary disease.

a. The vein lies just under the clavicle at the insertion site for the clavicular head of the sternocleidomastoid muscle. This is where the vein should be cannulated. The subclavian artery lies just beneath the anterior scalene muscle, which is just below the subclavian vein, with the lung just underneath the artery. For better landmark definition and separation of the vein from the pleura, a rolled-up towel can be placed between the scapulae.

b. There are two approaches to cannulating the subclavian vein: infraclavicular and supraclavicular. The infraclavicular approach is used more frequently.

1. 1 **Infraclavicular approach.** The needle is inserted under the clavicle approximately 1 cm lateral to the sternocleidomastoid muscle insertion point. The needle is then advanced horizontally, nearly parallel to the clavicle, toward the suprasternal notch.
2. 2 **Supraclavicular approach.** The vein is entered from above. The sternocleidomastoid muscle and the clavicle form an angle, and the needle is inserted at this point at a 45° angle. The vein should be cannulated no deeper than 2 cm below the skin surface.

c. If there is uncertainty whether artery or vein has been cannulated, transduce pressure through the needle or obtain a blood gas sample to differentiate vein from artery before dilatation.

d. An instructional video is available from the *New England Journal of Medicine* Web site (see reference).

3. The **femoral vein** may also be used for PA catheterization, with the advantages being ease of cannulation, easy compressibility, and absence of pneumothorax risk.

a. Palpate the femoral artery pulse at the level of the inguinal ligament. The femoral vein is usually located 2 cm medial to and 2 cm below the femoral artery. In some patients, the vein may lie closer to the artery. Sometimes, the Valsalva maneuver may make it easier to access the vein.

b. Unfortunately, there is a high risk of bloodstream infection, associated with central venous access from femoral veins. It is recommended in the Center for

Disease Control guidelines for the prevention of intravascular catheter-related infection that it not be used routinely for central venous access.

4. As an alternative access route, the **right median cubital vein** or **basilic veins** can be considered.

a. Access is usually obtained through typical placement of a peripheral IV in the median cubital vein, or via the basilic vein. Access is then upsized to a 5 French sheath in a sterile fashion. In the antecubital approach, a smaller pediatric PA catheter is utilized given the small size of the peripheral veins.

b. Placement may be technically more challenging because of venospasm. Further, the basilic, axillary, subclavian, and brachiocephalic veins must be navigated prior to reaching the RA, and this course may be tortuous. As such, the antecubital route is typically reserved for PA catheterization when the line is not intended to stay in place following the procedure, or for patients who have failed other access routes.

C. PA catheter insertion

1. After the introducer/sheath is placed and secured, the PA catheter can be inserted. Always test balloon inflation, flush the ports, and make sure the catheter is properly calibrated before beginning the procedure. After the PA catheter is tested, insert it through the protective sterile covering and then through the introducer. Keep the balloon deflated at this stage.

a. Ideally, **fluoroscopy and pressure waveforms should be used during PA catheter insertion for guidance**. The catheter should advance easily; if not, do not force the catheter, but make sure the introducer is properly positioned and flushed.

b. Once the catheter has been inserted 15 to 20 cm or after the right atrial (RA) tracing is seen, **inflate the balloon**.

c. Advance the catheter with the balloon up across the tricuspid valve. This may require turning the catheter clockwise as it is advanced. The RV tracing is visualized next, followed by the PA tracing, and, finally, the pulmonary capillary wedge pressure (PCWP) tracing (see Fig. 59.2).

d. Not infrequently, the RV tracing is accompanied by a few premature ventricular ectopic beats. In general, the PA tracing should be reached within 50 to 55 cm if the catheter is inserted from the IJ vein or subclavian vein or 65 to 70 cm if via a femoral or an arm approach. If the PA tracing has not been visualized by this point, the catheter is likely coiled in the RV. The balloon should be deflated and the catheter withdrawn. The process is repeated until proper placement is achieved.

e. Once the PCWP tracing is obtained, deflate the balloon and reobtain the wedge pressure by inflating the balloon with 1.5 cm^3 of air. If the PCWP tracing is obtained even when the balloon is deflated or with <1.5 cm^3 of air, the catheter has been advanced too far and needs to be pulled back. The pressure waveform should always be closely monitored when inflating balloon-tipped catheters to immediately identify this “overwedging.” The likelihood of PA rupture and infarction increases when catheters are overwedged. In general, wedging the catheter should be avoided in patients with severe PH.

2. It is easiest to float the catheter from the right IJ vein or either subclavian vein. From the femoral veins, it is typically more difficult, **especially in patients with significant tricuspid regurgitation, RA, or RV enlargement**. Often, the femoral PA catheter

needs to be inserted under fluoroscopic guidance and rotated in a continuous and clockwise motion, with the catheter tip resting just distal to the tricuspid valve until it begins to point upward. Forward motion is then applied to move the catheter into the PA. Alternatively, an S-shaped femoral Swan can be used. When using fluoroscopy, the camera should be in the anteroposterior position, and the balloon should be inflated under fluoroscopy.

3. Finally, check the catheter placement and check for pneumothorax after the procedure by obtaining a chest x-ray film. Catheter placement may be difficult in patients with low CO, severe tricuspid regurgitation, PH, or a dilated RA or RV.

4. Catheter advancement may be facilitated by a deep inspiration or, in more difficult cases, by a guidewire with a 0.021″ diameter (a "Swan wire"). The wire can be placed inside the distal lumen of the catheter, improving the stiffness and making the catheter easier to manipulate. The distal end of the guidewire should always be under manual control, and a hemostat can be placed on the end of the guidewire to ensure this.

FIGURE 59.2 Waveforms. ECG, electrocardiogram.

V. COMPLICATIONS.
See Table 59.2.

VI. TROUBLESHOOTING.
See Table 59.3.

VII. WAVEFORMS.
See Figure 59.2.

A. Right atrium. When interpreting hemodynamic data, it is helpful to align pressure tracings with simultaneous electrocardiography (ECG). RA systole occurs with the *p* wave (atrial depolarization) on the ECG and produces the *a* wave on the RA pressure (RAP) tracing. Atrial relaxation, the *x* descent, occurs with a decline in pressure. Tricuspid valve closure produces a slight upward deflection during the *x* descent, which is known as the *c* wave. The *c* wave follows the *a* wave, occurs within the PR interval, and correlates with RV systole. The *v* wave occurs near the end of the *t* wave on ECG and marks the rise in atrial pressure caused by atrial filling during early diastole. Finally, the *y* descent marks the opening of the tricuspid valve during RV diastole and emptying of the atrium. In the normal RA, the peak *a* wave is greater than the peak *v* wave.

TABLE 59.3 Troubleshooting in Right Heart Catheterization

Problems	Solutions
Arrhythmia	Catheter may be in the RVOT. Pull the catheter back or advance forward
No PCWP tracing	Catheter tip is usually not advanced far enough, balloon has ruptured, or fluoroscopy for guidance
Continuous PCWP tracing	Balloon is inflated or the catheter is too far advanced ("overwedged")
Abnormal tracing	Catheter tip is up against a vessel wall or is too far advanced
Damped tracing	Tubing is kinked, air or thrombus is in the catheter, or catheter tip is up a withdraw the catheter
Change in pressure tracing	Improper calibration, change in patient position or catheter location

B. PCWP, pulmonary capillary wedge pressure; RV, right ventricle; RVOT, right ventricular outflow tract.

C. Right ventricle. RV systole occurs with the QRS complex of the ECG (ventricular depolarization). With ventricular relaxation, the pressure declines and the tricuspid valve opens. During the continuous filling from the RA, a small *a* wave is produced that marks atrial contraction and occurs after the *p* wave and just before the QRS on the ECG. End-diastole is the point just after the *a* wave and just before ventricular contraction. The peak systolic and end-diastolic measurements are used for right ventricular pressures (RVPs).

D. Pulmonary artery. The normal pulmonary arterial pressure (PAP) tracing contains a *v* wave, which corresponds to RV systole and follows the QRS complex. During the relaxation period, pulmonic valve closure produces the incisura, a notch during pressure decline on the *v*wave. The trough of the pressure decline marks end-diastole. Pulmonic arterial systolic pressure, end-diastolic pressure, and mean pressure are recorded.

E. The **PCWP tracing** is a transmitted left atrial pressure (LAP) and is considered an approximation for left ventricular end-diastolic pressure (LVEDP), that is, LV preload. The waveforms are similar to an RAP tracing, with the *a* wave corresponding to left atrial (LA) systole, the *x*descent to relaxation, the *v* wave to filling, and the *y* descent to emptying. However, in contrast to the RA, the *v* wave is greater than the *a*wave in the (LA), and the *c* wave is not usually seen because of transmission through the pulmonary vasculature.

1. In the nonventilated patient, mean PCWP, the *a* wave, and the *v* wave should be obtained at end-expiration—when intrathoracic pressures are equal to the atmospheric pressure (the "peak" of the waveform tracing).

2. In ventilated patients, the PCWP should be obtained at the nadir of the tracing (the "valley").

VIII. PITFALLS OF THE PA CATHETER.

Although the PA catheter remains the gold standard in monitoring hemodynamics, care should be taken to avoid errors in measurement and interpretation. Clinical decisions based on misleading PA catheter data may adversely impact on patient outcome.

A. Calibration and referencing. Before the PA catheter enters the body, it should be flushed to eliminate bubbles and calibrated/zeroed at the level of the patient's midthorax, which approximates the location of the RA, that is, phlebostatic level. Serial hemodynamic measurements should be performed with the reference point moved to match the phlebostatic level, which changes with patient position.

B. Proper interpretation of PA catheter data is essential and must be carried out with an understanding of the clinical context.

1. A key to understanding the hemodynamics of PA catheterization is that RAP = RV diastolic pressure in the absence of tricuspid valve pathology, and that RV diastolic pressure + 5 mm Hg should approximate PA diastolic pressure in the absence of pulmonic valve disease. Further, PA diastolic pressure = mean LA pressure in the absence of intrinsic pulmonary arterial or veno-occlusive disease, and LA pressure = LVEDP in the absence of mitral valve disease.

2. Thus, PCWP is an accurate measurement of LV filling pressure, except in the following circumstances:

a. Pulmonary arterial hypertension disease (PCWP > LAP).

b. Mitral stenosis or obstructive LA myxoma (PCWP = LAP > LVEDP).

c. Mitral regurgitation (may have large *v* waves on PCWP, which may make the mean PCWP unreliable; LAP > LVEDP).

d. Acute aortic insufficiency or a noncompliant ventricle (LVEDP > LAP).

e. Alterations in pulmonary alveolar and intrathoracic pressures (e.g., in respiratory failure with high positive end-expiratory pressure) can also significantly alter the PCWP waveform.

IX.CARDIAC OUTPUT

A. May be calculated via the **Fick equation** or **thermodilution** methods.

B. Calculation of CO using the **Fick equation**:

1. Obtain patient's weight in kilograms.

2. Draw peripheral arterial blood gas to obtain systemic oxygen saturation (AO_2%).

3. Draw blood gas from the distal lumen of the PA catheter (VO_2%).

4. Draw hemoglobin.

5. $CO = [Wt \times 3\ mL\ O_2/kg]/[(AO_2\% - VO_2\%) \times 1.36 \times Hgb \times 10]$.

6. Oxygen consumption can be measured from a metabolic hood or a Douglas bag. It can also be estimated as 3 mL O_2/kg.

C. Measurement via **thermodilution** technique may be performed at the bedside but should be avoided in the setting of severe tricuspid regurgitation, intracardiac shunts, existing catheter thrombosis, and low CO.

1. Prefill syringes with 10 mL of room temperature indicator (usually normal saline); then connect the syringe to the distal port of the pulmonary artery catheter (PAC), which should rest in the RA.

2. Check the position of the catheter. Make sure you can obtain the PCWP tracing with 1.5 cm^3 of air and no less. Then deflate the balloon, and ensure the catheter tip rests in the proximal PA.

3. After properly attaching the tubing to the thermistor, inject the contents of the syringe five separate times. Discard the highest and lowest values, taking the mean measurement of the remaining three values.

X.CLINICAL SCENARIOS. See Table 59.4.

A. **Shock** (see Table 59.5). Four classes of shock are characterized: hypovolemic, cardiogenic, distributive, and anaphylactic.

1. **Hypovolemic shock** is due to a profound decrease in venous return and ventricular preload and can be caused by hemorrhage, dehydration, increased positive intrathoracic pressure, and depressed vasomotor tone. Hemodynamic data consist of decreased mean arterial pressure (MAP), CO, and PCWP with increased systemic vascular resistance (SVR).

2. **Cardiogenic shock** results from failure of the cardiac pump to maintain adequate output and can be caused by a change in loading conditions (decrease in preload

caused by tamponade or increase in preload caused by VSD), contractility (acute ischemia or MI), an abrupt increase in afterload, valvular heart disease, or pulmonary embolism.

a. Low MAP and CO but high PCWP and SVR characterize cardiogenic shock caused by LV dysfunction.

b. Contrary to classic teaching, patients in cardiogenic shock from predominant LV failure can have normal to reduced SVR. This drop in SVR in the setting of an MI is most commonly seen after a large anterior wall MI and among the elderly and is likely mediated by profound nitric oxide release in the setting of acute myocardial injury.

TABLE 59.4 Clinical Scenarios in Right Heart Catheterization

Clinical Scenarios	Data
RV infarct	↑RAP, ↓CO, ↓MAP, RAP > PCWP, steep *y* descent, square root sign tracing diastolic "dip and plateau")
Acute mitral regurgitation	↑PCWP, prominent *v* wave
Acute VSD	Oxygen saturation step-up from the RA to PA
Noncardiac pulmonary edema	Normal to low PCWP, with abnormal chest x-ray
Massive pulmonary embolism	↓MAP, ↓CO, ↑PAP, normal PCWP
Pulmonary arterial hypertension (cor pulmonale)	↑RAP, ↑RVP, ↑PAP, prominent *a* and *v* waves and normal PCWP. PA pressure may reach systemic levels
Tamponade	Diastolic equalization of pressures (RAP ≥ RV diastolic pressure ≥ P ↑PCWP Paradoxical pulse, blunted *y*descent, prominent *x* descent on R
Constrictive pericarditis	↑RAP, ↑PCWP dip and plateau in RVP tracing, M- or W-shaped jugu tracing
Tricuspid regurgitation	↑RAP, ↑RV EDP Blunted *x* descent, prominent *v* wave, steep *y*descent, a of RAP

c. CO, cardiac output; EDP, end-diastolic pressure; MAP, mean arterial pressure; PA, pulmonary artery; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RAP, right atrial pressure; RV, right ventricular; RVP, right ventricular pressure; VSD, ventricular septal defect.

d. In general, predominant elevation of RAP is indicative of RV failure, and isolated elevation of the PCWP is indicative of LV failure.

3. Distributive shock is caused by profound systemic vasodilation, most often in the setting of infection or systemic inflammation.

a. The hemodynamic indices characteristic of distributive shock are low MAP, PCWP, and SVR, but high CO.

b. A depressed CO as well as low MAP, PCWP, and SVR can characterize the late phase of distributive shock.

4. **Anaphylactic shock** caused by an allergic reaction causes profound systemic vasodilation. Although there are limited data describing hemodynamics in patients with anaphylactic shock, there appears to be a hyperkinetic phase, characterized by low SVR and high CO, as well as a later hypokinetic phase, dominated by profound hypovolemia with decreased CO.

B. **RV failure** (see Fig. 59.3 and Table 59.4) may be due to RV infarction, severe PH, pulmonary embolism, or increased preload caused by left-to-right intracardiac shunt.

1. An RV infarct (see Fig. 59.3) produces increased RAP and RV end-diastolic pressure, with low CO and MAP.

2. Because the RV dilates and becomes less distensible, a dip-and-plateau pattern on the RVP tracing is seen. On the RAP tracing, there is a steep *y* descent. In the setting of severe tricuspid regurgitation and RV infarction, the dip-and-plateau pattern is lost. A blunted *x* descent, prominent *v* wave, and steep *y* descent are then seen on RAP tracing.

TABLE 59.5 Interpreting Right Heart Catheterization Data in Shock

	MAP	PCWP	CO	SVR
Distributive	Low	Low	High	Low
Cardiogenic	Low	High	Low	High/norm
Hypovolemic	Low	Low	Low	High

3. CO, cardiac output; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

4. **FIGURE 59.3** Right ventricular infarction without tricuspid regurgitation (*left*); right ventricular infarction with tricuspid regurgitation (*right*). ECG, electrocardiogram; RAP, right atrial pressure.

C. **Acute MR** (see Fig. 59.4 and Table 59.4) may be due to papillary muscle dysfunction or rupture.

1. In this setting, the LA is subjected to a sudden increase in pressure. Regurgitation produces a large *v* wave in the PCWP tracing that occurs after the *T* wave on ECG.

A *v*-wave pressure that is twice the value of PCWP is considered to be abnormal.

2. In chronic MR, the *v* wave may be modest in amplitude because of chronic atrial dilatation.

3. Other causes of prominent *v* waves are severe tricuspid regurgitation and VSD.

D. **Tricuspid regurgitation** (see Table 59.4). The RA systolic wave may resemble the RV tracing. There is increased RAP and RV end-diastolic pressure, a blunted *x* descent, a prominent "*c*-*v*" wave, and a steep *y* descent on RAP tracing.

E. **Cardiac tamponade** (see Fig. 59.5 and Table 59.4). The hallmark of tamponade is diastolic equalization of pressures, where RAP = RVP = PCWP. The RA waveform is

characterized by a deep *x* descent and absent *y* descent (because of lack of RV filling at the beginning of diastole). In addition, RAP, RVP, and PCWP are increased.

F. Constrictive pericarditis (see Fig. 59.6 and Table 59.4) is characterized by brisk ventricular filling during early diastole and limited ventricular filling during late diastole. The constriction results in the elevation and equalization of RV end-diastolic pressure and LVEDP.

1. The dip-and-plateau waveform is seen in constrictive pericarditis as well as restrictive cardiomyopathy, RV infarct, and massive pulmonary embolism.

G. Massive pulmonary embolism (see Table 59.4). There is ventricularization of the PA waveform with rapid end-systolic descent and a hardly visible, or absent, dicrotic notch caused by obstruction in the PA.

H. Restrictive cardiomyopathy (see Table 59.6) includes a heterogeneous group of illnesses, such as hemochromatosis, amyloidosis, and endomyocardial fibrosis. This leads to impaired diastolic filling of the ventricles. There is a prominent *y* descent, but the dip-and-plateau waveform is less pronounced because of a pandiastolic hindrance to ventricular filling.

FIGURE 59.4 Acute mitral regurgitation. ECG, electrocardiogram; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure. **FIGURE 59.5** Cardiac tamponade. PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure. **FIGURE 59.6** Constrictive pericarditis. RAP, right atrial pressure; RVP, right ventricular pressure.

I. Pulmonary hypertension (see Table 59.4). PH is defined as a mean PAP >25 mm Hg at rest. It can be caused by elevated pulmonary venous pressures resulting from LV dysfunction, left-sided valvular disease, and/or volume overload (i.e., elevated PCWP). It may also be caused by intrinsic pathology within the pulmonary arterial bed, that is, pulmonary arterial hypertension (PAH).

1. PAH is defined as mean PAP >25 mm Hg at rest with PCWP <15 mm Hg. Compensatory changes in the right heart to chronic PH or PAH result in elevations in RV and PA pressures with prominent *a* and *v* waves.

XI. FORMULAS. See Table 59.7.

1.

1. **CO** by Fick equation in L/min:

$$CO = [Wt \times 3\ mL\ O_2/kg] / [(AO_2\% - VO_2\%) \times 1.36 \times Hgb \times 10],$$

where Wt is weight in kilograms, $AO_2\%$ is systemic arterial oxygen saturation, $VO_2\%$ is mixed venous oxygen saturation, and Hgb is hemoglobin concentration.

2. **Cardiac index (CI)** in L/min/m^2:
CI = CO/BSA,
where BSA is body surface area in m^2.

3. **Stroke volume (SV)** in mL/beat:
SV = CO/heart rate

TABLE 59.6 Differentiating Diastolic Dysfunction

	Constrictive Pericarditis	RV Infarct	Tampona
Pulsus paradoxus	Rare	Occasional	Frequent
Right atrial waveforms	Prominent *y* descent	Prominent *y* descent	Prominen
Equalization of diastolic pressures	Frequent	Frequent	Frequent
Dip and plateau (RV)	Frequent	Frequent	Absent

RV, right ventricular.

TABLE 59.7 Normal Values and Formulas

	Formula	N
RA		0
RV		S D
PA		S D M
PCWP	6–12 mm Hg	
CO	Fick equation: [Wt × 3 mL/kg] / [(Ao_2% – Vo_2% × 1.36 × Hgb × 10]	4
CI	CO/BSA	2
SV	CO/HR	4
SVR	[(MAP – CVP) × 80] / CO	7
PVR	[(PAP – PCWP) × 80] / CO	2
MAP	2/3 Diastolic BP + 1/3 Systolic pressure	7
Shunt fraction (Q_p/Q_s)	[Ao_2% – Vo_2%] / [PVo_2% – PAo_2%]	>

Ao_2%, peripheral arterial oxygen saturation; BP, blood pressure; BSA, body surface area; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; Hgb, hemoglobin; HR, heart rate; MAP, mean arterial pressure; PA, pulmonary artery; PAo_2%, pulmonary artery oxygen saturation; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVo_2%, pulmonary vein oxygen saturation often assumed to equal Ao_2 in left-to-right shunt; PVR, pulmonary vascular resistance; Q_p, pulmonary flow; Q_s, systemic flow; RA, right atrium; RV, right ventricle; SV, stroke volume; SVR, systemic vascular resistance; Vo_2%, mixed venous oxygen saturation; Wt, weight in kilograms.

4. **Pulmonary vascular resistance (PVR)** in dynes × s/cm^5:
PVR = [(mean PAP − PCWP) × 80] / [CO],
where PAP is pulmonary arterial pressure and PCWP is pulmonary capillary wedge pressure.

5. **Systemic vascular resistance** in dynes × s/cm^5:
SVR = [(MAP − CVP) × 80] / [CO],
where MAP is mean arterial pressure and CVP is central venous pressure (can also substitute RAP for CVP).

6. **Estimate of O_2 consumption = 125 mL/min/m^2 = 3 mL O_2/kg.**

7. **O_2 content = (AO_2% − VO_2%) × 1.36 × Hgb × 10.**

8. **CO = O_2 consumption/O_2 content**.

INTRACARDIAC SHUNT. The existence of an intracardiac shunt can be evaluated by using a PA catheter and performing a saturation "run." Blood samples for oximetry are obtained from the PA as well as regions of the RV, RA, superior vena cava, and inferior vena cava. With the catheter positioned in the PA, CO by the Fick equation can be obtained. As the operator manipulates and pulls the catheter back under fluoroscopic and pressure guidance, a blood sample from each location is aspirated. A left-to-right shunt is suggested when a step-up, or increase, in the oxygen saturation in one chamber exceeds the oxygen saturation of a proximal compartment by more than 7% in the case of an atrial shunt or more than 5% in ventricular or great vessel shunts.

In a normal setting, the effective pulmonary blood flow (Q_p) should equal the systemic blood flow (Q_s) (i.e., $Q_p/Q_s = 1$). However, with a left-to-right shunt, pulmonary blood flow is equal to systemic blood flow *plus the amount of shunt flow*. Conversely, in a right-to-left shunt, the effective pulmonary blood flow is decreased by the amount of shunt flow. The shunt fraction is the ratio of pulmonary to systemic flow, denoted Q_p/Q_s. For an atrial septal defect, the mixed venous oxygen saturation is computed as the sum of three times the superior vena cava saturation plus the inferior vena cava oxygen saturation, and the total is divided by 4.

. **Calculation of left-to-right shunt**

1. **Shunt fraction = pulmonary flow in L/min (Q_p)/systemic flow in L/min (Q_s)**

2. **Q_p = O_2 consumption / [10 × (PVo_2% − PAo_2%)],**
where PVO_2% is pulmonary vein oxygen saturation, and PAO_2% is pulmonary artery oxygen saturation.

3. **Q_s = O_2 consumption / [10 × (Ao_2% − MVo_2%)],**
where AO_2% is peripheral arterial oxygen saturation, and MVO_2% is mixed venous oxygen saturation.

4. **Simplified calculation** using saturation only:
Q_p/Q_s = (Ao_2% − MVo_2%) / (PVo_2% − PAo_2%)

Important note: A shunt fraction of >1.5 often necessitates shunt closure.

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CHAPTER 60

Endomyocardial Biopsy

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I. INDICATIONS AND CONTRAINDICATIONS.

The major current indications for endomyocardial biopsy (EMB) are monitoring for allograft rejection after cardiac transplantation and evaluating for potentially treatable forms of myocarditis. EMB is less used now as a diagnostic tool for routine patients with systolic or diastolic dysfunction because of the availability of accurate noninvasive imaging techniques such as magnetic resonance imaging. The role for EMB in other disorders, such as arrhythmogenic right ventricular dysplasia, remains controversial because the risks of the procedure and its diagnostic accuracy must be considered in relation to limited proven effective therapy. The 2013 American College of Cardiology/American Heart Association Guideline for Management of Heart Failure recommends that EMB be considered in heart failure patients when a specific diagnosis is suspected that would influence therapy (class IIa), but also concludes that biopsy should not be performed in the routine evaluation of heart failure (class III: harm). Potential indications and contraindications for EMB are listed in Tables 60.1 to 60.3.

II. PATIENT PREPARATION.

As with any other procedure, extensive patient education and informed consent are necessary before starting the procedure. Patients undergoing EMB should be informed that there is a very small chance (1% in experienced hands) of cardiac perforation, with potential urgent cardiovascular surgery and even death as a consequence.

Sedation is seldom needed but may help anxious patients better tolerate the procedure. Monitoring of heart rate by continuous electrocardiographic telemetry, noninvasive blood pressure, and pulse oximetry is essential throughout the procedure. The patient should be monitored for 2 to 4 hours after the procedure, as myocardial perforation with subsequent pericardial effusion may only become apparent some time after EMB. The patient is placed in a supine position. Venous access is obtained through the internal jugular (most common), subclavian, or femoral veins. Ultrasound guidance and maneuvers to increase central venous pressure such as Valsalva, leg elevation with a wedge, and Trendelenburg position are helpful in obtaining venous access. Most centers use fluoroscopy as the imaging method of choice to guide EMB. However, echocardiography can also be used, particularly when radiation exposure needs to be minimized, such as in pregnant women.

III. DEVICES

A. Sheath. Venous access is obtained using the Seldinger technique, and the sheath is always placed over a guidewire so as not to damage any vascular structures. A standard short sheath (11 cm, 7F or 8F) is generally sufficient for the right internal jugular or any subclavian approach. The intermediate-length sheath (24 or 35 cm) may be helpful to reduce venous angulation or to avoid damaging the vessel wall or a suture line when inserting the bioptome in patients with prior heart transplantation. For the left internal jugular approach, a longer sheath (40 cm, 7F) is used with a single- or double-curved tip based on operator preference and venous and cardiac anatomy. For a femoral approach, a curved 7F, 85-cm-long transseptal sheath is used, because it can be easily positioned into the right ventricle.

TABLE 60.1 Guideline and Consensus Statement Recommendations for EMB

Clinical Scenarios
Heart failure patients in whom a specific diagnosis is suspected that would drive changes in therapy on biopsy[a]
Routine evaluation of heart failure patients[a]
New-onset heart failure of <2-wk duration associated with a normal-sized or dilated left ve hemodynamic compromise[b]
New-onset heart failure of 2-wk to 3-mo duration associated with a dilated left ventricle and new arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk[b]
Heart failure of >3-mo duration associated with a dilated left ventricle and new ventricular arrhythmi or third-degree heart block, or failure to respond to usual care within 1–2 wk[b]
Heart failure associated with a DCM of any duration associated with suspected allergic reac eosinophiliab
Heart failure associated with suspected anthracycline cardiomyopathy[b]
Heart failure associated with unexplained restrictive cardiomyopathy[b]
Suspected cardiac tumors[b]
Unexplained cardiomyopathy in children[b]

B. EMB, endomyocardial biopsy.

TABLE 60.2 Conditions Involving the Heart in Which EMB Can Establish the Diagnosis, Liste Disease-Specific Therapy

Disease-Specific Therapy Available	Disease-Specific Therapy Not Av
Cardiac allograft rejection	Nongiant cell myocarditis
Cardiac amyloidosis	Arrhythmogenic right ventricular dy

TABLE 60.2 Conditions Involving the Heart in Which EMB Can Establish the Diagnosis, Liste Disease-Specific Therapy

Giant cell myocarditis	Anthracycline toxicity
Hypereosinophilic syndrome	Glycogen storage disease
Cardiac sarcoidosis	Rheumatic carditis
Cardiac hemochromatosis	Chagas disease
Lyme carditis	
Fabry disease	

C. DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy.

D. [a]Adapted from Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240–e327.

E. [b]Adapted from Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Circulation*. 2007;116:2216–2233; American Heart Association, Inc.

F. Bioptome. There are two basic types of bioptomes: (1) independent and stiff, which does not require a long sheath but does rely on the operator skill to be maneuvered safely into the right ventricle, and (2) flexible, which requires a longer sheath advanced into the right ventricle for positioning. Both resterilizable and disposable bioptomes are available. For internal jugular and subclavian approaches, 50 cm bioptomes are used, whereas for femoral access, the bioptomes used are longer (up to 105 cm).

IV. TECHNIQUE. Right ventricular endomyocardial biopsies can be performed from either the right or left internal jugular, subclavian, or femoral veins. If necessary, a left ventricular EMB can be obtained via the femoral artery approach, although this is rarely necessary.

TABLE 60.3 Relative Contraindications for EMB

Informed consent not obtained
Patient not cooperative (confused, agitated, etc.)
Profound hemodynamic compromise
No cardiac surgery backup available
Coagulopathy (INR > 1.5)
Mechanical tricuspid prosthesis
Significant right-to-left shunt (risk of air embolus)

TABLE 60.3 Relative Contraindications for EMB
Thinning of myocardium after MI or in case of ARVD
RA or RV thrombus

V. ARVD, arrhythmogenic right ventricular dysplasia; EMB, endomyocardial biopsy; INR, international normalized ratio; MI, myocardial infarction; RA, right atrial; RV, right ventricular.

A. Right ventricular biopsy

1. **Internal jugular vein approach.** After standard preparation and local anesthesia, the required anatomic landmarks are identified. A pilot puncture with a 22G needle can be made to localize the vein. The internal jugular vein is punctured with an 18G (or smaller) needle, and the sheath is introduced using standard technique. The bioptome, with jaws closed and tip straightened, is advanced under fluoroscopic or echocardiographic guidance across the atrial suture line (in allografts) until its tip lies against the lower third of the lateral right atrial wall. It is then rotated gently counterclockwise and simultaneously advanced into the right ventricular cavity. During this procedure, the tip is gently unstraightened. Rotation is continued until the catheter reaches the apical half of the right ventricle and the handle clamp points in the posterior direction. At this point, the tip of the bioptome rests on the interventricular septum. The position is confirmed by inability to further advance the bioptome, the generation of premature ventricular contractions, and fluoroscopic appearance. Generation of premature atrial contractions or absence of ventricular ectopy may indicate that the bioptome was advanced in the right atrium or in the coronary sinus. If there is any doubt about the position, the bioptome is withdrawn and the process repeated. Once in the desired position, the bioptome is withdrawn about 0.5 to 1 cm, the jaws are opened, and the bioptome is then advanced again. When it touches the endocardium, the jaws are closed and the bioptome is gently withdrawn with its jaws closed under continuous fluoroscopic guidance. A small tug is often felt while withdrawing, but excessive tugging and multiple premature ventricular contractions should prompt consideration of repositioning. Usually four to six biopsy specimens are obtained in different areas of the septum to reduce sampling error. Once the procedure is completed, the venous sheath is removed and hemostasis achieved.
2. **Femoral vein approach.** After standard preparation and local anesthesia, the required anatomic landmarks are identified. The right (more common) or the left femoral vein is punctured with an 18G (Cook) needle, and a 0.038-in. guidewire is advanced up to the right atrium. A long (85-cm) 7F sheath with dilator is advanced over the wire, and on entering the right atrium, the dilator is withdrawn. The tricuspid valve is crossed with the help of the guidewire (a balloon-tipped catheter can also be used), and the sheath is advanced into the right ventricle toward the intraventricular septum. The pressure tracing, occurrence of ventricular ectopy, and fluoroscopy are used to confirm the position. The side port of the sheath may be connected to a slow continuous intravenous infusion to prevent clot formation inside the sheath, especially if a long procedure is anticipated. A long nonsteerable bioptome is advanced through the sheath and is used to acquire samples. Biopsies are taken in a manner similar to that of the internal jugular vein approach.
3. **Subclavian vein approach.** After standard preparation and local anesthesia, the required anatomic landmarks are identified. The subclavian vein is punctured using an 18G (or smaller) needle followed by insertion of the sheath. The occurrence of

ventricular ectopy and fluoroscopic images are used to confirm a position pointing toward the interventricular septum. Biopsies are taken in a manner similar to that of the internal jugular vein approach.

B. Left ventricular biopsy

1. Femoral arterial approach. After standard preparation and local anesthesia, the required anatomic landmarks are identified. The right (more common) or left femoral artery is punctured with an 18G (Cook) needle, and a short 8F sheath is inserted while a 0.035-in.-long exchange guidewire is advanced up to the ascending aorta. A regular-length 7F pigtail catheter is advanced over the wire, and the aortic valve is crossed in the conventional manner. Afterward, the pigtail catheter is removed, while leaving the guidewire in the left ventricle, and exchanged with an 8F-long, curved guiding sheath. The tip of this sheath is directed toward the interventricular septum, distal to the mitral apparatus, away from the thinner posterobasal wall. The position of the sheath is carefully reconfirmed by obtaining fluoroscopic images in two angulations and pressure tracings, and 5,000 units of unfractionated heparin is given intravenously before insertion of the bioptome. A long, nonsteerable bioptome is then advanced through the guiding sheath, and biopsy samples are collected in a manner similar to the right ventricular approach. It is important to note that catheters must be aspirated and flushed after each biopsy, because air can enter the sheath and clots can form in the sheath after removing the bioptome. Heparin is not reversed with protamine at the end of the procedure in an effort to minimize thrombus formation at the biopsy sites.

VI. COMPLICATIONS. In general, EMB can be performed more safely in heart transplant recipients than in patients with native hearts, because of the scarred and thickened pericardium in transplanted patients.

A. Mortality. Procedure-related deaths have been reported to be <0.05% in contemporary series.

B. Cardiac perforation and tamponade. The reported incidence of cardiac perforation is 0.3% to 0.5%, which can rapidly result in tamponade. The risk can be minimized by careful monitoring of catheter position to ensure that biopsies are obtained from the thicker interventricular septum and by gentle catheter advancement and EMB procurement. Symptoms of chest pain during or after the procedure, shortness of breath, a pericardial rub, or altered hemodynamics should suggest potential perforation and should prompt urgent echocardiography to rule out a new pericardial effusion or tamponade. Patients in whom a new pericardial effusion is suspected or detected should be monitored in the hospital for evidence of increasing pericardial effusion or tamponade, and an echocardiogram should be repeated at intervals as necessary and before discharge.

In patients early after heart transplantation, the atrial suture line also poses a higher risk of perforation. Very gentle advancement of the bioptome (and pulling back if any resistance is felt) and use of a longer sheath to pass the suture line if needed will reduce this risk. Patients with suspected perforation should be closely monitored, and echocardiography, fluoroscopy, or cardiac computed tomography can be used to confirm the diagnosis.

Emergent pericardiocentesis or cardiac surgery may be necessary if hemodynamic compromise develops.

C. Thromboembolism. Right-sided thromboembolism during EMB is possible, but does not cause any clinically significant sequelae if it occurs. The risk of arterial

embolization during left ventricular EMB is higher, owing to the longer sheath, and may have catastrophic consequences. Using heparin during a left-sided approach and aspirating air and flushing the sheath before inserting the bioptome minimize the risk of embolism.

D. **Arrhythmia.** Occasionally, sustained atrial or, less commonly, ventricular tachycardia is induced by EMB. These arrhythmias are sometimes terminated by touching the wall of the right atrium or ventricle with the bioptome. Bradyarrhythmic episodes or bundle branch block induced by EMB is very rare. **In heart transplant patients, bradyarrhythmias respond only to β1-stimulants and not to atropine.**

E. **Tricuspid valve (or mitral valve for left ventricular biopsy) dysfunction.** The bioptome can damage the chordae or papillary muscle and produce significant valvular regurgitation. The risk of this complication is minimized by careful confirmation of bioptome position before sampling. The cumulative risk of this complication is greater in heart transplant patients because they undergo multiple serial EMB procedures.

F. **Damage to vena cava, coronary sinus, hepatic vein, and coronary arteries.** Gentle advancement of the bioptome, use of a longer sheath, retraction of bioptome whenever resistance is felt, and position confirmation with multiple fluoroscopic views may minimize these complications. Fistula formation from a coronary artery branch to the right ventricle has occurred following EMB but is rarely of clinical significance.

G. **Local complications.** Hematoma, local infection, and injury to the lung (pneumothorax, incidence 0.9%) and nerves (recurrent laryngeal palsy and Horner syndrome) are possible but rare while achieving vascular access. Careful identification of anatomic landmarks under ultrasound guidance reduces the risk of these complications.

H. **Pain.** The EMB itself is usually painless, but some patients experience some mild degree of pain when the bioptome touches the heart or when a biopsy is taken.

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CHAPTER 61

Short-Term Mechanical Circulatory Support Devices

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I. INTRODUCTION. Knowledge of the indications and operation of short-term mechanical circulatory support (MCS) devices has become vital to the practice of cardiovascular medicine. This chapter will provide essential information necessary for the management of patients treated with intra-aortic balloon pump (IABP) counterpulsation, Impella, TandemHeart, and extracorporeal membrane oxygenation (ECMO) therapy. More detail will be provided for IABP because it is the most commonly used short-term MCS device today.

II. IABP COUNTERPULSATION. The principal functions of the IABP are to (1) **support hemodynamics** in individuals with cardiogenic shock and to (2) **relieve medically refractory ischemia** in patients with severe coronary artery disease (CAD). The duration of support with IABP therapy is typically short, given the risk for complications with prolonged use.

A. Indications

1. Acute myocardial infarction (MI) with cardiogenic shock.

a. IABP therapy provides temporary hemodynamic stabilization in patients with cardiogenic shock caused by acute MI. Early studies including the **Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries I** trial comparing fibrinolytic regimens for acute ST-segment elevation MI (STEMI) demonstrated that early placement of an IABP in this cohort of patients was associated with lower 30-day and 1-year mortality.

b. In another study of 46 patients with acute MI and cardiogenic shock treated at community hospitals without angioplasty capabilities, simultaneous treatment with thrombolysis and an IABP was associated with an improved 1-year survival rate (67% vs. 32%) and successful transfer to a tertiary facility for revascularization when thrombolysis failed.

c. Contemporary studies do not support the use of routine IABP therapy in patients with acute MI complicated by cardiogenic shock. The highest quality evidence is the **Intra-aortic Balloon Pump in Cardiogenic Shock (IABP-SHOCK) II trial**, which demonstrated that among 600 patients with acute MI and cardiogenic shock able to

undergo timely percutaneous coronary intervention (PCI), IABP therapy did not reduce 30-day or 1-year mortality. One weakness of IABP-SHOCK II was a high rate of cross-over of control patients to IABP for reasons other than mechanical complications of acute MI. It is possible that rapidly decompensating patients may not have been enrolled, and if enrolled in the control arm, crossed over to IABP therapy. Thus, results may not be applicable to these patients.

d. However, the results of IABP-SHOCK II are supported by older studies from the **National Registry of Myocardial Infarction 2** and meta-analyses. In patients with acute MI, IABP therapy may be most useful in rapidly decompensating patients with cardiogenic shock or those who cannot undergo timely reperfusion.

e. Given the above, the **American College of Cardiology/American Heart Association (ACC/AHA) recently downgraded the recommendations for IABP therapy in acute MI complicated by cardiogenic shock** from class Ib (should be used) to **class IIa, level of evidence of B (can be used).** The benefits of an IABP in patients with acute MI without cardiogenic shock treated with PCI are uncertain, and this is not routinely recommended. In a randomized trial of 182 hemodynamically stable patients who underwent primary PCI for acute MI, prophylactic Intra-aortic balloon counterpulsation (IABC) for 2 days after the procedure reduced recurrent ischemia and reocclusion of the infarct-related artery but had no effect on survival or reinfarction. In the **Primary Angioplasty in Myocardial Infarction II** trial, 437 high-risk patients (age > 70 years, multivessel coronary disease, reduced ejection fraction [EF], vein graft disease, or persistent ventricular arrhythmias) treated with primary PCI for acute MI were randomized to ±1 to 2 days of IABP therapy after PCI. Patients treated with an IABP had a slight reduction in recurrent ischemia but had no reduction in mortality, reinfarction, or infarct-related artery reocclusion.

2. Refractory angina or myocardial ischemia awaiting revascularization

a. Patients with severe unrevascularized CAD with ischemic symptoms or hemodynamic instability refractory to medical therapy are highly likely to benefit from IABP therapy.

b. The ACC/AHA guidelines assign a **class I** recommendation in STEMI and a **class IIa** recommendation in unstable angina/non–ST-segment elevation MI for IABP placement in the setting of severe ischemia that is continuing or recurs frequently despite intensive medical therapy. In STEMI, refractory pulmonary congestion carries a **class IIb** recommendation for IABP placement.

3. High-risk PCI. Patients at high risk for complications during PCI include those with unprotected left main (LM) CAD, left ventricular dysfunction (EF ≤ 30%), severe multivessel CAD, the target vessel supplying >40% of the myocardial territory, and active congestive heart failure. Placement of an IABP in these high-risk patients affords the operator a longer duration of ischemia during balloon inflation and wire manipulation.

a. In a study of 219 patients undergoing unprotected LM stenting, elective IABP placement was associated with fewer intraprocedural major adverse cardiac events, including combined end points of severe hypotension, MI, need for urgent bypass surgery, and death.

b. The BCIS-1 trial randomized 301 high-risk patients to IABP placement prior to elective PCI. Whereas there was no difference in major adverse cardiac and cerebral events at 28 days, there was 12% cross-over from control to the IABP group, and after a

median follow-up of 51-months, all-cause mortality was lower in the IABP group (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.40 to 0.98).

4. **Mechanical complications of acute MI. Acute mitral regurgitation (MR)** and **ventricular septal defect (VSD)** are complications of acute MI that frequently cause rapid deterioration and cardiogenic shock. An IABP should be strongly considered as an adjunct to medical afterload reduction in hemodynamically significant MR or VSD following an acute MI. Placement of an IABP in the setting of STEMI and secondary acute mitral valve regurgitation is an **ACC/AHA class I** indication. Similarly, insertion of an IABP and prompt surgical referral are **class I** recommendations.

5. **Refractory ventricular arrhythmias.** Incessant ventricular tachycardia (VT) compromises left ventricular filling, reduces stroke volume, and causes or exacerbates ischemia. In patients with medically refractory VT, placement of an IABP improved hemodynamics, lessened ischemia, and controlled refractory ventricular arrhythmias in 86% of patients in a large case series. Placement of an IABP support in patients with STEMI and refractory polymorphic VT carries an **ACC/AHA class IIa** recommendation.

6. **End-stage cardiomyopathy/bridge to cardiac transplantation.** An IABP improves cardiac output (CO) and lowers filling pressures in patients with dilated and ischemic cardiomyopathy. It can be used for hemodynamic support before cardiac transplantation.

a. **Disadvantages** of prolonged IABP support in patients awaiting cardiac transplantation include a high risk of infection and the need for continuous bed rest.

b. However, with improved inotropic therapy and implantable left ventricular assist devices for patients awaiting cardiac transplantation, IABP therapy is now used infrequently for *prolonged* mechanical support in patients with end-stage cardiomyopathy.

7. **Decompensated severe aortic valve stenosis (AS) or severe MR.**

a. Severe AS can be managed with temporary IABP support to improve the stroke volume and reduce the transvalvular gradient before aortic valve (AV) replacement.

1. **1** In a study of 25 patients with severe AS and cardiogenic shock, IABP support was associated with prompt improvement in CO and filling pressures, allowing stabilization of patients before surgery.

2. **2** However, because aortic insufficiency often accompanies severe AS, careful monitoring early after initiation of IABP is recommended to ensure that aortic insufficiency is not worsened by the balloon pump.

b. When there is a complication of acute MI, severe MR because of any reason complicated by hypotension may require IABP pump therapy as a bridge to definitive surgical treatment.

8. **Low CO after cardiopulmonary bypass.** Patients with severe left ventricular dysfunction or those with prolonged runs on cardiopulmonary bypass can be difficult to wean from bypass after open heart surgery. This is usually because of stunned myocardium from prolonged cardioplegic arrest. For these patients, IABP support improves hemodynamics and facilitates weaning from bypass.

9. **Support during noncardiac surgery.** Patients with severe CAD, recent MI, or severe left ventricular dysfunction are at high risk for cardiac complications when they undergo noncardiac surgery. Case reports have demonstrated that high-risk patients are

stabilized hemodynamically and have acceptable postoperative outcomes when prophylactic IABP support is used during and after noncardiac surgical procedures.

B. Contraindications

1. **Aortic dissection.** Any type of aortic dissection (type A or type B; acute or chronic) precludes IABP use because of the potential of the balloon catheter to extend the dissection and to worsen ischemia of a peripheral vascular bed that may be involved by the dissection.
2. **Abdominal or thoracic aneurysm.** Using IABP with an abdominal or thoracic aneurysm can precipitate an acute aortic dissection, dislodgement of atheroemboli, or aortic rupture.
3. **Severe peripheral vascular disease**

a. The majority of the complications of IABP use are caused by vascular insufficiency in the accessed leg because of the **large size of the balloon sheath and catheter. This is especially prevalent in patients with iliofemoral peripheral artery disease (PAD).** In the past, the IABP catheters had been available only in 8F and 9.5F sizes; however, 7F catheters are available (although not commonly used). These have diminished the rate of complications because of obstruction of arterial flow.

b. **Limb ischemia and threatened limb viability** can occur when peripheral perfusion is compromised by the balloon catheter and sheath. The IABP catheter can be inserted without a sheath to reduce the diameter of obstruction in the iliac vessels. However, in patients with tortuous aortoiliac vessels, sheathless IABP insertion can be challenging.

c. Thus, severe PAD may be a contraindication to IABP insertion, depending on the degree of vascular compromise.

4. **Descending aortic and peripheral vascular grafts**

a. **Prosthetic descending aortic grafts and iliofemoral vascular grafts** are relative contraindications to IABC. Consultation with a vascular surgeon is recommended before attempting balloon pump insertion in these patients.

b. **Iliac artery stents** are not a contraindication to IABP placement. However, passage of the guidewire and balloon catheter through the stent must be performed under direct fluoroscopic guidance.

5. **Coagulopathy or contraindication to heparin**

a. The balloon catheter is thrombogenic. Intravenous (IV) heparin is typically given while the IABP is in place to prevent the development of thrombi on the balloon surface. This is especially important at inflation-to-beat ratios of 1:2 or 1:3. Patients with a contraindication to heparin, such as those with prior heparin-induced thrombocytopenia, can be **anticoagulated with alternative agents**, including direct thrombin inhibitors such as bivalirudin.

b. In very high bleeding risk patient, IABP placement is discouraged. However, if an IABP is used, a 1:1 inflation-to-beat ratio should be utilized, because anticoagulation is not absolutely necessary in this situation. A volume-wean strategy can be used to avoid the need for 1:2 or 1:3 ratios which require anticoagulation.

c. After cardiac surgery, heparin may be avoided because of the increased risk of intrathoracic bleeding; however, IABP support in such patients is usually of short duration, and 1:1 support is typically used, thus stroke risk is low.

6. **Moderate to severe aortic insufficiency.** As described below, the IABP inflates during diastole and deflates during systole. By inflating during diastole, the IABP can worsen aortic insufficiency when blood is displaced to the proximal aorta. Whereas severe aortic insufficiency is a contraindication to use, there is no consensus whether moderate aortic insufficiency is a contraindication. Therefore, **careful monitoring** of patients with aortic insufficiency that require IABP support is recommended.

C. Hemodynamics of balloon pump function

1. Decreased afterload

a. At the beginning of systole, the IABP rapidly deflates and creates negative pressure in the aorta. This reduces afterload, **reduces aortic end-diastolic pressure**, and improves ejection from the left ventricle (LV). This results in an augmentation of CO of approximately 20% and decreases the mean pulmonary capillary wedge pressure (PCWP) approximately 20%.

b. The hemodynamic benefit of an IABP is a reduction in left ventricular wall stress from decreased filling pressures and decreased afterload, which in turn improves stroke volume and CO (see Figs. 61.1 and 61.2).

2. Augmented coronary perfusion

a. IABP inflation is timed just prior to the **dicrotic notch**. The IABP thus inflates during diastole, displaces blood to the proximal aorta, **augmenting aortic diastolic pressure** and thus increasing coronary artery perfusion pressure. The augmentation of coronary perfusion pressure is more dramatic when systemic hypotension is present (see Figs. 61.1 and 61.2 for a schematic of the typical IABP pressure waveform).

b. Doppler flow studies have demonstrated that peak coronary flow velocity is increased with IABP support. However, there is no improvement in coronary flow past critical coronary stenoses (unless the obstructions are first relieved with percutaneous revascularization). Also, collateral coronary flow does not increase with IABP support. Thus, with severe, nonrevascularized CAD, IABP relieves ischemia more through decreased left ventricular wall stress and decreased myocardial oxygen demand by reducing afterload than through increased coronary perfusion.

D. Insertion technique

1. **Balloon sizing** is based on the patient's height. Four common balloon sizes are available: **50 cm3** for patients taller than 6′, **40 cm3** for patients between 5′ 4″ and 6′, **34 cm3** for patients between 5′ and 5′ 4″, and **25 cm3** for patients shorter than 5′. Balloon length and diameter increase with each larger size.

FIGURE 61.1 By inflating during diastole, the intra-aortic balloon pump increases coronary perfusion. Deflation of the balloon at the onset of systole decreases myocardial wall stress and oxygen demand and increases cardiac output. (Courtesy of Datascope Corp.

Copyright © 1992 Datascope Corp. All rights reserved.) **FIGURE 61.2** Proper timing of balloon function occurs when the balloon inflates on the downslope of the systolic pressure waveform and deflates before the onset of the next systolic waveform. The intra-aortic balloon pump inflation in diastole increases diastolic pressure to improve coronary artery perfusion and to increase mean arterial pressure. In addition, aortic end-diastolic pressure is reduced

when the balloon deflates in end diastole to lower afterload and myocardial oxygen demand. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.)

2. **Evaluating peripheral vasculature.** Proximal and distal pulses are assessed in both legs, and ankle/brachial indices can also be determined. The leg with the strongest pulses and/or the best ankle/brachial index score should be chosen for access.

3. **Insertion technique**

a. **Access and sheath insertion**

1. 1 After careful evaluation of clotting parameters and peripheral vasculature, the leg chosen for access should be shaved and prepped with antiseptic solution from the umbilicus to the knee.
2. 2 After infiltration with a local anesthetic, the femoral artery is accessed with an 18G introducer needle, and a 0.030″ × 145-cm J-tipped guidewire is advanced through the needle to the aortic arch under **fluoroscopic guidance**.
3. 3 The needle is removed, and a smaller 5F dilator is first inserted over the wire to dilate the subcutaneous tissues. The sheath, loaded with a larger dilator that is 1F smaller than the sheath, is inserted over the guidewire. The dilator is then removed. The guidewire should be left in place in the aortic arch beyond the left subclavian artery.

b. **Balloon insertion.** The two most commonly used balloon catheter sizes are 8F and 9.5F.

1. 1 The prepped, prewrapped balloon is taken out of its packaging and inserted over the guidewire with the guidewire pinned to prevent wire movement. This is performed quickly, because the balloon will unravel in a short amount of time, making insertion through the sheath difficult.
2. 2 The balloon is advanced until the proximal tip is positioned 1 cm below the left subclavian artery and 2 cm above the carina. The distal tip of the balloon is visualized under fluoroscopic guidance to ensure that it is out of the sheath.
3. 3 The guidewire is removed, and a syringe is used to immediately aspirate residual air from the balloon lumen, allowing it to backbleed. Delays in this step may allow for thrombus to form in the balloon lumen.

c. **Initial setup**

1. 1 The helium tubing and electrocardiogram (ECG) gating leads are then connected to the IABP console and the IABP inflation may begin.
2. 2 Balloon autoinflation is initiated from the console, the arterial line attached to the central lumen of the catheter is flushed, and the initial IABP inflation is at 1:2 (per cardiac cycle) while the timing is adjusted.
3. 3 Balloon inflation is then observed under fluoroscopic guidance to ensure that the balloon is completely out of the sheath. If the balloon is kinked or is not inflating fully, it should be repositioned by pulling the sheath back a few inches or it should be manually inflated.
4. 4 The sheath and balloon catheter are sutured in place, dressed using sterile technique, and the inflation is changed to 1:1.

d. **Insertion without fluoroscopy guidance.** Fluoroscopic guidance is strongly recommended for placement of the IABP. However, if fluoroscopy is unavailable (i.e., bedside IABP placement in a crashing patient), the distance from the angle of Louis to the umbilicus and then to the common femoral artery insertion site is measured to determine the approximate distance the balloon must be advanced. A chest x-ray (CXR) should be obtained as soon as feasible to confirm IABP position.

e. **Surgical insertion.** Occasionally, balloon pumps must be inserted surgically **by directly exposing the common femoral artery** or by suturing a 6- to 12-mm

prosthetic graft end-to-side to the femoral artery to provide a conduit for the catheter. Distal limb ischemia is reduced with these methods, but grafts must be removed surgically, and the femoral artery has to be directly repaired after IABP removal when surgical access is used. Balloon pumps can also be directly inserted into the ascending or thoracic aorta **during open heart surgery**.

f. Difficulties with access. A 5F sheath can be placed in the common femoral artery. Then contrast medium can be injected through the sheath or through a pigtail catheter to define the iliofemoral anatomy.

1. 1 If severe iliac or femoral artery obstruction is demonstrated, the balloon should be inserted on the contralateral side, the obstructions can be treated with peripheral angioplasty and stenting before balloon insertion, or the procedure can be aborted.
2. 2 If severe obstruction or aneurysmal dilatation of the distal abdominal aorta is demonstrated, the balloon catheter should not be inserted.

g. Tortuous iliofemoral vessels

1. 1 When the tortuosity of the iliofemoral vessels prevents passage of the 0.030″ guidewire supplied in the IABP kit, the standard sheath supplied with the IABP kit can be exchanged for an 8F (or 9.5F) Pinnacle sheath. Through this sheath, a 0.035″ Wholey wire can be used to traverse the tortuous vessels. A 5F JR4 coronary diagnostic catheter can then be advanced, and the Wholey wire exchanged for the IABP wire. The IABP catheter can then be advanced over the wire in the standard fashion.
2. 2 If tortuosity still precludes balloon advancement, the balloon guidewire can be removed, the Wholey reinserted, and a long (45 or 60 cm) flexible sheath can be placed in the descending aorta past the tortuous iliac vessels. A superstiff 0.038″ wire is then exchanged through the sheath. A 11″ IABP sheath is inserted over the superstiff wire, which provides more support for placement of the less flexible IABP sheath. The superstiff wire is then exchanged for the 0.030″ standard IABP wire through the sheath, and the balloon catheter is inserted over this wire into the proper position.

h. Sheathless insertion. In patients with PAD, the balloon catheter can be inserted without a sheath, directly over the guidewire, after appropriate dilatation of the subcutaneous tissue. Retrospective reviews have shown that limb ischemia is reduced with this technique. However, a sheathless balloon catheter cannot be repositioned once placed and has a greater potential to become infected from skin flora than a sheathed balloon catheter.

E. Postinsertion management

1. Monitoring

a. A CXR film is immediately obtained after IABP placement to verify the catheter position, even if fluoroscopic guidance has been used.

b. IV heparin is started once the balloon and sheath are secure to maintain the activated partial thromboplastin time at 50 to 70 seconds. Although recommended at all times, this is only absolutely necessary at ratios <1:1.

c. Daily CXR films are recommended while the IABP is in place so that the physician can check the position of the catheter. If the catheter needs to be repositioned, it can be manipulated through a sterile plastic sleeve placed over the part of the catheter that extrudes from the sheath while the balloon is placed on standby mode.

d. Daily hemoglobin and platelet counts are followed to monitor for hemolysis and thrombocytopenia.

2. Care of the patient with an IABP

a. All patients with an IABP in place should be closely observed in a **critical care setting. The patient should be kept supine in bed**, and peripheral pulses should be regularly evaluated for **possible limb ischemia** (dorsalis pedis/posterior tibial pulses should be checked every 6 to 8 hours with use of Doppler if necessary).

b. **The accessed leg should be secured** to prevent inadvertent or involuntary movement by the patient.

c. **Use of prophylactic antibiotics is not recommended** while the IABP is in place.

d. **Blood samples generally should not be obtained from the central lumen of the IABP** because the risk of clotting the lumen is increased, and air or small thrombi can be injected through the central lumen during flushing of the tubing after blood withdrawal.

F. Balloon pump triggering and timing

1. Triggering. Balloon pump inflation can be triggered by the surface ECG, the arterial pressure waveform, a paced rhythm, or an internal asynchronous mode.

a. Preferably, the surface ECG is used to trigger IABP inflation, which is appropriately delayed after the R-wave to begin at the time in the cardiac cycle when the AV closes (dicrotic notch).

b. If the IABP fails to trigger properly from the surface ECG, change the lead being evaluated, check surface electrode placement, or increase the QRS gain on the console monitor.

c. For patients with poor surface electrocardiographic tracings, the balloon can be triggered from the central arterial pressure waveform. Pacing spikes should be used to trigger the balloon in patients who are 100% paced.

d. In cardiac arrest or when the other triggering mechanisms are not working correctly, an internal asynchronous mode can be used to trigger the balloon to inflate at a regular interval.

2. Timing. Ideal balloon pump timing occurs when the balloon inflates on the downslope of the systolic pressure waveform before the dicrotic notch and deflates before the onset of the next systolic pressure waveform (see Fig. 61.2). Timing is usually adjusted manually, but it can be automatically adjusted by internal algorithms programmed in the console.

a. **Early inflation** (see Fig. 61.3) is defined as inflation of the IABP before AV closure (dicrotic notch).

There is premature closure of the AV with increased afterload, left ventricular wall stress, and myocardial oxygen demand. Stroke volume is decreased. It is corrected by delaying inflation until after AV closure.

b. **Late inflation** (see Fig. 61.4) is defined as inflation of the IABP well after closure of the AV.

There is diminished diastolic pressure augmentation and suboptimal coronary perfusion. It is corrected by adjusting inflation to occur just before the dicrotic notch.

FIGURE 61.3 With early balloon inflation, the aortic valve closes prematurely, and left ventricular wall stress and myocardial oxygen demand are increased. (Courtesy of Datascope

Corp. Copyright © 1992 Datascope Corp. All rights reserved.) **FIGURE 61.4** With late balloon inflation, there is suboptimal augmentation of diastolic aortic pressure and coronary perfusion. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.)

c. **Early deflation** (see Fig. 61.5) is defined as deflation of the IABP before isovolumic left ventricular contraction.

There is suboptimal diastolic augmentation, coronary perfusion, and afterload reduction, which then lead to increased myocardial oxygen demand. It is corrected by delaying deflation until just before the onset of systole.

d. **Late deflation** (see Fig. 61.6) is defined as deflation of the IABP after the onset of systole.

There is impaired left ventricular emptying, increased afterload and preload, increased myocardial oxygen consumption, and reduced stroke volume. It is corrected by adjusting deflation to occur just before the onset of systole.

e. **During arrhythmias.** Adequate augmentation with the balloon pump is difficult to achieve with tachyarrhythmias. When heart rate approaches 150 beats/min, there is insufficient time for the helium gas to shuttle in and out of the balloon with each inflation. With rapid atrial fibrillation, variable systolic pressure waveforms caused by inadequate left ventricular filling and rapid pulse rates make augmentation especially difficult. Adjusting balloon inflation to 1:2 can sometimes improve augmentation with tachyarrhythmias.

3. **Troubleshooting.** In the situation of **console alarms**, there may be the following problems:

a. **Loose connections** in the gas drive line or arterial pressure tubing

b. **Blood in the tubing.** If blood is detected in the gas drive lumen, put the balloon catheter on standby and evaluate for balloon rupture or entrapment.

FIGURE 61.5 With early balloon deflation, there is suboptimal augmentation of coronary perfusion and afterload reduction. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.) **FIGURE 61.6** With late balloon deflation, there is no afterload reduction, and myocardial oxygen consumption is increased. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.)

c. **Poor augmentation**—consider the following:

1. 1 Adjust the timing.
2. 2 Change the triggering mechanism.
3. 3 Evaluate inflation/deflation of the balloon and the catheter position under fluoroscopic guidance to detect balloon kinking.
4. 4 If the IABP is thought to be positioned in a false lumen of the aorta because of poor augmentation, 10 to 20 mL of contrast media can be injected through the central lumen of the catheter to evaluate the position under fluoroscopy.
5. 5 Patients with poor augmentation, despite appropriate placement and timing, should be closely evaluated for a vasodilatory process (such as sepsis, or systemic inflammation in the setting of cardiogenic shock).

G. Complications

1. **Vascular.** Common vascular complications of IABP include limb ischemia, hematoma around the access site, and bleeding from the access site. Rates of

vascular complications have varied in the literature from 5% to 20%, depending on the patient populations studied. However, a contemporary series showed the incidence of limb ischemia to be 2.3% and incidence of major limb ischemia to be 0.5% in 5,495 consecutive patients with IABP. Diabetes, female sex, preexisting peripheral vascular disease, history of smoking, and catheter size are all independent risk factors that are strongly associated with the development of ischemic vascular complications from IABP use.

2. **Ischemia**

a. If ischemia develops in the accessed leg, the balloon catheter and sheath should be removed and hemostasis obtained at the access site. Sheathless insertion or alternative access sites should be considered.

b. If ischemia is still present, consultation with a vascular surgeon is indicated. Surgical intervention for ischemic limbs caused by IABP catheters includes thrombectomy, surgical bypass grafting, and, rarely, amputation.

3. **Bleeding**

a. Bleeding around the access site develops in 1% to 5% of patients treated with IABP. It is usually controlled with prolonged manual pressure at the access site.

b. Hematomas that develop at the access site may require transfusion of blood products and, occasionally, direct arterial repair.

c. Pseudoaneurysms after IABP removal are rare but require surgical correction.

4. **Infection.** Infectious complications are rare and include access site infections, catheter infections, and bacteremia. No studies have addressed how frequently balloon catheters become infected and how frequently they need to be changed to limit infectious complications.

5. **Balloon rupture** should be considered if blood is detected in the gas drive line lumen or if balloon augmentation ceases.

a. Small leaks in the balloon can develop from damage to the balloon surface caused by inflation against calcified aortic plaques. Rates of balloon leak can be as high as 4.2%.

b. Potential complications for the patient include helium gas embolism and balloon entrapment when blood leaks into the balloon, clots, and prevents adequate deflation of the balloon for removal.

c. Use of standard sized balloons (40 cm^3) in patients shorter than 170 cm (5′ 6″) is associated with balloon rupture. This is thought to be caused by damage to the balloon when inflation occurs in the smaller and more plaque-laden distal abdominal aorta. Thus, a 34-cm^3 balloon should be used in patients shorter than 170 cm.

6. **Balloon entrapment** occurs when balloon rupture causes a clot to form within the balloon, preventing deflation during removal. When resistance is encountered during balloon catheter removal, balloon entrapment should be considered and fluoroscopy immediately carried out to assess the position of the retained catheter.

a. Management of balloon entrapment usually involves surgical extraction because forceful removal of a partially deflated balloon catheter could cause serious vascular injury.

b. Case reports have documented successful lysis of clots within the balloon by instilling thrombolytic agents through the gas drive lumen of the IABP catheter. The balloons were deflated after clot lysis and the catheters successfully removed.

7. **Red blood cell and platelet destruction.** Because of the shear forces of the balloon catheter, hemolytic anemia and mild thrombocytopenia can occur during IABP support. Daily hemoglobin and platelet values should be checked. Platelet counts <50,000 are unlikely to be caused by the IABP, and alternative causes should be sought.

8. **Other complications.** Rare complications of IABP use include acute renal failure, mesenteric ischemia, and paraplegia from plaque embolization leading to thrombosis of the renal, mesenteric, or spinal arteries, respectively. Aortic dissections and aortic perforations, although rare, usually occur during insertion.

H. Removing the IABP catheter

1. **Weaning.** Whether IABC needs to be weaned before the balloon catheter is removed depends on multiple factors, including the duration of the support, the hemodynamic status of the patient, and left ventricular function.

a. The usual practice is to change IABP inflation to 1:2 for a few hours and then to 1:3 with close hemodynamic monitoring.

b. At the same time, IV afterload reducing drugs such as nitroprusside are used to replace the afterload reduction provided by the IABP. If not tolerated, inotropic drugs such as dobutamine or milrinone are used to simulate the IABP's hemodynamic effects.

If weaning is tolerated hemodynamically, the balloon can then be removed.

c. Anticoagulation is necessary with IABP inflation ratios of 1:2 or 1:3, as during weaning. In patients unable to tolerate anticoagulation, a "volume-wean" may be performed instead. The IABP is kept 1:1, thus anticoagulation is not absolutely necessary. Balloon inflation volume is gradually reduced from full inflation to 75% to 50% inflation in a similar manner as above.

2. **Withdrawal of the balloon catheter and sheath**

a. IV heparin should be discontinued for at least 4 hours before removal of the catheter. The activated coagulation time is checked until it falls below 150 seconds or partial thromboplastin time normalized.

b. Percutaneously placed catheters can then be removed manually, but surgically placed catheters must be removed with direct arterial repair.

c. To begin removal of the balloon catheter, the balloon is changed to standby and the gas drive line is disconnected. Then, the balloon catheter is pulled back until resistance is met, indicating that the catheter is in the sheath. The sheath and the balloon catheter are then withdrawn together as a unit, but excessive force should never be applied.

3. **Hemostasis**

a. After the balloon is withdrawn, the puncture site is allowed to backbleed for 1 to 2 beats while pressure is held distal to the puncture site to evacuate proximal thrombi. Then manual pressure is applied proximal to the puncture site, and backbleeding is repeated to evacuate distal thrombi.

b. Manual pressure is then applied over the puncture site until adequate hemostasis is achieved (general rule is 3 minutes per sheath size: 24 minutes for an 8F sheath, 28.5 minutes for a 9F sheath).

c. A compressive dressing is applied thereafter.

4. **Monitoring during IABP removal**

a. During the application of manual pressure to the puncture site, the distal pulses in the leg should be continually assessed, and pressure should be adjusted to maintain adequate distal perfusion.

b. The patient should be confined to strict bed rest for 6 to 12 hours after the catheter and sheath have been removed, and the leg should be periodically assessed for signs of ischemia.

I. Changing the IABP catheter

1. Reasons for changing the IABP

a. When patients require prolonged IABP support, some clinicians change the catheter and sheath every 4 to 5 days to prevent infectious complications. However, there is no consensus on using this approach.

b. Other reasons for changing the IABP include balloon entrapment and rupture, kinking of the catheter or sheath (which prevents adequate balloon inflation), or fever (which may indicate bacteremia from a line infection).

2. **Simultaneous change.** In patients who are critically dependent on IABP support and who need the IABP changed for one of the above reasons, the catheter and sheath must be changed simultaneously with placement of a new IABP.

3. **Contralateral femoral artery**

a. When the contralateral femoral artery can be used, it is accessed and the sheath is placed. A guidewire is then positioned in the aortic arch while the old balloon is on standby.

b. Counterpulsation is reinitiated, and the new balloon catheter is prepared and readied for use.

c. The old balloon is then deflated and quickly withdrawn, while the new balloon catheter is placed over the guidewire from the contralateral femoral artery. This technique limits the period without IABP support during the change to <30 seconds.

d. Anticoagulation can safely be discontinued before and after a simultaneous change to aid in achieving hemostasis at the old access site.

4. **Same femoral artery**

a. When the contralateral femoral artery cannot be used, the old catheter and sheath must be removed and changed under direct vision.

b. The accessed femoral artery is exposed surgically, and a purse-string suture is placed around the preexisting sheath.

c. The old sheath is then removed, and tension is applied to the suture for hemostasis.

1. 1 The small dilator in the catheter package is directly inserted into the previous puncture site, and the guidewire is advanced to the aortic arch through it.
2. 2 The sheath is advanced over the guidewire into the proper position, and the purse-string suture is tied down.
3. 3 The balloon catheter is then inserted via the sheath, and the soft tissue and skin incision are closed with sutures.
4. 4 In emergency situations, the preexisting sheath can be rewired and a new balloon catheter inserted through the old sheath. However, infectious complications are high with this approach.

III. IMPELLA DEVICE. The Impella is a non-IABP short-term MCS device that operates via a microaxial flow pump based on the principle of an Archimedes screw (Fig. 61.7). The Impella catheter inlet area is placed retrograde across the AV into the mid-LV. A continuous impeller motor pump draws blood out of the LV and ejects it into the ascending aorta through the outlet area (Figs. 61.7 and 61.8). The Impella system comes in different sizes of varying levels of support, including the Impella 2.5 (2.5 L/min flow), Impella CP (3.5 L/min), Impella 5.0 (5 L/min), and Impella LD (5 L/min). The Impella 2.5 and CP can be placed percutaneously, whereas the 5.0 and LD devices must be placed surgically through a graft in the ascending aorta, subclavian, or axillary artery. In addition, the Impella RP recently received humanitarian device exemption for use in selected patients with isolated right-sided heart failure up to 14 days, but has not yet received full Food and Drug Administration (FDA) approval for use in the United States.

A. Indications. Impella carries similar indications as the IABP; however, it is able to generate more hemodynamic support and does have certain features that make it more or less desirable than IABP therapy depending on the circumstance. The specific FDA-approved indications for Impella are discussed below.

1. Cardiogenic shock. In 2016, the Impella received FDA approval for the treatment of ongoing cardiogenic shock within 48 hours of acute MI or open heart surgery as a result of LV failure not responsive to medical therapy or conventional treatment.

a. Data supporting this decision comes from a 415 patient analysis of the **RECOVER 1** study and the U.S. Impella registry (cVAD Registry), as well as safety analysis from the FDA medical device reporting ("MDR") database.

FIGURE 61.7 Impella CP catheter. The Impella 2.5, CP, and 5.0 catheters have several components. The distal-most end is a soft pigtail with a monorail guidewire port (EasyGuide lumen). Blood is sucked through the inlet area distal to the aortic valve (AV) and ejected from the outlet area above the AV. The Impella LD and RD have different structures and are not shown. (Image courtesy of Abiomed, used with permission.) **FIGURE 61.8** Impella placement (self-explanatory). (Image courtesy of Abiomed, used with permission.)

b. The Impella 2.5 and 5.0 are not intended for use >4 days, whereas the CP and LD are approved for use up to 6 days.

c. There have been few studies comparing hemodynamic parameters or outcomes in patients with cardiogenic shock treated with IABP or Impella.

d. The **ISAR-SHOCK** (Efficacy Study of LV Assist Device to Treat Patients with Cardiogenic Shock) study demonstrated improved hemodynamic parameters in patients treated with Impella 2.5 versus IABP but no difference in 30-day outcomes.

e. Similar to IABP and TandemHeart, the Impella carries a **class IIb** recommendation for use in acute MI complicated by cardiogenic shock.

2. "Protected" high-risk PCI. Patients undergoing high-risk PCI may benefit from Impella support during the procedure.

a. The **PROTECT I** study demonstrated the safety of Impella 2.5 during high-risk PCI; however, it did not have clinical outcome data.

b. The **PROTECT II** trial randomized 452 symptomatic patients with complex triple-vessel or unprotected LM CAD with LVEF ≤35% to Impella 2.5 or IABP support.

1. 1 The trial was stopped early because of futility at 69% enrollment, with no difference in the primary end point of major adverse events at 30 days.

2. 2 However, Impella provided superior hemodynamic support during the procedure, and there was a trend toward fewer major adverse events compared with IABP at 90 days (40.6% vs. 49.3%, $p = 0.066$ in the intent-to-treat population; 40.0% vs. 51.0% in the per-protocol population).

B. Contraindications

1. **Mechanical AV.** The Impella pigtail, inlet, and catheter must be advanced across the AV, and as such a mechanical valve precludes Impella placement.

2. **At least moderate AS or calcification.** The manufacturer advises against Impella placement if there is at least moderate AS (AV area ≤ 1.5 cm^2). Severe AV calcification may also complicate Impella placement.

3. **At least moderate aortic insufficiency (AI).** Similarly, the manufacturer advises against Impella placement in the presence of at least moderate AI.

4. **Severe PAD.** As with an IABP, severe PAD may preclude placement of a large femoral sheath. This may be of particular concern with Impella placement, because a 13F peel-away sheath is used for Impella 2.5, 14F for Impella CP, and the 9F Impella catheter remains in place (opposed to an 8F sheath for an IABP).

C. Hemodynamics of Impella function

1. **Reduced LV end-diastolic volume (LVEDV) and pressure (LVEDP).** The Impella directly offloads the LV by removing blood from the LV and ejecting it into the proximal aorta.

a. The effect is a direct reduction in LVEDV and LVEDP. This is in contrast to the IABP, which acts principally by reducing afterload and thus indirectly affects these parameters.

b. Other studies have demonstrated that Impella increases CO)/cardiac index (CI) and reduces PCWP, pulmonary artery diastolic pressure (PADP), and right atrial pressure (RAP).

1. 1 The **RECOVER II** study aimed to study hemodynamic parameters in Impella 2.5 versus IABP; however, it was terminated early because of lack of power (NCT00972270).

D. Impella insertion technique. The basic details of Impella insertion are described here. A complete description of percutaneous Impella 2.5 and Impella CP insertion are beyond the scope of this chapter.

1. Access is obtained in the common femoral artery.

a. For Impella 2.5, a 13F peel-away sheath is placed.

b. For the Impella CP, a 14F peel-away sheath is placed.

2. A 0.035″ guidewire is advanced to the aortic root. Over this, a diagnostic catheter (i.e., 6F AL1, multipurpose, or 4F to 5F pigtail) is advanced across the AV into the mid-LV cavity.

3. The 0.035″ guidewire is removed, and the 0.018″ Impella guidewire is advanced through the coronary diagnostic catheter. The coronary catheter is removed, and the Impella guidewire is left in place.

4. The Impella device is advanced over the guidewire in a monorail fashion (via the EasyGuide lumen). The Impella is positioned with the distal J-tip/pigtail approximately 3.5 cm beyond the AV. This should place the Impella inlet well below the AV. The outlet will sit approximately 1 cm above the AV if appropriately placed.
5. The guidewire is taken out, and the peel-away sheath is removed, leaving the 9F Impella catheter in place.
6. Position is finalized on fluoroscopy. The device is locked in place and dressed.

E. Monitoring and patient concerns

1. Echocardiogram

a. Essential to confirm proper Impella positioning

b. On transthoracic echo, Impella position can be confirmed in the parasternal short-axis view (Fig. 61.9).

1. 1 The Impella pigtail should be approximately 3.5 cm into the mid-LV, center cavity. The Impella catheter will straddle the AV.
2. 2 The Impella outlet should sit just above (ideally 1 cm) the AV.
3. 3 This is best appreciated with color Doppler flow—the dense mosaic turbulent flow should be above the AV, not below.

c. Position can also be confirmed in the apical four-chamber view (device should be 3.5 cm into the LV, center cavity).

1. 1 Lateral displacement may indicate tangling in the posterolateral mitral papillary muscle.

2. Target hemodynamics

a. The Impella is sensitive to preload and may suction the LV endocardium if the LV is underfilled.

1. 1 The LV will be in competition for volume with the Impella, and thus it is important to maintain slightly higher than normal filling pressures.
2. 2 Periodic IV fluids should be given to target a central venous pressure (CVP) of at least 12 mm Hg or a PCWP of 16 mm Hg if a pulmonary artery catheter is in place (as is our practice in patients with Impella).

FIGURE 61.9 Correct and incorrect Impella position by transthoracic echocardiography (TTE). **A:** Correct Impella position. There is a dense mosaic pattern of turbulence across the aortic valve (AV) near the catheter outlet area. **B:** Incorrect Impella position. Example of an Impella placed too far in the left ventricular (LV) or entangled in a papillary muscle. The mosaic pattern crosses the aortic valve. (Images courtesy of Abiomed, modified with permission.)

3. Anticoagulation

a. All patients should be on unfractionated heparin (UFH), target activated clotting time (ACT) 160 to 180 seconds, activated partial thromboplastin time 60 to 80 seconds.

b. If heparin is contraindicated, bivalirudin should be used instead.

4. Hemolysis

a. Given the constant motor action of the impeller, complete blood cell count should be checked daily, and patients monitored for signs of hemolysis or thrombocytopenia.

5. Peripheral pulses

a. Pulses should be monitored frequently in the leg with the Impella inserted (unless an alternative access site is chosen).

b. Limb ischemia may develop rapidly and an alternative access route should be chosen if this develops.

F. Understanding the Impella console. The Impella 2.5 and CP devices are more commonly encountered by cardiologists, as they can be placed percutaneously in the catheterization lab.

1. Normal Impella 2.5 and CP console (Fig. 61.10A)

a. Flow is directed by 8 "Power" or "P" levels that dictate how many RPM (and thus how much flow) the impeller generates.

b. The "placement signal" area should contain a pulsatile signal similar to the normal aortic waveform.

c. The "Motor Current" area should likewise appear pulsatile.

2. Incorrect placement—displaced into the aorta (Fig. 61.10B)

a. If the Impella is pulled back with both the outlet *and* inlet proximal to the AV (aortic side), there will be a position alarm and flows will drop.

b. The placement signal will still appear to have an aortic waveform; however, the motor current will be flat.

3. Incorrect placement—displaced into the aorta (Fig. 61.10B)

a. Likewise, if both the inlet *and* outlet are across the AV into the LV, there will be a position alarm and flows will drop.

b. The placement signal will appear to have an LV waveform; the motor current will be flat.

4. Normal Impella 5.0 console (Fig. 61.10B)

a. Similar to the Impella 2.5 and CP, the placement signal will be pulsatile. However, this actually reflects a pressure differential, unlike actual pressure as in the 2.5 and CP. The motor current will similarly appear pulsatile.

G. Troubleshooting the Impella device. Below, some common Impella alarms, causes, and management strategies are discussed.

1. Suction alarms

a. Causes

1. 1 Incorrect positioning
2. 2 Low intravascular volume

FIGURE 61.10 Impella console. **A:** Normal appearance of the console for an Impella 2.5 or Impella CP. **B:** Incorrect placement—device pulled back into aorta. **C:** Incorrect placement—device too far into LV. **D:** Normal appearance of the console of an Impella 5.0. Images courtesy of Abiomed, modified with permission.

3. 3 Right ventricular (RV) failure
4. 4 Entrainment of thrombus into the Impella cannula

b. Management

1. 1 Evaluate/reposition catheter
2. 2 Assess volume status: target CVP 12 mm Hg, PCWP 16 mm Hg
3. 3 Assess RV function
4. 4 Reduce P level temporarily. Increase back to desired P level once suction resolved.

2. Position alarms

a. Causes

1. 1 Incorrect positioning too far into LV, or too far back into aorta
2. 2 Use console placement signal and motor current signals to determine location.

b. Management

1. 1 Care must be taken when repositioning to avoid aortic, AV, or ventricular injury; imaging guidance with fluoroscopy or echocardiography recommended.
2. 2 Drop down to P2 during any repositioning attempt.

3. Low native heart pulsatility/position unknown

a. Causes

1. 1 Low native heart function
2. 2 May not generate sufficient pressure across AV
3. 3 Placement signal dampened, motor signal dampened or flat
4. 4 Placement monitoring suspended at <1.5 L/min

b. Management

1. 1 Confirm Impella placement.
2. 2 Assess hemodynamics (i.e., need for increased preload, ionotropic therapy).

H. Additional important considerations

1. Identifying right-sided heart failure

a. May cause reduced flows from Impella

b. May see suction alarms *despite elevated CVP*

1. 1 PCWP may be low or normal, reflecting reduced left-sided filling despite elevated right-sided pressures.

2. Need for cardiopulmonary resuscitation (CPR)

a. CPR should commence as needed.

b. Impella should be turned down to P2.

c. Upon return of spontaneous circulation, Impella position should be immediately reconfirmed with bedside echocardiography, fluoroscopy, or CXR and controller.

d. Once position confirmed, may return to desired P level.

I. Complications

1. Traumatic complications

a. Hemolysis and thrombocytopenia

1. 1 The constant, rapid rotation of the impeller may cause clinically significant hemolysis and/or thrombocytopenia in 5% to 10% of patients.

b. AV or aortic root injury

1. 1 AV injury may lead to significant AI.
2. 2 Usually occurs during device placement or repositioning.
3. 3 Care should be taken when advancing the device across the AV.
Imaging guidance is recommended.

c. Functional MR

1. 1 May occur due to entangling of Impella with papillary muscle or due to chordal rupture from the device

d. Ventricular arrhythmia

1. 1 Catheter irritation of the LV may induce VT and/or ventricular fibrillation by nature of an R-on-T premature ventricular complex

e. Device thrombosis or cerebrovascular accident (CVA) (rare)

1. 1 Anticoagulation with UFH is recommended in all patients.

f. LV perforation, free wall rupture (rare)

J. **Impella removal.** The Impella should be removed when PCI is complete and/or hemodynamics has improved. If placed for cardiogenic shock, it is important to replace the Impella with adequate inotropic or afterload reduction therapy, similar to that with an IABP. Given the size of the arteriotomy, it is recommended that the device be pulled only by clinicians with significant experience, once ACT is <150 seconds. Approximately 45 minute to 1 hour is generally needed to obtain hemostasis.

IV.TANDEMHEART

A. Overview

1. The TandemHeart (Cardiac Assist Inc., Pittsburgh, PA) is a temporary MCS device that can be percutaneously inserted.
2. It **provides left atrial to iliac artery bypass via a transseptal puncture** and is powered by an external continuous centrifugal pump that has a maximum speed of 7,500 rpm and can produce flow up to 5 L/min.
3. The TandemHeart provides direct left ventricular unloading, and thus decreases cardiac filling pressures, cardiac workload, and myocardial oxygen demand.
4. **Contraindications** include significant AI, VSD, significant peripheral vascular disease, and contraindications to anticoagulation.

B. Insertion technique

1. This device can be implanted in a catheterization laboratory or hybrid operating room. First, both femoral venous and arterial access is obtained. Angiography of the iliac arteries and distal vessels should be obtained to assess for appropriate bilateral iliac artery run-off and exclude significant peripheral vascular disease.
2. A transseptal puncture is performed using the provided transseptal catheter. Once transseptal puncture is performed, the interatrial septum is dilated in two stages (with 14F and 21F dilators).
3. A 22F inflow cannula is advanced into the left atrium under echocardiographic and fluoroscopic guidance.
4. The outflow cannula is 15F or 17F and it is placed in the femoral artery. The cannula is advanced over a stiff guidewire into the common iliac artery.
5. After deairing, the cannulae are connected to the external pump.
6. A continuous infusion of heparinized saline is required for anticoagulation of the circuit and full systemic anticoagulation is required.
7. Complications of insertion include tamponade, major bleeding, critical limb ischemia, and residual atrial septal defect.

C. Data

1. The initial prospective feasibility study prospectively evaluated the short-term hemodynamic impact of the TandemHeart. The device was implanted in 18 patients with a mean duration of support of 4 ± 3 days. There was a significant improvement in PCWP, pulmonary arterial pressure, CO, and systemic blood pressure. During support, 27% (5/18) had major bleeding requiring transfusion and 11% (2/18) required a surgical antegrade perfusion cannula because of limb ischemia.

2. This device has been used largely to support high-risk PCIs. A number of case series have been published with the largest series from the Mayo Clinic, with 54 patients who were supported with the TandemHeart for high-risk PCI. In addition to hemodynamic improvement, procedural success was 97% with 87% 6-month survival and 13% vascular complications.

3. The TandemHeart has been compared to IABP in two small multicenter, randomized trials in patients with acute MI and cardiogenic shock. There was some improvement in hemodynamic parameters with the TandemHeart; however, the meta-analysis combining these studies did not suggest any mortality benefit.

V.ECMO

A. Overview. Improvements in technology have driven a rapid adoption ECMO in adults in recent years. ECMO has evolved into an important therapy for patients with refractory cardiogenic shock in the cardiac intensive care unit.

Venovenous (VV) ECMO is commonly used in patients with isolated refractory hypoxemic respiratory failure, and thus is not the focus of the current section. In **venoarterial (VA) ECMO**, blood is drained from the venous system and circulated extracorporally by a mechanical pump capable of delivering up to 5 L/min of flow. When outside of the body, the blood passes through an oxygenator and heat exchanger, where hemoglobin is saturated with O_2, and CO_2 is removed. Blood is returned to the arterial circulation, providing both cardiovascular and respiratory support (Fig. 61.11).

B. Indications. Advantages of VA ECMO over other forms of short-term MCS include the ability to support RV, LV, or biventricular failure at high flow rates and the potential to support patients with concomitant respiratory failure. Data on the indications for ECMO are limited to case series and cohort studies and are supportive of ECMO use in the following circumstances:

1. Cardiogenic shock
   a. In absence or after acute MI
   b. Mechanical complications of acute MI or structural heart disease
   c. Fulminant myocarditis
   d. Acute right-sided heart failure (including pulmonary embolism)
2. Postcardiac arrest (extracorporeal CPR)
3. Bridge to definitive treatment
   a. VAD or heart transplantation
   b. Post-VAD or transplant graft dysfunction
4. Failure to wean from cardiopulmonary bypass after cardiac surgery

C. Absolute contraindications. There are few absolute contraindications to VA ECMO use, but these include

1. Active hemorrhage or inability to tolerate anticoagulation
   a. ECMO requires the use of anticoagulation for prevention of CVA.
   b. As such, extreme caution should be utilized in patients with active bleeding or a predisposition to bleeding (extreme thrombocytopenia, disseminated intravascular coagulation, recent surgery, recent intracranial injury, etc.).
2. Irreversible cardiac failure without potential of advanced therapies
   a. If recovery is unlikely and not a candidate for definitive therapy, ECMO is a "bridge to nowhere" and should not be offered.

1. 1 The patient's VAD or transplant candidacy should be carefully considered prior to ECMO initiation if possible, as concomitant renal failure, hepatic failure, neurologic status, advanced age, and/or social barriers may exclude advanced therapies.

FIGURE 61.11 Venovenous (VV) and venoarterial (VA) ECMO schematic. **A:** In VV ECMO, blood is drained from inferior vena cava (IVC) or right atrium (RA), passed through a pump, gas exchanger, and heater and returned back through the central venous circulation. **B:** In traditional VA ECMO, blood is drained from the IVC or RA, passed through a pump, gas exchanger, and heater and returned back through the femoral arterial circulation. ECMO, extracorporeal membrane oxygenation.

D. Relative contraindications

1. Small peripheral vasculature, prior peripheral arterial bypass, and/or severe PAD

a. Inability to tolerate large cannula insertion into a common femoral artery because of small body size or severe PAD may preclude peripheral ECMO placement.

b. May result in ipsilateral lower extremity ischemia.

c. Can minimize risk by insertion of an antegrade perfusion catheter which redirects a portion of the infused blood down the ipsilateral leg.

d. Surgical ECMO placement into the axillary, subclavian, or central aorta vasculature may be considered.

E. ECMO insertion

1. Catheters are placed percutaneously by Seldinger technique using the largest cannulas tolerated for the patient's circulation.

a. A venous cannula is placed in the inferior vena cava or right atrium (RA) for drainage.

b. An arterial catheter is placed in the right (or left) common femoral artery.

c. Access sites may be tailored to the patient's needs.

1. 1 As above, severe PAD may dictate need for axillary or central cannulation.

2. 2 Use of the internal jugular veins may be used instead of the femoral veins, and subclavian artery insertion may allow for patient ambulation on ECMO.

F. ECMO hemodynamics, practical considerations, and monitoring. There is institutional variability in how ECMO is managed. Below are our suggestions on how to manage ECMO in a patient with cardiogenic shock.

1. **Flow rate**

a. Flow is increased until satisfactory. Goal is to provide enough flow to rest LV, but not excessive flow as this will reduce preload and CO.

2. **Arterial and venous oxyhemoglobin goals**

a. Usual goals are an arterial oxyhemoglobin >90% and venous oxyhemoglobin 70% to 80% (measured on the ECMO venous line).

3. **Tissue perfusion**

a. Provide adequate tissue perfusion as measured by blood lactate and peripheral BP.

b. Our practice is to place an arterial line in either upper extremity, because the mean arterial pressure (MAP) reflects peripheral and cerebral pressure.

c. MAP below 60 mm Hg off of the peripheral arterial line may predispose to peripheral and/or cerebral hypoperfusion.

d. Inotropic agents or additional MCS (such as IABP or Impella) may be indicated if venous oxyhemoglobin remains poor.

e. Pressors may be indicated if MAPs are poorly supported despite ECMO, suggestive of a concomitant vasodilatory process.

4. **Continuous venous oximetry**

a. The machine constantly measures venous oxyhemoglobin saturation in the ECMO venous return.

b. When venous oxyhemoglobin is below target, consider

1. 1 Increasing ECMO flow rate
2. 2 Providing intravascular volume (i.e., low preload)
3. 3 Anemia/need for packed red blood cells (PRBC)
4. 4 Decreasing systemic oxygen uptake by reducing body temperature

5. **ECMO oxygenation and sweep**

a. The ECMO circuit provides 100% FiO_2 through the oxygenator.

b. Oxygenation is thus determined by the flow rate.

c. Elimination of CO_2 is determined by adjusting the rate of countercurrent gas flow through the oxygenator (called the "sweep").

6. **Ventilator support**

a. Our practice is to limit ventilator support to minimize oxygen toxicity, barotrauma, and ventilator-induced lung injury.

b. Positive end-expiratory pressure (PEEP) should be minimized, as PEEP reduces preload and thus CO.

c. Minimize plateau airway pressures (<20 cm H_2O) and FiO_2 (<0.5).

d. As ECMO is weaned, flow will increase flow through the native circulation including the lungs, and thus may need to increase ventillatory support at this time.

7. **Additional patient monitoring**

a. **"Chugging"**

1. 1 Low intravascular volume will result in "chugging" (periodic movements of the ECMO venous line and reduced ECMO flow).
2. 2 Consider blood loss, hemolysis, and/or volume loss from other sources.
3. 3 Provide intravascular volume for goal CVP >12 mm Hg.

b. **LV contractility**

1. 1 ECMO may increase afterload (given blood return through the femoral artery) and reduces preload (as above).
2. 2 Bedside transthoracic echocardiography and a peripheral arterial line can be used to assure AV is opening.
3. 3 Failure of AV to open may result in thrombus formation in the LV.
4. 4 Ionotropic agents and/or IABP may be needed to augment LV contractility if AV fails to open.

c. **Anticoagulation**

1. 1 Goal ACT 180 to 210 seconds, or partial thromboplastin time (PTT) ~1.5 times normal
2. 2 Can be reduced if bleeding develops

d. **Thrombocytopenia and hemolysis**

1. 1 Platelets are continuously consumed as they are activated by exposure to the ECMO surface.

1. (a) Consider platelet transfusion for goal >100,000/μL (goals will vary from institution).
2. 2 Hemolysis is frequent given turbulent flow.
1. (a) Monitor for anemia and need for PRBC transfusion.

e. Other supportive measures

1. 1 Swan-Ganz catheterization may be helpful in measuring right-sided pressures and PCWP, although it should not be used to titrate venous oxyhemoglobin (given variable flow through native circulation). As ECMO is weaned, Swan-guided therapy is increasingly important.
2. 2 ECMO does not provide ultrafiltration; hemodialysis should be considered if necessary.

G. Complications

1. Severe bleeding

a. The most common complication from VA ECMO is severe bleeding, estimated to occur in up to 30% to 40% of patients on ECMO.

b. May be due to anticoagulation, platelet dysfunction, and/or placement technique

c. Can be limited by careful targeting of ACT or PTT and maintaining adequate platelet count

2. Thromboembolism

a. Most often because of thrombus formation in the ECMO circuit or air embolism. Estimated to occur in 5% to 6% of patients

b. Risk limited by careful targeting of ACT or PTT and careful operation of the ECMO machine. A sudden change in the pressure gradient across the oxygenator suggests a thrombus has developed.

c. Stasis of blood in the LV is another potential cause. Frequent echocardiography is important to assure AV is opening.

d. Heparin-induced thrombocytopenia is another potential cause. If develops, heparin should be stopped, and an alternative anticoagulant (i.e., argatroban) should be considered.

3. Limb ischemia and cannulation-related complications

a. Estimated to occur in 15% to 20% of patients

b. Limb ischemia may be limited by use of an antegrade perfusion catheter or central ECMO cannulation. See discussion above.

c. Vessel perforation, dissection, and other complications are rare but may occur due to the large caliber arterial catheter.

4. Infection

a. Estimated to occur in ~30% of patients.

b. Most often because of venous and arterial cannulae. Patients on ECMO are also predisposed to develop ventilator-associated pneumonia.

5. Pulmonary hemorrhage

a. Occurs due to LV distention in severe LV dysfunction, elevated pulmonary venous pressures, and thrombocytopenia

b. May require consideration for percutaneous or surgical atrial septostomy

6. Coronary or cerebral ischemia

a. Fully oxygenated blood from the ECMO circuit first perfuses the contralateral leg and abdominal organs, whereas blood ejected from the heart preferentially perfuses the coronary arteries, upper extremities, and brain.

b. The arterial oxygen concentration of blood perfusing the heart, upper body, and brain may be significantly lower than blood in the lower extremities.

c. To detect this, periodic arterial oxyhemoglobin saturations should be taken from the upper extremity (i.e., pulse oximetry or from arterial line).

1. 1 Reduced peripheral oxygen levels may require infusion of blood into the RA.

H. Weaning ECMO

1. Weaning from ECMO in cardiogenic shock, patients should be monitored for recovery of LV function as ECMO flow is decreased. Signs of LV recovery include increased aortic pulsatility on arterial line tracings and LV contractility on echocardiogram, along with stable venous oxyhemoglobin and lactic acid concentration.

2. As ECMO is weaned, there will be increased blood flow through the right heart and lungs. As such, ventilator requirements may increase.

a. In patients with concomitant respiratory failure because of cardiogenic pulmonary edema, patients should be diuresed as much as possible prior to weaning ECMO to minimize ventilator requirements once ECMO is weaned.

3. Consideration should be given to need for ionotropic therapy, IV afterload reduction, and/or IABP placement as ECMO is liberated.

4. ECMO cannulae can then be removed. This may be performed at bedside with prolonged manual compression (at least 30 to 45 minutes for femoral arterial access). Surgical repair of the arteriotomy site may be needed in certain patients.

a. Low doses of protamine can be administered to reverse anticoagulation and facilitate hemostasis just prior to ECMO liberation.

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CHAPTER 62

Left Heart Catheterization

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Amar Krishnaswamy

I. INTRODUCTION. In 1958, Dr. Mason Sones and colleagues at the Cleveland Clinic performed the first selective coronary arteriographic procedure. Since then, left heart catheterization (LHC) has become an important tool in diagnostic cardiology. More than 1.5 million cardiac catheterizations are performed yearly in the United States. Despite the advent of other imaging modalities, coronary arteriography remains the clinical gold standard for determining the presence of significant coronary artery disease (CAD).

LHC is an invasive procedure with serious potential risks. To be competent in LHC, a cardiologist-in-training must perform at least 300 catheterizations, serving as primary operator on 200. During training, the operator must be supervised by a cardiologist who is already competent in the procedure. Because there is the ability to treat a lesion with percutaneous intervention at the same time as the diagnostic angiogram, it is important to have a plan regarding how to use the information obtained.

II. INDICATIONS. The American College of Cardiology and the American Heart Association (ACC/AHA) have created appropriate-use criteria (AUC) to guide physician decision making on performing diagnostic cardiac catheterizations. Common clinical scenarios were created and graded by various panel members on a 1 to 9 scale. The scenarios were placed into the three categories of "appropriate" (score 7 to 9), "may be appropriate" (score 4 to 6), and "rarely appropriate" (score 1 to 3; see Table 62.1 for a summary). The Society for Cardiovascular Angiography and Interventions has created an AUC calculator app to support clinical decision making for diagnostic cardiac catheterization in the individual patient (available at www.scai.org).

TABLE 62.1 Indications and Contraindications to Left Heart Catheterization

Indications[a]	Contraindications[a]
• Acute myocardial infarction	• Active bleeding
• Unstable angina	• Coagulopathy
• Chronic stable angina, uncontrolled by medications	• Acute or chronic renal failure
• Abnormal stress test	• Active infection
• Ventricular arrhythmias	• Severe anemia
• Left ventricular dysfunction	• Electrolyte abnormalities
• Valvular heart disease	• Inability to lie supine (i.e., decomp

TABLE 62.1 Indications and Contraindications to Left Heart Catheterization

• Preoperative coronary assessment for cardiovascular surgery	• Malignant hypertension
• Preoperative risk assessment for noncardiovascular surgery	• Extensive comorbidities—risk o benefit
• Periodic follow-up after cardiac transplantation	• Patient unable to cooperate or do

[a] See text for full details.

III.

A. Acute myocardial infarction (MI). LHC is given an appropriate indication (score 7 to 9) for routine use in acute MI, particularly in those who will likely undergo primary percutaneous cardiac intervention, those in cardiogenic shock or with other evidence of hemodynamic instability, or those with mechanical complications who are likely to undergo surgical repair. It can be used with the goal of performing primary angioplasty in patients with acute ST-segment elevation MI. There is evidence of the benefit of an early invasive strategy in stable patients with high risk non–ST-segment elevation MI. Patients with persistent pain or unresolved electrocardiographic changes after thrombolytic therapy are recommended to undergo LHC.

B. Unstable angina. LHC in the setting of unstable angina is considered appropriate. Patients who have refractory symptoms despite medical therapy should be considered for an early invasive strategy.

C. Chronic stable angina. LHC is considered appropriate for purposes of revascularization in chronic stable angina for patients whose angina is poorly controlled by medicines or who are intolerant of antianginal medications.

D. Abnormal stress test. A stress test that is classified as high risk is a class I indication for LHC. High-risk findings include >10% ischemic myocardium on single-photon emission computed tomography myocardial perfusion imaging or stress positron emission tomography, or two more segmental wall motion abnormalities on stress echo or stress cardiac magnetic resonance. Transient ischemic dilation and a large drop in ejection fraction with stress are also considered high risk. High features on exercise stress testing include an ST-depression of 2 mm, especially in multiple leads or persisting into recovery 6 minutes, an ST-elevation of 2 mm in leads without Q-waves, a drop in blood pressure of >10 mm Hg with exercise, or development of ventricular tachycardia. These indications hold true even if the patient is asymptomatic. Intermediate-risk stress tests in symptomatic patients are considered appropriate. Symptomatic patients with discordant stress test findings are also appropriate for LHC.

E. Ventricular arrhythmia. A history of resuscitated cardiac arrest with return of spontaneous circulation with a suspicion of CAD is appropriate for LHC. Ventricular fibrillation or sustained ventricular tachycardia with or without symptoms is considered an appropriate indication for LHC.

F. Left ventricular dysfunction. LHC can provide an estimate of left ventricular function and regional wall motion. Left ventricular dysfunction or a new segmental wall motion abnormality of an unknown cause is an appropriate indication for LHC to rule out CAD.

G. Valvular heart disease. LHC can be performed to assess the severity of outflow tract obstruction (aortic stenosis and hypertrophic obstructive cardiomyopathy). It can also

help quantify aortic and mitral regurgitation (MR). With the advancements in Doppler and color echocardiography, the major role of cardiac catheterization is to provide confirmatory data and to rule out CAD as part of the operative workup. LHC is appropriate in patients requiring valve surgery who are at risk for CAD. Most centers perform LHC before valve surgery in those older than 50 years to rule out clinically silent CAD. Younger patients may require LHC if cardiac risk factors are present or if coronary reimplantation may be needed as part of the surgery (homograft implantation, ascending aorta replacement, or Ross procedure).

H. Preoperative. LHC is performed before ascending aortic aneurysm surgery or in some cases of ascending aortic dissection surgery. It is also performed on patients with congenital heart disease to evaluate lesions such as ventricular septal defects and to rule out concomitant coronary anomalies or atherosclerotic disease, if symptomatic. In patients with angina or a positive stress test who are to undergo high-risk surgery, LHC is given a class I indication.

IV. CONTRAINDICATIONS.

The following are the relative contraindications to LHC (see Table 62.1).

A. Coagulopathy. Coagulopathy must be corrected before elective catheterization. The usual recommendation for patients on warfarin (Coumadin) is to discontinue it 72 hours before the procedure. In elective cases, an International Normalized Ratio of <1.8 is a cut-off that is often used for the femoral approach. If the patient is on heparin infusion, this is usually stopped 2 hours before the procedure. A platelet count of <50,000 substantially increases the risk of bleeding. After thrombolytic therapy, bleeding is more likely and elective catheterization is best deferred; however, if the indication for the procedure is urgent, it is possible to proceed with caution, with blood products kept ready for support as needed. Body habitus is also a factor in deciding what level of anticoagulation is acceptable before a catheterization. Obesity increases the chances of bleeding (if multiple attempts at access are needed) and makes bleeding more difficult to detect. The use of **radial artery access for LHC may substantially lower bleeding complications** and is strongly recommended in patients at high bleeding risk or coagulopathy. This recommendation is especially true in patients presenting with acute coronary syndromes when anticoagulants and antiplatelet agents are frequently used.

B. Renal failure. A rising creatinine is generally a reason to defer elective cardiac catheterization. In a patient on dialysis, catheterization is generally timed immediately after the dialysis. In a patient with stable but chronic kidney disease, catheterization may be performed with an awareness of the increased risk of needing dialysis. Limited use of contrast and adequate hydration are important to minimize the risk of contrast-induced nephropathy in this population.

C. Dye allergy. A history of allergy to previous contrast administration should be sought. Although an allergy to shellfish and seafood has been linked to contrast reactions in some studies, other studies dispute such a relationship and do not need routine steroid preparation. Treatment of patients with a history of dye allergy is described in Section **IV.F.2**.

D. Infection. Active infection is a reason to defer elective cardiac catheterization. Local skin infection at the site of the potential puncture is also undesirable. Fungal infection

in groin creases should be controlled before elective cardiac catheterization by the femoral approach; this is a particular concern in obese patients.

E. Laboratory abnormalities. Severe anemia, hypokalemia, or hyperkalemia should be corrected before the elective procedure. In the presence of digitalis toxicity, elective catheterization is best deferred.

F. Decompensated heart failure (HF). Severe HF raises the risks of cardiac catheterization. It is best to optimize medical therapy before elective catheterization. At a minimum, the patient should be able to lie supine without respiratory insufficiency.

G. Severe peripheral vascular disease. Symptoms of claudication warrant careful assessment of pulses. An inadequate lower extremity pulse favors an upper extremity approach. A synthetic vascular graft that is older than 6 months is not a strict contraindication to catheterization, but special care should be taken in gaining access as well as in obtaining hemostasis; however, the risk of embolization of friable atheroma or thrombus is heightened, and this risk increases with the age of the graft.

H. Abdominal aortic aneurysm (AAA). Presence of an AAA requires special care during a cardiac catheterization (see subsequent text). A radial approach obviates the need to cross the AAA altogether.

I. Uncontrolled severe hypertension. Blood pressure should be controlled before elective cardiac catheterization to maximize the safety of the procedure. In particular, severe bleeding can occur at the access site after sheath removal if the patient is very hypertensive, especially if above 180/100 mm Hg.

V.PATIENT PREPARATION

A. Informed consent. A detailed discussion with the patient (and family) should outline the indication for the procedure, as well as the alternative treatment and diagnostic options. Specific mention of the serious risks of complications, such as death, MI, stroke, arrhythmia, bleeding, radiation exposure, and kidney failure, must be made (see complications in subsequent text). The possible need for emergency coronary artery bypass grafting (CABG) should be noted. The risk of serious complications should be individualized. Informed consent should be documented in the medical record prior to an elective or urgent case.

B. Precatheterization assessment. Before proceeding with an LHC, a detailed clinical assessment is necessary, including a comprehensive history and physical examination. All peripheral pulses should be palpated, and arterial bruits, if any, should be documented before the catheterization as a baseline for future reference. In addition, an electrocardiogram and laboratory data, including a comprehensive metabolic panel, complete blood count, and coagulation studies, should be obtained for all patients. Abnormalities in the laboratory parameters, if any, should be addressed before proceeding with LHC. Urine human chorionic gonadotropin should be checked in female patients prior to the catheterization when appropriate.

C. Medications. If percutaneous coronary intervention is likely, pretreatment with aspirin 325 mg by mouth (PO) should be given before the catheterization, because it has been shown to improve outcomes with angioplasty. If stenting is a strong possibility, clopidogrel 300 to 600 mg PO should be given as a loading dose before the procedure in elective cases and consideration of ticagrelor in the acute coronary syndrome. Metformin

should be stopped at the time of the procedure, although the risk of lactic acidosis is extremely low in a patient with normal creatinine.

D. Education. Patients should be warned that they might feel a hot sensation lasting about 30 seconds because of the injection of ionic contrast dye. Some patients may also feel nauseated. Patients should be specifically instructed to cough when they hear anyone in the room say "cough." This maneuver accelerates resolution of dye-induced bradycardia.

E. Equipment. Before performing a cardiac catheterization, it is essential to ensure that the monitoring equipment is fully functional. Continuous electrocardiographic monitoring of heart rate (HR), rhythm, and ST-segments, an automated blood pressure cuff, and continuous pulse oximetry are mandatory. Resuscitation equipment should be tested and ready. In particular, defibrillators and intubation trays must be available next to the patient. If a long procedure is anticipated, many operators prefer placement of a Foley or Texas urinary catheter. Before beginning the procedure, the fluoroscopy and cine equipment should be tested. The usual frame rate of cine film is set at 15 to 30 frames/s; however, 10 to 15 frames/s may be used without a significant loss in picture quality. Lower frame rates will decrease the radiation exposure to the patient and the operator.

F. Contrast dye

1. Choice of contrast. Ionic contrast dye was historically used during most cardiac catheterizations. Currently, low-osmolar nonionic dye, which is now only slightly more expensive, is standardly used. The literature supports that nonionic dye produces less left ventricular dysfunction, bradycardia, nausea, and hypotension. There are many types of low-osmolar nonionic and iso-osmolar nonionic agents. No data currently supports the use of one type over another in terms of complications such as contrast-induced nephropathy.

2. Dye allergy

a. Premedication. If a patient reports an allergy to contrast dye or a history of prior anaphylactoid reaction, it is customary to premedicate with steroids and antihistamines. Protocols vary widely. Common regimens include 50 mg of oral prednisone administered 13, 7, and 1 hour (q6h) prior to the procedure along with diphenhydramine 50 mg intravenously (IV) or orally 1 hour prior to the procedure. Intravenous steroids can be substituted in place of oral steroids 1 hour prior to the procedure (hydrocortisone 100 mg IV once). With a history of possible life-threatening contrast allergies, it is also prudent to administer small quantities of contrast (1 mL) and observe the patient for a few minutes before proceeding.

b. Treatment. If a patient develops any sign of an allergic reaction, treatment should be prompt. If signs such as hives or rashes develop, treatment with diphenhydramine is usually sufficient. Hydrocortisone is also often given, although its effects may not manifest for several hours. In cases of oropharyngeal edema, bronchospasm, or hypotension, 0.3 mL of 1:1,000 epinephrine should be administered subcutaneously. With refractory symptoms, 10 μg/min of intravenous epinephrine can be administered until symptoms abate.

c. Latex allergy has become increasingly recognized as a clinical entity, especially in patients who are health-care workers. True latex allergy can include urticaria, angioedema, laryngospasm, bronchospasm, and anaphylaxis. If a patient describes a possible latex allergy, allergy testing, including skin testing and rapid antigen serum testing, should be considered. Patients with latex allergy should be scheduled as the first case of the day to avoid latex dust from previous procedures. Written protocols outlining materials to be avoided

should be strictly followed. A cart with latex-free items should be made available. Latex-free catheterization laboratories are becoming more frequent.

d. Sedation. Commonly used sedatives include the benzodiazepines midazolam 1 to 2 mg IV or lorazepam 1 to 2 mg IV. Some operators use fentanyl 25 mg IV or morphine 1 to 2 mg IV for pain relief. Diphenhydramine 25 or 50 mg IV can also be used for sedation. Continuous pulse oximetry should be followed to ensure that sedation has not been excessive. In patients with tentative hemodynamics, minimizing the sedation may be imperative.

e. Radiation safety. Radiation poses a threat to laboratory personnel; therefore, every effort should be made to reduce exposure. The source is scatter from the x-ray beam originating under the table. Lead aprons (with at least 0.5-mm-thick lead lining) and thyroid collars are mandatory to minimize radiation exposure. Leaded eyeglasses and cap should also be considered. Radiation badges are worn on the lead apron and outside the thyroid collar to monitor cumulative radiation exposure. A leaded acrylic shield should be used between the patient and the operator closest to the patient. Standing further from the table reduces radiation exposure by the inverse square of the distance. A number of additional steps can be taken to minimize radiation to both the operator and the patient. Fluoroscopy and, in particular, cine time should be minimized. The image intensifier should be positioned as close as possible to the patient to reduce radiation scatter. To decrease radiation, higher magnification should be used judiciously. “Coning down” on a region of interest with the use of collimators can also reduce the amount of radiation, as can the use of lung field collimators. Right anterior oblique (RAO) views produce less radiation scatter for the operator than left anterior oblique (LAO) views. Higher cine frame rates increase radiation exposure; use of 10 or 15 frames/s produces less radiation exposure than use of 30 to 60 frames/s. In the rare situation that a pregnant patient needs catheterization, a lead apron should be used. This precaution should also be considered for premenopausal women.

VI. ACCESS SITE

A. Femoral artery. Femoral artery cannulation is the most common form of arterial access for cardiac catheterization (see Fig. 62.1). The table should allow enough movement to perform fluoroscopy of the femoral heads. Anatomic landmarks are then identified. The inguinal ligament is located. Then the femoral pulse is palpated approximately 2 cm (finger-breadths) below the inguinal ligament; this marks the site of arterial access. The use of fluoroscopy or ultrasound should strongly be considered to guide access. Fluoroscopy can be used to locate the femoral head and also the calcifications of the femoral artery (if present) when the pulse is difficult to palpate. The entry point on the skin is located over the inferior border of the femoral head. Care must be taken not to enter the artery above the inguinal ligament, because this increases the chance of retroperitoneal bleeding. Arterial entry that is too low must also be avoided, because this can lead to pseudoaneurysm or arteriovenous fistula formation. Once the site is anesthetized, an 18G Cook needle is inserted into the artery. Upon nearing the artery, a side-to-side motion of the needle indicates a position either medial or lateral to the artery. Up-and-down motion indicates correct positioning. In addition, when the needle is above the artery, it transmits the arterial pulsation to the fingertips. Once brisk arterial blood return is established, a 0.035″ J-tipped 45-cm guidewire is inserted, the needle is withdrawn, and an arterial sheath with a dilator is placed over the wire. Sheath size is dictated by the procedure being planned: generally 4 or 5F for diagnostic procedures and 6 or 7F for coronary interventional procedures.

B. Radial artery. Increasingly, operators now use the radial approach as the default approach. The radial approach has been associated with fewer bleeding complications when compared with the femoral approach and does not require a long period of immobilization of the patient afterward. It is thus also preferred by many patients. Radiation exposure and procedural time may be increased in the operator still learning this technique; however, this difference does not persist among experienced operators.

FIGURE 62.1 Landmarks for right femoral artery puncture.

To obtain vascular access from the radial site, the Allen or Barbeau test should be performed prior to radial artery catheterization to assess for ulnar flow to the palmar arch. Local anesthetic is injected. The radial site should be roughly 1 to 2 cm above the styloid process. Either an 18G angiocath needle using a "through and through" technique or a micropuncture needle (22G) using "front wall" technique is inserted at 30° to 45° into the radial artery. A sheath is advanced in the same manner as described above using the Seldinger technique. Local infusions of nitroglycerin and/or verapamil can be injected to decrease radial artery spasm. Heparin 3,000 to 5,000 IU should be given to decrease the risk of radial artery occlusion. Once access is obtained, a similar process of advancing a catheter over a guidewire is performed as in other access sites. Diagnostic and interventional procedures can be performed via the radial artery using traditional catheters (typically a JL 3.5 and JR 4) as well as a number of catheters designed specifically for radial access such as the Jacky and Tiger catheters.

C. Brachial. In certain patients, it may be desirable to perform the catheterization by a brachial approach in whom the radial and/or femoral access is not feasible. Percutaneous brachial is similar to the femoral approach described above.

D. Special situations. In patients with prosthetic femoral grafts, it may be preferable to first place a small dilator and through this advance a stiffer 0.035″ wire to facilitate sheath placement and avoid kinking at the arteriotomy. This technique is also useful in obese patients or those with significant subcutaneous scar. If a synthetic graft is old, fluoroscopy can be performed to determine if the graft is heavily calcified—a sign that it may not seal well after sheath removal. In patients with tortuous or diseased vessels, a Wholey wire or Terumo glidewire can be used to advance catheters up the aorta. If marked iliac tortuosity is present and causes inability to torque catheters, a long sheath can be used to straighten out the iliac vessel. At times, a stiffer wire can provide better support to advance catheters. In patients with an AAA for whom a femoral approach is chosen, exchange wires may be used for every change of catheter to avoid passing the wire through the aneurysm with each catheter change. The use of a softer wire (such as a Wholey wire) may prove less traumatic to the vessel, as can use of a JR 4 to direct the guidewire.

E. Catheters. The catheters commonly used for coronary angiography include the Judkins and the Amplatz systems. For the left coronary artery (LCA), the size of the Judkins left (JL) catheters ranges from JL 3.5 to JL 6. The Amplatz left (AL) catheters used commonly range in size from AL I to AL III. (Fig. 62.2 shows the shapes of the JL and AL catheters.) Similarly for the right coronary artery (RCA), the Judkins right (JR) catheters range in size from JR 3.5 to JR 6. The Amplatz right (AR) catheters commonly used range from AR I to AR III. In addition, there is also an AR-modified catheter. (Fig. 62.3 shows the shapes of the JR and AR coronary catheters commonly used.) Other catheters used

include the multipurpose catheters (multipurpose A1, A2, B1, and B2 catheters), which can be used for cannulating the LCA, RCA, and bypass grafts. For aortocoronary bypass grafts, the right or the left coronary bypass catheters may be used, although the JR 4 catheter itself may be adequate. The internal mammary artery (IMA) may be cannulated using either the IMA or the IMA special catheters, although again the JR 4 catheter may be adequate (see Fig. 62.4).

VII. TECHNIQUE

A. Engaging the vessel

1. **Left coronary artery.** Catheters are flushed with heparinized saline and passed through the sheath over a J-tipped guidewire. Using fluoroscopic guidance in the LAO projection, the left main coronary artery is cannulated, typically with a JL 4 (see Fig. 62.2). The catheter tip should be coaxial to the left main coronary artery. In patients of shorter stature, a JL 3.5 (see Fig. 62.2) catheter may be necessary, or a JL 5 or 6 in larger patients. Generally, the size of JL catheter chosen is related to the diameter of the ascending aorta (i.e., JL 5 for patients with an ascending aorta diameter of 4 cm; see Fig. 62.2). If the catheter does not engage the left main ostium easily, torqueing the catheter may help. With the JL catheters, unless the aorta is dilated and provides no hinge point for the JL catheter, counterclockwise rotation moves the catheter tip anteriorly and clockwise rotation moves it posteriorly.

FIGURE 62.2 Catheters used for cannulating the left coronary artery. AL, amplatz left; JL, judkins left. **FIGURE 62.3** Catheters used for cannulating the right coronary artery. 3DRC, no torque right coronary catheter; AR, amplatz right; JR, judkins right; Mod, modified. **FIGURE 62.4** Other catheters used for cardiac catheterization. IM, internal mammary; LCB, left coronary bypass catheter; MP, multipurpose; PIG, pigtail; RCB, right coronary bypass catheter.

Care should be taken to prevent the catheter from too deeply engaging ("deep-seating") the left main coronary artery. The pressure waveform must be observed for **damping** (a decrease in the systolic pressure) or **ventricularization** (when the waveform looks like a ventricular pressure tracing), both of which indicate a need to pull the catheter back and also raise the possibility of significant left main CAD. An adequate amount of dye reflux should be seen, unless ostial disease is present. Injection of contrast should be gentle and pressure gradually increased ("ramping"). Enough contrast should be injected to opacify the entire coronary artery and ensure reflux into the aorta. Injection force should be forceful enough to prevent "streaming," the inadequate opacification of coronary arteries that can create the illusion of stenoses. Care should be taken to inspect the injection syringe for air bubbles before each injection and to hold the syringe upright while injecting.

2. **Right coronary artery.** Catheterization of the RCA is usually performed using a JR 4 in the LAO projection (see Fig. 62.3). The RCA is usually located anteriorly in the right sinus. As the catheter is slowly pulled back 2 cm above the aortic valve, it is rotated clockwise (i.e., anteriorly) to engage. If the JR 4 does not easily engage the RCA or if the pressure dampens, ostial disease, spasm, selective intubation of the conus (which arises separately 50% of the time), or anatomic variation in the direction of the proximal RCA should be suspected. A cusp view can be taken to clarify these situations. Care should be taken

to avoid subselectively intubating the conus branch because of risk of dissection or ventricular arrhythmia.

If difficulty is encountered in engaging the RCA because of the orientation of the ostium, a 3DRC can be useful (see Fig. 62.3). An Amplatz or multipurpose catheter (see Figs. 62.3 and 62.4) can be useful for an upwardly or downwardly angled ostium or a more anterior or posterior origin. The most common cause of an incomplete LHC is a high and anterior RCA. To locate its ostium, less clockwise torque should be applied to the catheter so that it faces more anteriorly. Less dye is needed to opacify the RCA than the LCA; overinjection can cause ventricular fibrillation. Sometimes, if a catheter is tenuously engaged, particularly in the right coronary ostium, a deep breath can dislodge it and should be avoided.

3. **Left internal mammary artery (LIMA).** Catheterization of the LIMA is done either in the posteroanterior or RAO projection; in the LAO projection, the LIMA overlies the left subclavian artery and is not adequately visualized. First, the catheter (usually a JR 4 catheter or an IMA catheter; see Figs. 62.3 and 62.4) is positioned by pulling it back in the aortic arch while applying counterclockwise torque until it enters the left subclavian artery. At this point, many operators will obtain an RAO angiogram of the left subclavian artery to rule out a stenosis proximal to the LIMA and visualize the angle of take-off of the LIMA. The wire (J-tipped guidewire or Wholey wire) is then advanced into the subclavian artery. Next, the catheter is advanced over the wire into the subclavian artery, the wire is removed, and the catheter is slowly pulled back with a slight counterclockwise (i.e., anterior) rotation until it engages the ostium of the LIMA. Movements around the ostium must be gentle to reduce the risk of dissection of the vessel; frequent test injections are helpful. In addition, use of a 5F catheter will likely result in less trauma to the ostium. Turning the head to the left or right and pulling the arm caudally are maneuvers that can help engage the LIMA. If the ostium points downward at a sharp angle, the IMA or IMA special catheter provides greater angulation. If the ostium cannot be engaged successfully, a nonselective angiogram can be taken with the tip of the catheter as close to the ostium as possible. A blood pressure cuff should be inflated above systolic pressure in the left arm to facilitate dye movement down the LIMA. If radial access is preferred, left radial access provides a direct route to engage the LIMA.

4. **Right internal mammary artery (RIMA).** Catheterization of the RIMA is similar to that of the LIMA. The catheter (either JR 4 or LIMA; see Figs. 62.3 and 62.4) is placed in the innominate artery by pulling it back in the aortic arch while applying counterclockwise rotation. The wire is advanced to the right subclavian artery. Care must be taken to avoid the right carotid artery. The wire is removed and the catheter is pulled back with slight clockwise (i.e., anterior) rotation until it engages the ostium of the RIMA. If radial access is preferred, right radial access provides a direct route to engage the RIMA.

5. **Saphenous vein grafts (SVGs).** Catheterization of SVGs depends on the specific type of graft. The grafts are by necessity anastomosed to the anterior surface of the aorta. The orientation of SVGs from caudal to cranial is usually as follows: RCA, left anterior descending artery (LAD), diagonal branches of LAD, and marginal branches of left circumflex coronary artery (LCX). In the LAO view, grafts to the RCA usually point to the patient's right, whereas grafts to the left system are usually oriented more to the patient's left. It is the practice of some surgeons to place circular graft markers around the ostia of the vein grafts on the outer surface of the aorta. Injections into presumed vein graft stumps should be forceful to ensure that the graft is truly occluded, as opposed to poor opacification from a tenuously

engaged catheter. ***Review of the operative note is mandatory before catheterization to know where grafts were placed***. In particular, it should be noted whether any LIMA or RIMA grafts are in situ or free (attached to the aorta). A previous catheterization, if done, should be reviewed. Particular attention should be paid to the location of the grafts. The relative relationship with surgical clips should be noted, along with review of any chest computed tomography (CT) scans, because this will save time and effort in finding grafts during the catheterization. If a graft cannot be found or a stump identified during a catheterization, an aortogram can be performed (see Section VI.E).

a. **SVG to RCA.** Engaging this graft can be as simple as pulling back on the JR 4 as it sits in the ostium of the RCA while in the LAO projection. Often, this graft has a steep downward orientation from the aorta. In this situation, a multipurpose catheter can be useful in engaging the graft. Alternatively, a right bypass catheter or a right-modified Amplatz catheter can be useful in engaging the RCA graft.

b. **SVG to LAD.** The graft to the LAD is most easily engaged in the RAO view (in which the graft will point anteriorly, or to the right side of the screen). It may be necessary to move the catheter up and down along the anterior surface of the aorta several times. Left bypass, left Amplatz, and multipurpose catheters are all alternative catheters that can be used.

c. **SVG to LCX.** To engage this graft, it is necessary to withdraw the catheter from the SVG to the LAD by pulling back, while remaining in the RAO projection. If the catheter does not fall into place, clockwise rotation of the JR 4 at an area cranial to the SVG to LAD graft ostium may locate the LCX graft. The technique is otherwise similar to that for engaging the graft to the LAD.

B. Imaging the vessels

1. **Normal coronary anatomy.** The left main coronary artery originates from the left coronary cusp and bifurcates into the LAD and an LCX, although it sometimes trifurcates to include a ramus intermedius. The LAD courses along the anterior interventricular groove, supplying numerous septal perforators and a variable number of diagonal branches to the anterolateral wall of the left ventricle before it continues to the apex. The LCX courses along the left atrioventricular (AV) groove, providing a variable number of marginal branches to supply the lateral wall. In some institutions, the first marginal branch is called the high lateral branch of the circumflex, with subsequent branches called lateral or posterolateral branches depending on their destination. The LCX continues in the AV groove for a variable distance. In patients in whom the LCX is dominant (see subsequent text), the LCX reaches the posterior interventricular groove and gives rise to a posterior descending artery (PDA) branch.
The RCA originates from the right coronary cusp and courses along the right AV groove, providing atrial branches (to the right atrium) and marginal branches (to the right ventricle). A conus branch originates as the first branch from the proximal RCA to supply the right ventricular outflow tract; about half of the time, this branch has a separate ostium. It is usually unnecessary to visualize a separate conus branch, unless collaterals to the LAD are suspected. The RCA gives off a branch to the sinus node about 60% of the time (otherwise a left atrial branch of the LCX serves this function). The first major branch the distal RCA gives off is the PDA, in a right dominant system. **Dominance** refers to which artery gives off a PDA and supplies the posterior part of the heart. In about 85% of patients, this will be the RCA; in 7%, the RCA and LCX will be codominant; and in another 8%, the LCX will be dominant. The

PDA courses along the inferior interventricular groove, providing septal perforators to supply the inferior septum. After giving off a PDA, the RCA continues as a posterolateral segment supplying a variable number of posterior ventricular branches. From this posterolateral segment, the RCA usually (90% of the time) provides a branch to supply the AV node.

2. **Basic principles.** Several views of the coronary arteries are required to prevent excessive overlap of vessel segments and to delineate the severity of stenoses. A general principle that is useful is that in an RAO view, the spine is on the left of the screen and conversely, in an LAO view, the spine is on the right of the screen. Cranial views bring the silhouette of the diaphragm into the field of view. The diagonal and obtuse marginal branches tend to move in synchrony, because they supply the lateral aspect of the heart, whereas the LAD is located on the anterior portion of the heart. The AV continuation of the LCX lies in the AV groove, and (in patients with sinus rhythm) it has an "atrial kick" to it. This type of atrial kick can also be seen in atrial branches from either the LCX or the RCA. In the RAO view, a diagonal branch, and not the LAD itself, usually lies on the heart border. In the LAO view, the LAD runs along the border of the heart silhouette, not the diagonal branches. Caudal angulation tends to move posterior vessels (such as the posterolateral branches of the RCA or the obtuse marginal branches of the LCX) inferiorly. Cranial angulation tends to move posterior vessels superiorly.

   Panning motion should be smooth and slow. It is best to wait for two to three systolic cycles and focus on proximal vessels before panning down the length of the artery of interest. It is important to pan to look for collaterals.

3. **Different views** (see Figs. 62.5 to 62.11)

a. **Left coronary artery.** There is wide variation in the sequence of views obtained. Many operators start with a posteroanterior view and focus on the left main coronary artery, sometimes with a coned-down view to improve resolution. The problem with a pure posteroanterior view is that there is significant overlap with the spine. Therefore, a little bit of RAO angulation ("shallow RAO") can be used to get the coronaries off the spine. A steeper amount of RAO provides greater separation of the LAD from the LCX. A slight amount of caudal angulation can be used to decrease the foreshortening of the proximal circumflex in the straight RAO view and to place the diagonals below the LAD. Therefore, a **20° RAO, 20° caudal** is often the first view, displaying the entire left coronary system. This view also provides a good view of the proximal LCX and of the origin of a ramus intermedius branch, if present. The contour collimator (called the wedge or the shield) should be moved to the upper right of the screen over the lung fields. A **30° RAO, 25° cranial** view can be used to separate the diagonals from the LAD, placing them above the LAD. A posterior–anterior view (PA) with **40° cranial** angulation can be useful in viewing the mid and distal portions of the LAD. The **45° LAO, 30° cranial** view is good for separating the LAD from its diagonal branches, especially for vertically oriented hearts. There should be enough LAO angulation to position the LAD off the spine. This view can also be good for a left-sided PDA branch. Steeper degrees of LAO further separate the LAD from the LCX and move the LCX off the spine, but they can also cause the origins of the diagonals to overlap the LAD and cause the distal LAD to overlap the diaphragm. The **45° LAO, 30° caudal** ("spider" view) is useful for looking at the left main coronary artery and its bifurcation. The proximal LAD is typically foreshortened, unless the heart is horizontal in orientation. There must be enough LAO to get the cardiac silhouette off the spine. Minimal to no panning is required.

FIGURE 62.5 Posteroanterior view of left coronary artery. LAD, left anterior descending artery; LCX, left circumflex coronary artery; LMCA, left main coronary artery; OM_1, obtuse marginal branch 1; OM_2, obtuse marginal branch 2; OM_3, obtuse marginal branch 3.
FIGURE 62.6 Right anterior oblique caudal view of left coronary artery. LAD, left anterior descending artery; LCX, left circumflex coronary artery; LMCA, left main coronary artery; OM_1, obtuse marginal branch 1; OM_2, obtuse marginal branch 2; OM_3, obtuse marginal branch 3. **FIGURE 62.7** Left anterior oblique cranial view of left coronary artery. LAD, left anterior descending artery; LCX, left circumflex coronary artery; LMCA, left main coronary artery.
FIGURE 62.8 Left anterior oblique caudal view of left coronary artery. LAD, left anterior descending artery; LCX, left circumflex coronary artery; LMCA, left main coronary artery.
FIGURE 62.9 Right anterior oblique cranial view of left coronary artery. LAD, left anterior descending artery; LCX, left circumflex coronary artery; LMCA, left main coronary artery.
FIGURE 62.10 Left anterior oblique view of right coronary artery. PDA, posterior descending artery; PV, posteroventricular; RCA, right coronary artery. **FIGURE 62.11** Right anterior oblique view of right coronary artery. PDA, posterior descending artery; PV, posteroventricular; RCA, right coronary artery.

b. Right coronary artery. The RCA is usually viewed in LAO and RAO views. The **30° RAO** view provides a good view of the mid-RCA and also of the PDA, which is laid out lengthwise. The **40° LAO** view provides a good view of the proximal and mid-RCA and, if cranial angulation is added, a good view of the posterolateral arteries. The **PA with 30° cranial** can provide a useful view of the origins of the PDA and posterolateral branches at the distal RCA bifurcation.

c. Bypass grafts. An LAO view and an RAO view are required to visualize the body of the graft. Additional views are dictated by the grafted vessel. A particularly useful view for the LIMA–LAD anastomosis is the lateral view; cranial LAO and cranial RAO views can also be useful. The graft to the diagonal can be visualized in the cranial LAO and cranial RAO views. The graft to the marginal branch can be seen in the RAO and lateral views. The graft to the distal RCA can be visualized in the cranial LAO and lateral views.

4. Congenital coronary artery anomalies. Coronary artery anomalies should be suspected if there is an absent coronary artery and a large area of myocardium that appears unperfused. The most common anomaly is an absent left main coronary artery trunk, in which the LAD and the LCX have separate ostia (incidence 0.47%). If the LAD is first cannulated, the LCX can be engaged with a clockwise rotation; sometimes one size larger catheter (JL 5) is needed. Likewise, if the LCX is first cannulated, counterclockwise rotation, perhaps with a smaller-sized catheter (JL 3.5), is needed to engage the LAD. Other common anomalies in order of occurrence are the LCX originating from the right sinus of Valsalva or the ostium of the RCA (0.45%) and the RCA originating from the ascending aorta above the sinus of Valsalva (0.18%). The RCA originating from the left sinus of Valsalva is the next most common anomaly, originating superior and anterior to the left main (0.13%).

The origin of the left main artery from the right sinus is even less common (0.02%), but it can result in sudden death if the left main artery passes between the aorta and the pulmonary artery (extremely rare). The left main artery can also pass into the ventricular septum (most common), anterior to the pulmonary artery or posterior to the aorta. The 30° RAO view can help define the relationship between the coronary artery and the great vessels. If the course is septal, septal perforators can be seen originating from the left main. The Amplatz (left or right, depending on the cusp of origin) and multipurpose catheters are especially useful in cannulating anomalous coronary arteries.

Although not truly a congenital anomaly, every angiographer should be aware of **myocardial bridging**. This is an apparent narrowing of a coronary artery (usually the mid-LAD) that is present only during systole. There have been reports of bridging involving the diagonal branches of the LAD, the marginal branches of the LCX, and the distal RCA. Because the majority of coronary blood flow occurs during diastole, myocardial bridges are rarely pathologic. Nitroglycerin, by dilating epicardial vessels, can make bridging seem even more pronounced. A phenomenon similar to bridging can occur in hypertrophic obstructive cardiomyopathy, in which septal perforators from the LAD become obliterated during systole.

5. **Quantification of coronary stenosis.** It is important to always obtain at least two perpendicular views of each coronary artery lesion. A single view, or even multiple views, can miss an eccentric lesion. Severity of a lesion is based on percent diameter stenosis compared with a "normal" reference segment. Lesions are generally classified as severe if 70% or more narrowed in the LAD, LCX, and RCA or 50% or more in the left main artery. When measuring the size of vessels and stenoses, it is useful to note that a 6F catheter has an external diameter of 2 mm. Formal quantitative coronary angiography or use of calipers can improve the measurement of coronary artery stenoses. Quantitative coronary angiography decreases the interobserver and intraobserver variabilities of grading stenosis severity.

6. **Limitations of coronary angiography.** Sometimes the severity of a lesion is difficult to gauge based on visual angiographic estimates alone, particularly in the presence of diffuse disease. Angiography only provides an outline of the lumen, the so-called luminogram. In addition, the angiogram can underestimate the presence of atheroma because of outward remodeling of the arterial wall (the Glagov phenomenon). Furthermore, angiography can only visualize arteries >200 μm in diameter. The physiologic importance of 40% to 70% stenoses cannot be determined by angiography alone, and flow limitation should be demonstrated before percutaneous intervention. Techniques such as intravascular ultrasound and determining the fractional flow reserve can aid in determining whether ambiguous lesions on angiography are significant. See Chapter 63, Percutaneous Coronary Intervention, for more details on these adjunct techniques of imaging and diagnosis.

C. Crossing the aortic valve

1. **Normal aortic valve.** The pigtail catheter is most commonly used to cross native aortic valves. Tissue valves can also be crossed, but crossing mechanical valves (e.g., St. Jude, Björk-Shiley, and Medtronic-Hall) risks catheter entrapment and is best avoided. The catheter should be viewed as a "9" in the ascending aorta in the RAO projection and then advanced to loop above the aortic valve to form a "9" shape. When pulled back very slowly, the catheter should fall into the commissure and it can then be rapidly advanced into the left ventricle during systole with the aid of the J-wire placed in the pigtail loop. Having the patient take a deep breath and hold it while the pigtail catheter is being unlooped can facilitate the

passage of the catheter into the left ventricle. Sometimes the guidewire itself may be useful in crossing the valve, in which case the catheter is simply advanced over the guidewire into the left ventricle.

D. Aortic stenosis. In more severe cases of aortic stenosis, difficulty may be encountered in passing any catheter across the aortic valve. In this circumstance, a 0.035″ straight-tipped wire along with a 5F AL1 diagnostic catheter can be used to cross the valve. If this method is elected, some operators recommend a 5,000 IU bolus of heparin. The timer should be started, and not more than 3 to 4 minutes should be allowed per attempt at crossing to avoid clot formation. Between each attempt, the wire should be withdrawn and wiped, blood aspirated and discarded, and the catheter flushed. Special care must be taken during this maneuver to avoid perforating the aortic cusps or potentially dissecting the coronary ostia. The combination of a Feldman catheter and a Rosen wire is an alternative approach to cross stenotic aortic valves.

E. Left ventriculography

1. **Set-up.** The pigtail catheter (commonly the angled version) is positioned in the mid-cavity of the left ventricle. The pigtail catheter should look like a "6" in the RAO projection. If the pigtail catheter twists with each beat, this indicates that it is caught in the mitral valve apparatus and needs to be repositioned. The monitor should be observed for ectopy. Once a stable rhythm is present, ventriculography can proceed. First, the left ventricular end-diastolic pressure (LVEDP) should be measured on a 40 scale. In patients with an elevated LVEDP (>25 mm Hg), a left ventriculogram is generally contraindicated. If the decision to proceed with the left ventriculogram is made, sublingual nitroglycerin should first be given to lower the LVEDP. Digital subtraction can be used instead of cinefluoroscopy to obtain the left ventriculogram. This allows a smaller amount of contrast to be used, although this may not allow proper assessment of MR if that is necessary. With digital subtraction, the view must be carefully centered because panning is not possible. **The left ventriculogram is best avoided in patients with critical aortic stenosis, significant left main artery disease, or severe left ventricular dysfunction. Ventriculography should not be attempted with a single end-hole catheter because of the risk of cardiac perforation, ectopy, and poor-quality images.**

2. **Views.** The **30° RAO** view is used to look at the overall left ventricular function. In particular, the anterior, apical, and inferior walls can be assessed (see Fig. 62.12). The RAO view is also useful to assess **MR**. The regurgitation is graded on a scale of 1 to 4; 1 represents trace MR, with mild left atrial opacification that clears with one beat; 2 represents a mild to moderate degree of opacification, although less than that of the left ventricle; 3 represents moderate to severe opacification of the left atrium equal to that of the left ventricle; and 4 represents severe MR with complete opacification of the left atrium greater than that of the left ventricle. Panning toward the left atrium may be needed if MR is present. The catheter itself can cause MR if it is caught in the mitral valve apparatus or if it induces premature ventricular contractions. The correlation between angiographic and echocardiographic MR is excellent. The **60° LAO** projection allows evaluation of the septum and the posterior and lateral walls (see Fig. 62.13). Ventricular septal defects are best identified in the LAO projection with slight cranial angulation. If biplane imaging capability exists, RAO and LAO views of the left ventricle can be obtained simultaneously.

3. **Settings.** For a ventriculogram, the flow injector can be set at a rate of 10 to 12 mL/s for a total volume of about 25 to 30 mL, with a rate rise of 0.2 second (to minimize ectopy and to keep the catheter from moving abruptly) and a pressure of 600 PSI. The exact settings will vary depending on the size of the heart and the need to limit contrast.

F. **Aortography.** Aortography is usually performed in the LAO position, with the catheter about 2 cm above the aortic leaflets. Compared with a ventriculogram, a larger volume of contrast is needed to opacify the aorta. The flow injector is set to a higher total volume than for the left ventriculogram, usually about 30 to 45 mL at a rate of 15 to 20 mL/s. No rate of rise is necessary, and a pressure limit of 900 to 1,200 PSI is used. **Aortic insufficiency** can be identified with a grading system similar to that of MR; 1 represents trace aortic insufficiency that clears from the left ventricle with each beat; 2 represents mild left ventricular opacification that takes more than one beat to clear; 3 represents moderate left ventricular opacification equal to that of the aortic root; and 4 represents complete opacification of the left ventricle greater than that of the aortic root. Diseases of the aorta such as aneurysms or dissection can be identified. An aortogram can aid in visualization of anomalous coronary arteries or grafts that are difficult to engage; however, the absence of filling of a bypass graft on an aortogram does not exclude its presence. The aorta must be completely opacified to ensure that grafts are seen. Left coronary grafts are best seen in the RAO projection, and right coronary grafts in the LAO projection.

A descending aortogram can be performed with the pigtail catheter placed in the descending aorta slightly. A JR 4 can be used to obtain selective renal arteriograms by turning the tip of the catheter so that it points to either the left or the right in the posteroanterior view. The catheter is then gradually pulled back when it is in the vicinity of the renal artery ostia until it engages. Common and external iliac angiography is usually performed in either the anteroposterior or contralateral projections.

Carotid angiography is sometimes necessary to confirm the degree of carotid artery stenosis seen on a noninvasive study. A variety of catheters (the Headhunter and Newton series) can be used to selectively cannulate the common carotid artery, although often the routine JR 4 catheter is adequate and advanced to the proximal vessel over a soft wire (i.e., Wholey wire). These catheters are advanced to the aortic arch over a guidewire and pulled back to engage the artery of interest. There is up to a 0.5% to 1% risk of stroke with this procedure. Digital acquisition and use of nonionic contrast are mandatory.

FIGURE 62.12 Thirty-degree right anterior oblique view of the left ventricle. **FIGURE 62.13** Sixty-degree left anterior oblique view of the left ventricle.

G. **Pharmacologic testing.** In patients in whom coronary artery spasm is suspected, intravenous methylergonovine can be given to provoke spasm. Once significant angiographic stenosis has been ruled out, 0.05 mg of intravenous methylergonovine is administered. If the patient develops his or her typical chest pain or ST-elevation on electrocardiographic monitoring, the coronary arteries are catheterized immediately. The electrocardiographic changes can help determine which coronary artery to cannulate first. If there are no electrocardiographic changes or chest pain, the right coronary artery (which is statistically more likely to have spasm) and then the left coronary artery should be reimaged 5 minutes after methylergonovine has been administered. A positive response consists of a focal area of spasm that is relieved by intracoronary nitroglycerin (a usual dose of 100 to

200 μg). Diffuse spasm can be physiologic and is also managed with nitroglycerin and verapamil (also 100 to 200 μg). Because the half-life of methylergonovine is longer than that of sublingual nitroglycerin, it is important to realize that spasm can recur after a dose of nitroglycerin. If the initial dose of methylergonovine does not provoke a response, an additional dose of 0.2 mg can be given a few minutes after the first. Alternatively, some operators prefer giving a single dose of 0.2 mg.

Intracoronary vasodilators such as nitroglycerin are often used in the assessment of coronary anatomy. For example, if the operator is unsure if what appears to be ostial disease of a coronary artery may in fact be catheter-induced ostial spasm, an intracoronary injection of nitroglycerin and repeat angiography can help clarify. For more on the use of intracoronary vasodilator therapy (including nitroglycerin, nitroprusside, and adenosine) in the assessment and treatment of CAD, please see Chapter 65, Transthoracic Echocardiography.

VIII.POSTCATHETERIZATION CARE

A. Sheath removal (femoral). The sheath is removed once the procedure is complete. After the sheath is removed, hemostasis is generally obtained with direct manual pressure of the fingertips over the pulse, without sterile gauze to obscure the view. Pressure is held for approximately 20 minutes (about 3 minutes for each French size) until there is no bleeding. Manual pressure remains an important technique because of low cost, good safety profile (complication rate <0.23%), short learning curve, and ability to be employed despite femoral artery dissection, significant peripheral vascular disease, or a low stick. To shorten the time of manual pressure, hemostatic pads can be used. These products are impregnated with a procoagulant mixture that causes local vasoconstriction and potentiates clot formation. Care must be taken to intermittently allow adequate blood flow to the distal extremity. It is, therefore, best if one can directly visualize the extremity to assess its color. In patients with severe aortic stenosis or significant left main CAD, laboratory personnel should be prepared to rapidly manage a vagal episode, which can be life threatening in these situations. Adequate administration of anesthesia before removal of the sheath decreases the chance of a vagal reaction.

Bed rest is generally required for 4 to 6 hours after a femoral sheath is removed, although some operators require 1 hour for each French size. Two hours of keeping the arm straight is necessary after a brachial. During the postprocedure observation period, it is necessary to monitor the HR, temperature, blood pressure, urine output, distal pulses, and the access site (for pain, bleeding, or hematoma). Using sandbags over the groin site is discouraged. Before discharge, it is best to have the patient ambulate under observation. Specific discharge instructions should include the possibility of late access site bleeding and the need to hold pressure and call for emergency help.

Intravenous fluids are often given after a cardiac catheterization. The osmotic load of the contrast dye can cause a large diuresis. Intravenous fluids (e.g., normal saline at 100 mL/h for several hours) can prevent volume depletion. Care should be taken in patients with a history of congestive HF, in whom liberal intravenous fluids could contribute to pulmonary edema.

B. Sheath removal (radial). Radial artery hemostasis is generally performed by using one of the designed compression bands such as TR Band (Terumo) or RadiStop (St. Jude Medical). The band is secured snuggly around the arteriotomy site prior to sheath

removal. The sheath is slowly removed simultaneously as the band is tightened/inflated. The band pressure is adjusted to the minimum pressure needed to obtain hemostasis so that distal flow is not obstructed, a term coined "patent hemostasis." This technique lowers the risk of radial artery occlusion after the procedure. Palpating a radial artery pulse distal to the band after placement and monitoring flow during compression with the use of a pulse oximeter placed on the thumb are important steps used to ensure adequate palmar arch flow during compression. The band pressure is slowly lessened over a period of time (beginning typically 60 to 90 minutes after placement) to ensure hemostasis has occurred. If radial spasms occur, more analgesia/sedation or intra-arterial nitroglycerin (0.2 mg) can be given prior to sheath removal to improve patient comfort.

C. Compression/vascular closure devices. The use of femoral artery closure devices offers the advantages of improved patient comfort, early sheath removal, early hospital discharge, and the ability to continue anticoagulation in certain patients. There are a number of currently available products that include compression devices such as the FemoStop (RADI Medical Systems), percutaneous sutures (Perclose; Abbott), nitinol clip (StarClose; Abbott), extravascular collagen implant (Angio-seal; St. Jude Medical), and gel/sealant based (Mynx; Cardinal Health, and Exoseal; Cordis). Many other types of closure devices are currently under investigation and are likely to be available in the near future.

1. The **FemoStop** is a pneumatic compression device that can be used for holding pressure in cases of prolonged bleeding. The **C clamp** is a mechanical clamp that can also be used for holding prolonged pressure. If either of these devices is employed, direct supervision of the patient is required.
2. The **Perclose** (Abbott) is a percutaneous vascular suture device that allows immediate ambulation (of course, after the effects of any sedation given during the procedure have worn off). Before its use, a femoral artery should be taken to ensure that the sheath has been placed above the femoral artery bifurcation. The device is currently available in 6, 8, and 10F sizes. The Perclose also allows for preclosure in large-bore access.
3. The **StarClose Vascular Closure System** (Abbott) is a percutaneous vascular closure device that employs a nitinol clip. Before its use, a view of the femoral artery should be taken to ensure that the sheath has been placed above the femoral artery bifurcation. The device is delivered through a sheath onto the arteriotomy site, and the clip takes hold of the tissue in a circular manner and closes off the arteriotomy site.
4. The **Angio-seal** (St. Jude Medical) hemostatic puncture closure device can be used to obtain hemostasis in an uncomplicated femoral. Before deploying the Angio-seal, it is advisable to obtain an angiogram of the femoral artery to ensure that the entry site of sheath is above the bifurcation of the common femoral artery. It is available in 6 and 8F sizes. A biodegradable collagen plug is deployed at the femoral artery puncture site using a guidewire and special sheath. No manual pressure is required, and ambulation can begin after 1 hour. The disadvantage of this device is the introduction of foreign material that could be a potential source of infection, and repeat arterial puncture cannot be performed at the same site for about 45 to 60 days.
5. The **Mynx** (Cardinal Health) delivers a polyethylene glycol sealant that dissolves over 30 days. The Mynx does not require a sheath/catheter exchange because it

remains in the extravascular space. The **Exoseal** (Cordis) uses a similar method with a polyglycolic acid plug.

IX.COMPLICATIONS

A. Death. There is a 0.1% risk of death from LHC. This risk is substantially higher in patients undergoing urgent catheterization for acute coronary syndromes. In addition, patients with left main CAD, severe aortic stenosis, or severe left ventricular dysfunction are known to be patient subgroups with a particularly increased risk. Advanced age increases the risk of death.

B. Myocardial infarction. There is a 0.05% risk of MI from LHC. MI can result from coronary dissection, disruption of a preexisting atheromatous plaque, and a large air embolus or a thrombus. Patients with acute coronary syndromes have a higher risk of MI.

C. Stroke. Stroke occurs in 0.05% of catheterizations. There is a risk of stroke from an inadvertent air embolus or thrombus. The presence of aortic atheroma is a risk factor for embolic complications. Dislodgement of atheromatous debris in the aorta can lead to a stroke. This risk can be minimized by the use of 260-cm exchange wires for catheter changes in patients with known aortic disease.

D. Coronary artery dissection. Engagement of the coronary arteries can rarely cause dissection. It is most often due to the injection of contrast through a catheter that is not coaxial to the coronary artery, causing rupture of a preexisting plaque, or placement of the catheter too deeply into the coronary artery. Particular caution should be used with Amplatz catheters.

E. Coronary artery spasm. Engagement of the coronary arteries, in particular the RCA, can cause spasm. This is best treated with withdrawal of the catheter. Subsequent reengagement and administration of intracoronary nitroglycerin (100 to 200 µg) may also be necessary for more rapid resolution of spasm.

F. Renal failure. Contrast dye can precipitate renal failure in any patient, although certain patients (those with elevated creatinine, diabetes, proteinuria, or dehydration) are at higher risk. Adequate prehydration with normal saline can reduce this risk. In some cases (especially in diabetics with renal insufficiency and those with renal artery stenoses), patients may need to be admitted to the hospital for hydration for several hours before the LHC to minimize risk of contrast-induced nephrotoxicity. Numerous agents have been studied to lower the risk of contrast-induced kidney injury; however, results are conflicting. **The best way to minimize contrast-induced renal failure is to limit the amount of contrast used**. Biplane cineangiography can maximize the amount of information obtained with each view.

G. Emergency CABG. There is a risk of needing emergency CABG as a complication of the catheterization (e.g., dissection of the left main coronary artery). There is also the possibility of identification of critical disease, such as severe left main CAD, that may prompt emergency CABG as the most expedient treatment.

H. Arrhythmias. A risk of ventricular fibrillation (0.5%) exists with catheterization. This rhythm is treated with electrical defibrillation. In particular, overinjection of contrast into the RCA can cause ventricular fibrillation. Contrast dye (less, so nonionic dye) can cause transient bradycardia, best dealt with by having the patient cough and by minimizing the amount of dye injected with each angiographic procedure.

I. **Heart failure.** The osmotic load of contrast dye can put a patient with diminished cardiac or renal function into overt pulmonary edema. In patients with severe cardiac or renal disease, injection of contrast should be limited.

J. **Vagal reaction.** If a patient develops hypotension and/or bradycardia, a vagal reaction should be considered. It is a common occurrence when local anesthetic is being administered or when the sheath is being removed. Adequate anesthesia can help prevent such reactions. In a patient with severe aortic stenosis or left main CAD, a vagal reaction can be life threatening.

K. **Vascular**

1. **Femoral.** Pseudoaneurysms, arteriovenous fistulas, arterial thrombosis, and peripheral emboli are possible vascular complications. Careful technique can minimize these events. In particular, paying attention to puncture location and obtaining adequate hemostasis after sheath removal are the best ways to decrease vascular complications. Bruits should be auscultated both before and after the procedure. A new bruit may indicate a vascular complication. **Ultrasound** is an essential part of managing groin complications. If there is a large pseudoaneurysm present, surgery may be required after a trial of ultrasound-guided compression. Percutaneous injection of thrombin into the pseudoaneurysm has proven to be a more effective alternative to compression. Small pseudoaneurysms (<2 cm) tend to close spontaneously but should be followed by serial ultrasound examinations. An arteriovenous fistula that does not close spontaneously in 2 to 4 weeks may require surgical repair.
2. **Radial.** For a radial approach, an Allen or Barbeau test must be performed to assess the patency of collateral ulnar circulation in the event of radial artery occlusion. The risk of radial artery occlusion is very low if measures are taken to prevent the same including the use of heparin, small sheath sizes, and patent hemostasis.

L. **Bleeding.** Access site bleeding can be significant. If there is a great deal of oozing around the sheath, it can be exchanged for a sheath 1F size larger. Adequate manual pressure is usually sufficient to stop bleeding after sheath removal. It is a typical practice to check the activated clotting time in patients who had been on heparin before the procedure and only proceed with sheath removal if the clotting time is below 160 seconds. Some institutions use protamine (1 mg/100 IU heparin) to reverse heparinization, but this exposes the patient to the potential for allergic reactions to protamine (namely, hypotension). A feared complication is **retroperitoneal bleeding**. If a patient complains of severe back pain after a catheterization, this should be considered. An unexpected drop in hemoglobin after a catheterization should also raise this possibility. Obese patients, in particular, can have a major bleed without obvious external signs. Noncontrast CT scan of the abdomen and pelvis can diagnose a retroperitoneal bleed, but it is important to assess the patient's clinical stability before sending them to such a study. Patients who have developed a documented retroperitoneal hematoma or are suspected of having this complication are monitored closely in an intensive care unit, often with continuous blood pressure assessment using an arterial line, and receive aggressive volume resuscitation with fluids and blood products until self-resolution with reversal of anticoagulation or definite treatment.

Bleeding and vascular complications are lower with the radial approach compared with the femoral approach. When a hematoma occurs, it can be subtle and can occur more proximally in the arm because of wire perforation of a small artery during sheath or catheter insert. An elastic wrap or blood pressure can be applied to assist in compression.

M. Infection. There is a risk of infection, as with any invasive procedure. This risk can be minimized with proper attention to sterile technique. There is usually no need for prophylactic antibiotics. However, some operators do give antibiotics after use of a percutaneous vascular suture device in patients who are at elevated risk for infection, such as obese or diabetic patients. Endocarditis prophylaxis for patients with valvular heart disease or prosthetic valves is unnecessary.

N. Neuropathy. There is a slight risk of damage to the femoral nerve from inadvertent puncture. Femoral hematoma (or retroperitoneal bleeding) can also cause compromise of the femoral nerve. Function usually improves with time, but complete recovery can take several months.

O. Allergy. As discussed above, contrast dye can cause adverse reactions, ranging from hives to anaphylaxis. Severe anaphylactoid reactions to contrast dye occur in about 0.1% of cases and less with newer nonionic contrast agents. Local anesthetics can also cause reactions because of specific allergies to the amide or ester component or to the preservative.

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CHAPTER 63

Percutaneous Coronary Intervention

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I.INTRODUCTION

A. Coronary atherosclerosis may result in a flow-limiting stenosis that leads to myocardial ischemia and/or myocardial infarction (MI). Andreas Gruentzig first managed these lesions percutaneously on September 16, 1977, when he advanced a fixed-wire, distensible balloon across a stenosis in the mid–left anterior descending (LAD) artery and briefly inflated it to 6 atm (90 psi). This procedure was termed percutaneous transluminal coronary angioplasty (PTCA). With the advent of stents and other therapeutic coronary devices, these procedures are now more broadly termed percutaneous coronary intervention (PCI). It is estimated that more than 1 million PCI procedures are completed in the United States and approximately 2 million worldwide annually.

B. The field of interventional cardiology continues to evolve rapidly, as a result of many important advances in equipment, strategies, and adjunctive medication. These advances have been paralleled by a concomitant improvement in the safety and efficacy profile of PCI. The assimilation of a large body of basic and clinical research encompassing all areas of interventional cardiology continues to redefine the standard of care paradigm.

II.PCI INDICATIONS

A. **Central tenet.** Although there is no substitute for sound clinical judgment, PCI is generally reserved for patients in whom there is an **objective demonstration of substantial myocardial ischemia or symptoms as well as angiographic demonstration of obstructive coronary disease**. PCI may not be indicated for asymptomatic or mildly symptomatic patients who have only a small area of viable or jeopardized myocardium, have no objective evidence of myocardial ischemia, have other life-limiting disease processes, or have lesions that have a low likelihood of success (Tables 63.1 and 63.2).

B. **ST-segment elevation myocardial infarction (STEMI). Primary PCI should be the preferred treatment strategy for patients presenting with STEMI to a facility experienced with and capable of performing PCI.** Randomized trials have demonstrated that clinical outcomes are improved when such patients are emergently transferred to centers able to perform primary PCI as opposed to therapy with thrombolytics—despite a significant delay (mean time of 44 minutes) in time to therapy because of transport. This seems especially true of patients presenting 3 to 12 hours after symptom onset, where the superiority of primary PCI becomes clearly evident. In those presenting within 3 hours of

symptom onset, mortality data would suggest that either therapy is equally efficacious in appropriate candidates. **For a more thorough discussion of the management of STEMI, please refer to Chapter 1.**

C. **Non–ST-segment elevation acute coronary syndrome (NSTEACS).** Unstable angina and non–ST-segment elevation myocardial infarction (NSTEMI) are considered part of the spectrum of NSTEACS. Given that individual patients presenting with unstable angina/NSTEMI are at widely varying risk for subsequent morbidity and mortality, early and aggressive risk stratification including cardiac catheterization with subsequent percutaneous or surgical revascularization (rather than noninvasive stress testing) is recommended. This recommendation is supported by a number of clinical trials comparing an early invasive to delayed conservative strategy. **For a more thorough discussion of the management of NSTEACS, please refer to Chapter 2.**

TABLE 63.1 Standard PCI Evaluation

History
• Symptoms (angina, dyspnea, paroxysmal nocturnal dyspnea, syncope)
• Previous MI
• Previous cardiac interventions (PCI, CABG)
• Comorbidities (diabetes mellitus, hyperlipidemia, hypertension, etc.)
Medications (glucophage, statins, aspirin, thienopyridines, etc.)
Allergies (contrast dye, latex, etc.)
Physical examination (murmurs, jugular venous pressure, pulses, bruits, edema)
Laboratory data (creatinine, potassium, hemoglobin, platelets, INR)
Other tests (ECG, echocardiogram, stress tests)
Informed consent including risks, benefits, alternatives

D. CABG, coronary artery bypass grafting; ECG, electrocardiogram; INR, international normalized ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

TABLE 63.2 Considerations for Every PCI

Review clinical and angiographic risk factors
Develop strategy and anticipate problems
Surgical backup
Access
Anticoagulation and antiplatelet therapy
Consider diagnostic adjuncts (e.g., PA line)
Consider therapeutic mechanical adjuncts (e.g., IABP)

TABLE 63.2 Considerations for Every PCI
Guidewire
Device (e.g., angioplasty, stent)
Closure of vascular access site
Post-PCI destination (telemetry ward, CICU)

E. CICU, cardiac intensive care unit; IABP, intra-aortic balloon pump; PA, pulmonary artery; PCI, percutaneous coronary intervention.

F. Chronic stable angina. A significant proportion of all PCI procedures are performed in the elective setting for chronic stable angina. Whereas recent trials have questioned the mortality benefit of PCI or coronary artery bypass grafting (CABG) over optimal medical therapy in stable coronary artery disease (CAD), revascularization still remains the most rapidly effective treatment strategy for patients with angina. **For a more thorough discussion of the management of stable CAD, please refer to Chapter 6.**

III. CONTRAINDICATIONS. The only absolute contraindication to PCI is **significant active bleeding**, given the absolute need for procedural anticoagulation and continued dual antiplatelet therapy (DAPT). Relative contraindications include a bleeding diathesis, unsuitable or high-risk coronary anatomy (e.g., chronic total occlusion in the absence of ischemia or diffuse distal disease), recurrent in-stent restenosis (ISR), and a short life expectancy because of a comorbid condition.

IV. PROGNOSIS. A patient's clinical status and coronary angiogram are powerful predictors of outcome. Certain clinical and angiographic variables have repeatedly been associated with adverse events (Table 63.3).

V. ANGIOGRAPHIC/PROCEDURAL/CLINICAL SUCCESS. Angiographic success is defined as a residual stenosis <50% with PTCA or <20% with stenting with thrombolysis in myocardial infarction (TIMI) 3 flow and is achieved in 96% to 99% of patients. The definition of procedural success is angiographic success without major in-hospital complications (i.e., death, CABG, or MI). Clinical success is defined as procedural success with relief of the symptoms and signs of myocardial ischemia.

VI. Complications

A. The incidence of complications (death 0.5% to 1.4%, periprocedural MI, and emergency CABG surgery 0.2% to 0.3%) has consistently decreased over the past 20 years with the advent of stents, new and more effective antiplatelet therapies, improved equipment, and increasing reliance upon evidence-based strategies.

B. Abrupt closure is the most common cause of a major adverse cardiac event (MACE) and typically occurs within 6 hours of intervention. The most common cause of abrupt closure is suboptimal stent expansion or dissection followed by thrombus, spasm, and side branch occlusion. In the mid-1980s, the risk of abrupt closure approached 5%. The common use of periprocedural contemporary antithrombotic therapies and stent deployment has reduced this risk to <1% in modern practice. Risk factors for abrupt closure include presentation with acute MI, poor coronary flow postintervention (i.e., less than TIMI II), complex lesion morphology (i.e., class C lesions), and suboptimal result as judged by angiography or intravascular ultrasound (IVUS) imaging.

C. **Atheroembolism and thromboembolism** probably occur to varying degrees in all interventions, but are most frequently encountered in cases involving degenerated vein grafts, in patients presenting with acute coronary syndromes (ACSs), and in cases using directional/rotational atherectomy. Distal embolization can result in "no-reflow" (decreased coronary flow), abrupt closure, and periprocedural MI. Thromboembolism can be minimized by using aspiration catheters (e.g., Pronto, Export, Extract) or rheolytic thrombectomy (Possis AngioJet) to remove thrombus; however, the most effective measure is effective anticoagulant and antiplatelet therapy. The prevention of atheroembolus, most often encountered during vein graft intervention, is frequently addressed with the use of a filter device (e.g., FilterWire EZ) or proximal flow occlusion device (e.g., Proxis) to trap and remove the debris before it reaches the distal vascular bed. Intracoronary administration of vasodilators such as adenosine (36 to 72 µg repeatedly), nitroprusside (50 to 200 µg), and verapamil (200 µg) has been shown to prevent and manage no-reflow, but have no effect in preventing creatine kinase–muscle/brain (CK-MB) elevation.

TABLE 63.3 Clinical and Angiographic Predictors of Adverse Outcomes

Clinical Predictors	Angiographic Predictors
• Older age	• Thrombus
• Unstable angina	• Bypass graft
• Acute MI	• Left main trunk
• Cardiogenic shock	• Lesion > 20 mm in length
• CHF	• Excessive tortuosity of proximal segment
• Left ventricular function	• Extremely angulated lesions > 90°
• Multivessel coronary disease	• Total occlusion >3 mo old and/or bridging collate
• Diabetes mellitus	• Inability to protect major side branches
• Renal impairment	• Degenerated vein grafts with friable lesions
• Peripheral vascular disease	• Unprotected left main trunk
• Small body size	

D. CHF, congestive heart failure; MI, myocardial infarction.

E. **Coronary perforation** is typically identified using the Ellis classification: type I: extraluminal crater without extravasation; type II: pericardial or myocardial blush without contrast jet extravasation; type III: extravasation through frank (>1 mm) perforation; type III cavity spilling: perforation into an anatomic chamber, coronary sinus, and so on. Coronary perforation is estimated to occur in 0.1% to 1.14% of routine PCI cases, 0.25% to 0.70% of cases using directional atherectomy, up to 1.3% of cases using rotational atherectomy, and 1.9% to 2.0% following excimer laser angioplasty. Contrast extravasation is typically evident in the majority of cases at the time of PCI; however, up to 20% of cases can present several hours after the procedure and are frequently due to hydrophilic wire

perforation of a small vessel. Treatment usually requires prolonged balloon inflation and reversal of anticoagulation. Transthoracic echocardiography should be immediately performed in the setting of clinical instability in order to evaluate for the presence of a pericardial effusion and/or tamponade, in which case urgent pericardiocentesis is required. Covered stents, coils, or surgical repair may be required for definitive management.

F. **Vascular access site complications** remain the most common complication of PCI and occur in up to 5% of patients. The most common are blood transfusion (3%), arteriovenous fistula (<2%), pseudoaneurysm (up to 5%), acute arterial occlusion (<1%), and infections (<0.1%). Shorter anticoagulation regimens, weight-adjusted heparin, use of bivalirudin, early sheath removal, vigilant monitoring of activated clotting times (ACTs), smaller sheaths, avoidance of routine venous sheath insertion, and widespread adoption of radial artery access have all contributed to a reduction in complications. Stopping heparin after PCI and substituting clopidogrel for warfarin has also resulted in a reduction of bleeding and coronary complications.

G. **Contrast-induced nephropathy** defined as increase in Cr >0.3 above baseline occurs in 3% to 7% of patients, and the risk increases 10-fold for patients with serum creatinine >2.0 mg/dL, especially in the presence of diabetes mellitus. Data regarding methods to prevent renal failure are not definitive, but the most proven benefit is seen with conservative contrast utilization. In addition, use of biplane imaging can significantly reduce the amount of contrast required. Numerous studies have provided mixed results on the benefits of saline infusion before catheterization, administration of *N*-acetylcysteine (NAC) 600 mg po or intravenous (IV) bid for 1 day before and after the day of catheterization, single bolus dose NAC prior to contrast load, using nonionic contrast dye, infusion of a sodium bicarbonate solution, and periprocedural IV administration of 5 to 10 g of ascorbic acid (vitamin C).

H. Contrast-mediated reactions can be serious. Anaphylactoid reactions occur in 1% to 2% of patients receiving iodinated contrast. These reactions can be severe in 0.10% to 0.23% of patients. The risk of a severe reaction can be effectively decreased by using nonionic contrast, preprocedural corticosteroids (i.e., prednisone 40 to 60 mg) given the evening before and the morning of the procedure, and the use of $H_1$and H_2 blockers. If a patient presents for emergent PCI (i.e., STEMI) without having undergone preprocedural steroid preparation, the emergent administration of hydrocortisone 100 mg IV and diphenhydramine 25 to 50 mg IV is reasonable and is shown to be safe in small series. In patients undergoing an elective procedure, caution is prudent and a full premedication regimen is recommended.

I. Stent thrombosis (ST) is discussed later in Section **XI.F**.

VII.EXPERIENCED OPERATORS/CENTERS

A. Procedural volume is an important predictor of PCI complications. **Elective PCI** should be performed in high-volume centers (>200 interventions per year, with an ideal minimum of >400 cases per year) by operators with an acceptable annual volume (>75 cases per year) at institutions with fully equipped interventional laboratories, experienced support staff, and an on-site cardiovascular surgical program. **Primary PCI for STEMI** should be performed in similarly experienced/skilled centers by operators who perform >75 elective cases per year and intervene on at least 11 cases of STEMI per year. **Elective PCI should not be** performed by low-volume operators (<75 cases per year)

in low-volume centers (<200 cases per year), regardless of the availability of on-site cardiothoracic surgery, because of the increased risk of suboptimal outcomes. Referral to a larger regional center is recommended in this situation.

B. In cases of STEMI, there is an inverse relationship between the number of primary angioplasty procedures performed by an operator and in-hospital mortality. The data suggest that both door-to-balloon time and in-hospital mortality are significantly lower in institutions that perform a minimum of 36 primary angioplasty procedures per year.

VIII. SURGICAL BACKUP.

Emergency surgical intervention is a rare event and is required in 0.3% to 1.0% of cases of PCI, usually because of complications that cannot be addressed percutaneously or to provide urgent hemodynamic support. The most common reasons for emergency CABG surgery are dissection resulting in acute vessel closure, perforation, inability to retrieve a stent or other device, or aortic dissection. Emergency CABG after PCI has a mortality rate of 15% and periprocedural MI rate of 12%. The internal mammary artery may not be harvested, and surgery should not be delayed because of abciximab. Data from the Atlantic Cardiovascular Patient Outcomes Research Team and Primary Angioplasty in Acute Myocardial Infarction with No Surgery On-Site trials suggest that **primary PCI for STEMI** can be safely and effectively performed in centers that **do not** perform elective PCI and do not have on-site cardiac surgery capabilities if they implement a carefully developed and proven strategy capable of rapid and effective PCI (including an experienced operator with >75 total PCIs and at least 11 primary PCIs for STEMI per year) with a predetermined transfer plan to a nearby center with on-site surgical backup.

IX. SHEATHS, GUIDES, AND WIRES

A. Typical guide access is radial access with 6F sheath. A modified Seldinger technique is used to obtain access over a soft wire using fluoroscopic guidance.

B. Another arterial access involves placing a 6F to 8F short sheath in the common femoral artery using the modified Seldinger technique (long sheaths, such as 23 or 35 cm, can be used if there is significant tortuosity and/or additional support is required). Using fluoroscopic guidance when entering the femoral artery above the inferior margin of the femoral head but below the pelvic rim increases the likelihood of entering the common femoral artery at a compressible site above the common femoral artery bifurcation and below the inferior epigastric artery. The superficial/profunda femoral artery bifurcation is best seen in the ipsilateral 30° to 40° projection. The brachial and radial arteries can accommodate up to 7F and 6F sheaths, respectively. Ulnar artery and digital arch patency should be confirmed via the Allen and/or Barbeau test in case the radial artery becomes occluded (approximately 3% to 5%). Radial access improves hemostasis and earlier ambulation but may have slightly increased radiation exposure. The choice of coronary equipment is no longer limited because of technologic advances in 6F to 7F compatible devices.

C. Larger guide size (7F or 8F) provides extra support and permits the use of larger rotational atherectomy burrs and use of simultaneous kissing stents. For straightforward lesions, a 6F system is typically adequate. The XB (extra backup) and Amplatz guiding catheters provide good support; the Amplatz guide is especially effective in cases of an acutely angled left circumflex artery, anomalous left circumflex artery originating from the right sinus, very anteriorly originating right coronary artery, or a tortuous/calcified right

coronary artery. The Amplatz guide catheter is also the most likely catheter to traumatize the ostial/proximal coronary artery in inexperienced hands because of its tendency to deeply engage the vessel.

D. The coronary lesion is initially crossed with a 0.014-in. diameter coronary wire, which serves as a "rail" for devices such as balloons and stents. The choice of a wire depends on the wire tip's stiffness, and support characteristics. Stiff tips are helpful to penetrate chronic total occlusions but increase the risk of vessel dissection or perforation. Hydrophilic wires are quite slippery and may be used to cross tortuous high-grade lesions, but can easily cause dissection or end-vessel perforation. Support wires also typically have stiffer tips and are primarily used as a supportive rail to deliver coronary equipment through tortuous vessels. Generally, most operators routinely use a "workhorse" wire (i.e., Runthrough, Prowater, or Balance MiddleWeight) and have "favorite" stiff (e.g., Miracle Bros series), hydrophilic (e.g., Whisper and Pilot series), and support (e.g., GrandSlam and Balance HeavyWeight) wires for use in appropriate situations. Both short (approximately 180 cm) and long (approximately 300 cm) wires are available. Most operators prefer the routine use of a rapid exchange (Rx) system, which uses a monorail that permits easy exchange over a short wire, although situations that require an over-the-wire system may be better served with the use of a longer wire to avoid dislodging the wire during equipment exchanges.

X.DIAGNOSTIC ADJUNCTS

A. IVUS (anatomic)

1. An IVUS catheter generates a cross-sectional tomographic image of both the lumen and the vessel wall. This complementary imaging modality can be invaluable when repeated angiographic views fail to determine the mechanism and/or significance of a coronary lesion. IVUS has proven helpful in assessing adequacy of coronary stent deployment, mechanism of ISR (neointimal hyperplasia vs. inadequate stent expansion), a coronary lesion at a location difficult to image by angiography, a suboptimal angiographic result after PCI, coronary allograft vasculopathy after cardiac transplantation, coronary calcium when considering rotational atherectomy, and plaque location/circumferential distribution to guide directional coronary atherectomy. Further, IVUS can be indispensable in assessing the appropriate vessel size, especially during ACS when factors such as thrombus and vasoconstrictive substances can lead to significant stent undersizing.

2. IVUS provides anatomic, not physiologic, information. However, a lumen area <4.0 mm^2 in the proximal LAD, left circumflex, or right coronary artery or <6.0 to 7.0 mm^2 in the left main trunk suggests the presence of a hemodynamically significant lesion.

B. Optical coherence tomography (OCT). Similar to IVUS, OCT images are obtained by passing the catheter over a guidewire in the coronary artery. The catheter acquires images during an automated pullback over 5.6 cm and requires the clearance of blood in the vessel, thereby necessitating a 10 to 15 cc contrast injection with each acquisition. In comparison with IVUS, it provides much greater image resolution but a more shallow penetration. The superior image quality allows an evaluation of stent apposition, poststent dissection, and analysis of plaque characteristics and plaque rupture. Recently, investigators have used OCT to evaluate endothelial stent coverage, which in the future may allow a further tailoring of antiplatelet therapy at the patient-specific level. Currently, there

is a paucity of clinical outcomes data using OCT, but interest in this imaging modality is gaining momentum, with supportive data likely to follow.

C. Coronary flow reserve (CFR) (physiologic)

1. A 0.014-in. wire capable of measuring coronary flow velocity permits assessment of epicardial and microvascular resistance. This information is helpful in determining whether a moderate-grade coronary stenosis (i.e., 30% to 70% stenosis) is hemodynamically significant. The ratio of hyperemic to basal flow is known as the CFR and is determined by giving an intracoronary vasodilator such as adenosine (36 to 64 µg). A normal CFR is 3 to 5. A CFR <2.0 is abnormal and is consistent with a flow-limiting epicardial stenosis or increased microvascular resistance.

2. The effect of the microvasculature can be eliminated by measuring the CFR in two vessels: the lesion-containing vessel and a normal-appearing vessel. This allows calculation of the relative coronary flow reserve velocity ($rCFR = CFR_{target}/CFR_{reference}$). A nonhemodynamically significant stenosis has an rCFR value of <0.8 and is similar in prognostic value to negative stress testing. Unlike fractional flow reserve (FFR), CFR depends on hemodynamic and microcirculatory changes. In general, FFR is the preferred diagnostic modality for assessing the hemodynamic significance of a coronary lesion.

D. FFR (physiologic). A 0.014-in. wire with a pressure transducer is placed distal to a coronary stenosis and the translesional gradient measured. This allows calculation of the FFR, which is the ratio of this distal coronary pressure to aortic pressure (Pd/Pa) during maximal hyperemia. A vasodilator such as adenosine (IV infusion 140 µg/kg/min or intracoronary 36 to 64 µg) is used. A coronary artery without flow-limiting coronary obstruction would have an FFR of 1.0. An FFR value of <0.75 to 0.80 is consistent with a hemodynamically significant obstruction with accuracy greater than 90% and positively correlates with myocardial ischemia on stress testing. Unlike CFR, the FFR reflects only the epicardial artery lesion. Prospective studies have demonstrated that an FFR-guided strategy to direct PCI of intermediate lesions results in less stents deployed, with a significant decrease in morbidity and mortality compared with an angiography-only strategy (8.4% vs. 23.9%, $p = 0.02$). The FAME 2 trial further demonstrated that, in patients with stable CAD and hemodynamically significant stenoses (FFR < 0.80), FFR-guided PCI in addition to best available medical therapy decreased the need for urgent intervention compared with those receiving best available medical therapy alone.

E. Instantaneous wave-free ratio (iFR; Volcano Corporation). Using wave-intensity analysis, a period of diastole in which equilibration occurs between pressure waves from the aorta and distal microcirculation was identified at approximately 75% into diastole (ending 5 ms before the R-wave). This wave-free period satisfied the requirements of FFR to have minimal and constant coronary resistance, and the Pd/Pa during this wave-free period was termed the "instantaneous wave-free pressure ratio," or iFR. Using this proprietary pressure measurement modality, it was subsequently demonstrated that for iFR values lower than 0.86 or greater than 0.93, there was a strong correlation with hemodynamically significant and nonhemodynamically significant FFR values, respectively (using an FFR cut point of 0.80). For values falling within the "gray zone" between 0.86 and 0.93, performing confirmatory FFR or another modality to define lesion severity is recommended. One appealing measure of utilizing iFR is that it does not require a vasodilator or hyperemia to evaluate a lesion as it is a resting pressure-derived index of

stenosis severity, therefore it has the potential to save time and reduce costs during the procedure.

F. Pulmonary artery catheter (physiologic). A balloon-tipped Swan–Ganz catheter advanced to the pulmonary arteries allows measurement of right and left heart filling pressures as well as the cardiac output. This information can be helpful in patients presenting with cardiogenic shock, during high-risk PCI in the setting of severe left ventricular (LV) dysfunction, when there is a question of pericardial tamponade or when the cause of hemodynamic deterioration is unclear.

XI. THERAPEUTIC DEVICES

A. Percutaneous transluminal coronary angioplasty. The coronary balloon remains the backbone of endovascular intervention, although it is almost never used as a stand-alone therapy. The initial gain in the coronary lumen achieved by balloon inflation results in localized dissection of the intima (and often the media) plus distension of the adventitia. The dissection is covered by platelet-rich thrombus and later by new intimal layers. As a result of these inevitable dissections, the abrupt closure rate is 4% to 7%, although the use of more potent contemporary antithrombotic therapies has reduced this rate. The 6-month angiographic restenosis rate of 30% to 40% is another downside to PTCA.

B. Bare-metal stents (BMS)

1. Present-day coronary stents are flexible, laser-cut and polished, balloon-mounted, and expandable, slotted tubes composed of either stainless steel or metal composites such as cobalt–chromium. They have proven effective in treating dissections and reducing the incidence of abrupt closure, emergency CABG (<1%), and restenosis. First implanted in 1986 and used for emergency treatment of coronary dissection after angioplasty, the early era of the intracoronary stent placement was plagued by high rates of subacute closure despite intensive anticoagulation regimens that often led to bleeding complications and prolonged hospitalization. Evolution of stent design, high-pressure implantation of stents, and advances in periprocedural antithrombotic regimens led to a rapid reduction in procedural complication rates and marked improvement in the ease of stent delivery.

2. Although subacute vessel closure may still occur in a small percentage of cases following stent implantation, by providing a scaffold and reducing elastic recoil, BMSs reduced the published rates of restenosis from >50% following PTCA alone to 20% to 30%. **Restenosis risk is increased in patients with small reference vessel size, smaller postprocedural luminal diameter, or high degree of residual stenosis, long lesion length, diabetes, lesion location in the LAD artery, and presence of untreated edge dissection during the procedure.**

C. Drug-eluting stents (DES). The Achilles heel of BMS has been ISR. Antiproliferative agents such as sirolimus, paclitaxel, zotarolimus, and everolimus arrest cell division during the mitotic growth phase. The use of polymers to coat these agents onto a stent's surface and provide controlled, local drug delivery has dramatically reduced neointimal hyperplasia and thereby ISR. The "first-generation" DESs, introduced generally in 2003, were rapidly embraced and occupied almost 90% of the stent market by 2005. Although early studies raised concerns about higher rates of in-stent thrombosis in DES compared with BMS, subsequent large trials especially with second- and third-generation DES demonstrated similar ST rates for BMS and DES (see complete discussion below). In

the current practice there is almost no advantage for BMS except some financial considerations. Even the difference in DAPT duration postprocedure between the two stents is disappearing (see below). There are a number of DESs available, with various studies supporting their clinical use. Whereas a thorough discussion of trial data is outside the scope of this chapter, a brief overview of the currently available DES is summarized below and in Table 63.4.

1. **Endeavor, Resolute, and Resolute Integrity (Medtronic) zotarolimus-eluting stents (ZES).** The ZESs are considered second-generation DES. The Endeavor DES elutes zotarolimus from a cobalt–chromium Driver stent platform. The Resolute stent makes use of the Driver platform with a newly designed polymer that allows a delayed release of the drug for out to 3 months. The Resolute Integrity stent elutes zotarolimus from Medtronic's Integrity stent platform.
2. **Xience (Abbott Vascular, CA) and Promus (Boston Scientific, MA) everolimus-eluting stent (EES).** Along with the ZES discussed above, the EESs are also considered "second-generation" DES.

D. Bioresorbable polymer DES

1. **Synergy (Boston Scientific, MA).** As long-term outcome data became available for first- and second-generation DES, there was an increasing focus on late adverse events and inherent limitations related to implanting permanent metallic scaffolds and polymers—specifically, incomplete endothelialization, persistent inflammatory reactions, loss of native vessel curvature and vasoregulation, and neoatherosclerosis. Approved by the Food and Drug Administration (FDA) in October 2015, the Synergy stent became the first bioresorbable polymer DES available in the United States. Whereas it also elutes everolimus from a platinum–chromium platform, the polymer which does so is absorbed over time, leaving the patient with what is then in effect a BMS (in contrast to the durable-polymer DES discussed above, in which the polymer remains permanently on the stent surface even after drug elution has completed).

E. Bioabsorbable vascular scaffolds (BVS; Abbott Vascular, CA). Bioabsorbable scaffolds were developed to incorporate the early benefits of DES—mechanical support to the artery to prevent elastic recoil and allow healing as well as controlled antiproliferative drug delivery to prevent ISR—while leaving no permanent metallic scaffold in the artery, which has been postulated to allow a return of normal vascular physiology and access to the vessel, should future surgical revascularization be required. The Absorb BVS (Abbott Vascular, CA) features a semicrystalline poly-L-lactic acid resorbable scaffold with an everolimus-coated poly-DL-lactide polymer that has a controlled drug release profile similar to the cobalt–chromium Xience EES. It was approved by the FDA in July 2016 and became the first BVS commercially available in the United States.

F. Stent thrombosis is defined as early (<30 days), late (30 days to 1 year), and very late (>1 year). It may be the result of stent-, procedure-, patient-, and antiplatelet therapy–related factors, and minimizing the risk of ST requires a conscious consideration of each of these issues. Compared with thrombosis of native coronary arteries, ST is associated with a higher thrombus burden and less frequent procedural success, all of which results in a much higher rate of death, recurrent MI, and recurrent ST.

TABLE 63.4 Coronary Stents Approved in the United States

TABLE 63.4 Coronary Stents Approved in the United States

Name	Manufacturer	Stent Material	Drug	Notes/Comments
BMS				
Integrity	Medtronic	Cobalt–chromium	N/A	
Vision	Abbott Vascular	Cobalt–chromium	N/A	
VeriFLEX	Boston Scientific	Stainless steel	N/A	
REBEL	Boston Scientific	Platinum–chromium	N/A	
Durable-Polymer DESs (currently in use)				
Xience	Abbott Vascular	Cobalt–chromium	Everolimus	Pivotal trials: SPIRIT series
Promus	Boston Scientific	Platinum–chromium	Everolimus	Pivotal trials: PLATINUM ser
Taxus Ion	Boston Scientific	Platinum–chromium	Paclitaxel	Pivotal trial: PERSEUS
Endeavor	Medtronic	Cobalt–chromium	Zotarolimus	Pivotal trials: ENDEAVOR se
Resolute	Medtronic	Cobalt–chromium	Zotarolimus	Pivotal trials: RESOLUTE se
Bioabsorbable Polymer DESs (currently in use)				
SYNERGY	Boston Scientific	Platinum–chromium	Everolimus	First bioresorbable polyme (October 2015) Pivotal trials: EVOLVE series
Bioabsorbable Vascular Scaffolds				
Absorb	Abbott Vascular	Biodegradable polymer PLLA	Everolimus	First bioresorbable scaffold t Pivotal trials: ABSORB serie
Previously Approved ("First-Generation") DESs (no longer in use)				
Cypher	Cordis/J&J	Stainless steel	Sirolimus	Discontinued in 2011 Pivotal trials: RAVEL, SIRIU
Taxus	Boston Scientific	Stainless steel	Paclitaxel	Pivotal trials: TAXUS series

G. BMS, bare-metal stent; DES, drug-eluting stent; FDA, Food and Drug Administration; PLLA, poly-L-lactic acid.

1. **Stent-related factors.** Following BMS implantation, the vascular endothelium typically grows over the stent struts in 2 to 4 weeks, thereby eliminating contact between the stent and circulating platelets with a concomitant reduction in thrombotic risk. In

contrast, **reendothelialization following DES implantation is significantly retarded** because of the antiproliferative effect of the coating polymer, thereby allowing for strut/platelet contact up to several years post-PCI (similar to the historical use of brachytherapy). In meta-analyses of large trials, the **overall incidence of ST is similar in both BMSs and DESs (0.5% to 1.0% per year).**

2. **Procedure-related factors. Incomplete stent apposition to plaque/vessel wall, inadequate stent expansion (i.e., stent undersizing to the vessel), and stent-edge dissection** all increase the risk of ST. Whereas angiography may indicate all of the above problems, stent sizing is routinely underestimated by the angiogram alone. Further interrogation of the vessel using IVUS or OCT (discussed in Sections **X.A** and **X.B**, respectively) may be necessary to optimize the chances of success and minimize the risk of ST. Additional risk factors for ST include long lesion length, small artery diameter, and complex lesion morphology (i.e., bifurcation stenting and chronic total occlusion).
3. **Patient-related factors.** Comorbid risk factors not only are important in assessing the relative benefit of DES but also increase the risk of ST. For instance, patients with **diabetes, impaired LV function, and renal disease** not only derive greater benefit from the antirestenotic properties of DES but also present a greater risk of ST. **Premature cessation of DAPT** (because of nonadherence, need for surgery, bleeding complications, or financial considerations) as well as poor clopidogrel response (seen in up to 15% of patients) also increase the risk of ST, especially in patients treated with DES.
4. **Duration of antiplatelet therapy.** In patients with ACS, the use of at least 12 months of DAPT is recommended for its established benefit in reducing MACE over aspirin alone. With respect to stent safety alone, however, use of 4 to 6 weeks of clopidogrel is sufficient to allow endothelialization of BMS. For DES, numerous authors have demonstrated that early cessation of DAPT is a significant predictor of ST. The optimal duration of DAPT after DES implantation is not known and likely depends on integrating multiple patient-specific ischemic and bleeding risks. The DAPT trial is the largest of the randomized trials that have compared longer to shorter duration DAPT after PCI. It randomly assigned 9,961 patients who had been successfully treated with 12 months of aspirin and either clopidogrel or prasugrel to continue receiving the same $P2Y_{12}$ receptor blocker or placebo for an additional 18 months (on the background of all patients continuing low-dose maintenance aspirin). The rates for both coprimary end points of ST and a composite of all-cause mortality, MI, or stroke were significantly lower with prolonged DAPT (0.4% vs. 1.4; hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.17 to 0.48 for ST, and 4.3% vs. 5.9%; HR 0.71, 95% CI 0.59 to 0.85 for the composite end point). The reduction in events with prolonged DAPT was mostly attributable to a lower rate of MI (2.1% vs. 4.1%; HR 0.47, $p < 0.001$); however, moderate and severe bleeding rates were significantly increased in patients treated with prolonged DAPT (2.5% vs. 1.6%, $p = 0.001$). Additional prespecified subanalyses suggested a greater benefit of prolonged DAPT in patients who received PCI for ACS (p-interaction = 0.03). Furthermore, the rate of MI not related to the stented site was also lower in patients treated with prolonged DAPT (1.8% vs. 2.9%; HR 0.59; $p < 0.001$), accounting for 55% of the total reduction in MI seen with prolonged DAPT. This suggests there may be a possible benefit from DAPT attributable to the prevention of adverse events from plaque rupture at sites remote from the stented index lesion. Of note, other smaller randomized trials, including PRODIGY, DES-LATE, and ARCTIC-Interruption did not show a decrease in ischemic events with prolonged

DAPT. These and other trials have been studied together in several meta-analyses including up to 10 randomized control trials and representing over 30,000 patients, which have found a significantly lower rate of MI and ST with prolonged DAPT at the expense of significantly higher rates of bleeding. In a meta-analysis which included only studies comparing shorter duration (3 to 6 months) to 12 months of therapy (including the SECURITY, ITALIC, ISAR-SAFE, OPTIMIZE, EXCELLENT, RESET, and PRODIGY trials), there was no significant difference in the risk of all-cause death (HR 0.89, 95% CI 0.66 to 1.20) for 6 months of DAPT compared to 12 months or longer. However, each trial was noted to have one or more significant limitations, such as small sample size or enrollment of lower risk patients, and there was significant heterogeneity among the included trials. In summary, the optimal duration of DAPT must be tailored to the individual patient taking into account specific bleeding and ischemic risks, as well as cost. Our practice is to continue DAPT for at least 12 months following DES placement, and in patients who have tolerated this, continue either their current agent for up to 30 months, or for patients taking a third-generation $P2Y_{12}$ consider switching to clopidogrel for months 13 to 30 based on individualized bleeding risk. Several trials are underway to assess the safety and efficacy of discontinuing aspirin while continuing monotherapy $P2Y_{12}$inhibition following stent implantation.

5. Although DESs have dramatically reduced the incidence of ISR and MACE, especially in patients with diabetes and complex coronary lesions, a mounting body of evidence suggests an increased risk of late and very late thrombosis following the discontinuation of antiplatelet therapies. Therefore, **the decision to use BMS or DES in any given patient requires a thorough evaluation** of factors that may predispose the patient to premature discontinuation of DAPT. In our catheterization laboratory, BMS use is very rare and generally reserved for patients who require revascularization before urgent noncardiac surgery and/or have malignancy or other significant bleeding issues which preclude DAPT continuation.

H. Covered stents. Covered stents use a material such as polytetrafluoroethylene (PTFE), which covers the stent struts and seals off the vessel wall from the stent lumen. The Jomed covered stent has PTFE sandwiched between two Jostents. This covered stent is approved for use after coronary perforation by the FDA, but requires reporting of their use in this situation as a sentinel event. FDA approval can also be obtained on a case-by-case basis in patients with coronary aneurysm.

I. Cutting balloon atherectomy

1. These balloons were initially developed to create a "controlled dissection." A cutting balloon has three to four longitudinally mounted, razor-sharp atherotomes. These atherotomes cut into both plaque and vessel wall and allow vessel dilatation at a lower balloon pressure. Success in the treatment of balloon-resistant lesions led to FDA approval in 1995. Although randomized data have shown no difference between cutting balloon angioplasty and PTCA, many operators use this device in lesions with high elastic recoil (i.e., ostial or bifurcation lesions) before DES. The AngioSculpt device consists of a balloon surrounded by a nitinol cage that prevents balloon slippage and scores the plaque. An alternative to these specialized balloons is to place a second guidewire as a "buddy" in the coronary artery, which serves as a makeshift cutting device at the lesion during balloon inflation over the first wire.

2. Cutting balloons have also found a niche in the treatment of ISR. Regular balloons often slip when inflated across these rubbery lesions. The Restenosis Reduction by

Cutting Balloon angioplasty Evaluation III trial randomized 521 patients to cutting balloon or PTCA before stenting (with angiographic or IVUS guidance) and demonstrated a significantly lower rate of angiographic restenosis in the cutting balloon before stenting group, primarily with IVUS guidance. The "buddy wire" technique may also be useful to increase friction and minimize balloon slippage in the treatment of ISR. It is important to use a second wire that does not have a hydrophilic coating in order to maximize effectiveness.

3. Care must be taken not to oversize cutting balloons, because perforation can occur. Placing these balloons through stent struts or down tortuous vessels can result in atherotome entrapment, as can a perforated balloon. These balloons should only be inflated to 6 to 10 atm in order to decrease the likelihood of balloon rupture.

J. Rotational atherectomy

1. Rotational atherectomy uses a 160,000 rpm, diamond-coated burr (i.e., drill bit) that is advanced over a 0.009-in. wire to the coronary lesion. The process generates microparticulate debris that embolize and may attenuate the coronary microcirculation, inducing transient myocardial stunning, periprocedural MI, and LV dysfunction in the region of the target vessel. Therefore, although limited clinical data suggest that rotational atherectomy can be safely performed in patients with depressed LV function in the hands of an experienced operator, it is not recommended.

2. Compared with plain balloon angioplasty, rotational atherectomy increases the chance of procedural success but has not been shown to reduce the risk of restenosis or MACEs in de novo or restenotic lesions. Although the use of rotational atherectomy has declined, it is recommended before stenting in patients with severely calcified lesions, undilatable lesions, chronic total occlusions, and bifurcation lesions to help ensure proper stent expansion and apposition in balloon-resistant lesions.

3. Familiarity with the device is essential. Sluggish coronary flow can occur, requiring a vasodilator such as verapamil, nitroprusside, or adenosine. Perforation occurs in approximately 1% of patients, typically when significant tortuosity forces the burr to the outside edge of a curve. Prophylactic pacing or aminophylline is frequently required if rotational atherectomy is performed in the vessel supplying the atrioventricular (AV) node. Rotational atherectomy is typically contraindicated in patients with thrombus, dissection, or severely reduced LV systolic dysfunction.

K. Orbital atherectomy

1. Orbital atherectomy, similar to rotational atherectomy, is a vessel preparation treatment to facilitate successful stent deployment for severely calcified lesions which utilizes a rotating burr to ablate plaque into particles small enough to be cleared by the reticuloendothelial system without the requirement for distal embolic protection devices. The device differs from rotational atherectomy in that the burr is flexible and the depth of plaque ablation can be changed by altering the speed of rotation. The Diamondback 360 Orbital Atherectomy System (Cardiovascular Systems, Inc.) employs a unique proprietary mechanism of differential sanding and centrifugal force and received FDA approval for coronary use in October 2013. The foundation for its use was established in the ORBIT II trial, in which 443 patients were treated with orbital atherectomy in an open-label registry. Following orbital atherectomy, successful stent delivery was possible in 98% of patients.

L. Excimer laser

1. The excimer (*excited* and di*mer*) laser catheter (excimer laser coronary atherectomy, ELCA) tip is brought into contact with the target lesion. It creates ultraviolet light (308 nm) at a rate of 25 to 40 pulses/s from a high-energy, metastable, dimeric molecule of xenon and chloride. This provides 45 mJ/mm^2, which can ablate 0.5 mm of tissue per second, and reduces the target tissue to gas and subcellular debris. The size of the lumen created is equivalent to that of the catheter (0.9 mm diameter).
2. The ELCA was approved by the FDA in 1992 for total occlusions, moderately calcified stenoses, balloon crossing/dilatation failures, ostial lesions, bypass grafts, and long diffuse disease. It is contraindicated in angulated lesions, coronary dissection, thrombotic lesions, and severely calcified lesions. However, long-term clinical data have failed to demonstrate a significant restenosis benefit, and routine use increases the complication rate in comparison with plain balloon angioplasty. Therefore, the American College of Cardiology (ACC)/American Heart Association (AHA) PCI guidelines do not recommend the use of ELCA as a primary strategy for revascularization, and its use in the present day is typically limited to cases of stent underexpansion and lesion modification in refractory ISR.

M. Thrombectomy

1. **Aspiration thrombectomy.** As intracoronary thrombus is frequently found in patients presenting with STEMI, the use of a catheter to aspirate thrombus from the infarct artery is intuitively attractive. However, although thrombus burden can be reduced by using manual aspiration thrombectomy, evidence from large-scale clinical trials does not demonstrate a significant benefit from its routine use. The three largest and most rigorously conducted randomized controlled trials (RCTs) to examine manual thrombectomy in STEMI are the TAPAS (n = 1,071), TASTE (n = 7,244), and TOTAL (n = 10,732) trials. Whereas the TAPAS trial and meta-analyses of early trials suggested increased perfusion and reduced clinical events (including all-cause mortality) among STEMI patients receiving aspiration thrombectomy, this finding was not replicated in the subsequent larger TASTE and TOTAL trials which both showed no significant difference for their primary end points. Furthermore, in the TOTAL trial, the key safety outcome of stroke occurred significantly more frequently at both 30 and 180 days in the patients who received thrombectomy (HR 2.0). In the 2015 ACC/AHA focused guideline update on the management of STEMI, aspiration thrombectomy was downgraded to a class IIb indication. Currently, the most widely used aspiration catheters include the Pronto LP, PriorityOne Export, and Extract (from smallest to largest lumen size; all these are compatible with a 6F system except the Extract which requires 7F).
2. **Rheolytic thrombectomy.** The Possis AngioJet is the dominant rheolytic thrombectomy device. The device is a 5F double-lumen, flexible catheter that contains a hypotube through which six high-speed saline jets create a low-pressure area at the tip (approximately −760 mm Hg), which serve to macerate and aspirate the thrombus back into the catheter lumen in accordance with the Venturi–Bernoulli principle. This catheter has proven to be successful in thrombotic vein grafts, for which it received FDA approval in 1998. Temporary prophylactic pacing is recommended when treating vessels supplying the inferior wall, because of potential temporary AV block. Temporary ST-segment elevation is frequent. Perforation can occur in vessels <2.0 mm in diameter because of the high-pressure saline injection. Although small studies using the AngioJet in the setting of ACS have been

encouraging, prospective randomized data demonstrating a clinical benefit have been lacking. The AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction trial randomized patients with acute MI to AngioJet thrombectomy followed by PCI or PCI alone and concluded that mortality rates (4.6% vs. 0.8%, $p < 0.02$), infarct size (12.5 ± 12.1% vs. 9.8 ± 10.9%, $p = 0.02$), and MACE rates (6.7% vs. 1.7%, $p < 0.01$) were considerably **higher** in those undergoing thrombectomy. Although not used in the routine care of patients, the AngioJet still holds a place in the interventional armamentarium for patients with overwhelming clot burden that is not adequately addressed by aggressive aspiration thrombectomy alone.

N. **Filters.** A collapsible microporous polyurethane net attached to a nitinol ring anchored distally to a 0.014-in. guidewire can be advanced across high-risk saphenous vein graft (SVG) or carotid stenoses and then deployed downstream of the lesion. When deployed, these porous devices appear as a windsock or umbrella and allow blood to flow through while filtering any debris larger than 80 to 100 µm. Advantages are ease of use and avoidance of prolonged ischemia. Potential disadvantages are incomplete sealing, passage of smaller particles through the filter pores, overloading of the device, and spillage during device retrieval. The FilterWire EX Randomized Evaluation trial prospectively randomized 650 patients undergoing PCI of diseased SVGs to either the EPI FilterWire EX or the PercuSurge GuardWire embolic protection device and revealed equal efficacy of both types of devices in regard to the primary end point of death, periprocedural MI, and target lesion revascularization (TLR) at 30 days. This trial led to FDA approval of the FilterWire EX for use in degenerated SVGs.

XII.SVG INTERVENTIONS

A. Saphenous vein bypass grafts are frequently used in CABG surgery. However, 7% occlude the first week, 15% to 20% occlude the first year, and by the tenth year 50% of SVGs are occluded and 25% are severely degenerated. Redo CABG is high-risk surgery with high rates of morbidity and mortality that approach 7% to 10% nationally. At the Cleveland Clinic, the rate is 1.8%. A patient with a patent internal mammary artery graft to the LAD artery makes redo surgery less appealing. Patients with no prior arterial conduit, multiple failed SVGs, multivessel disease, and depressed LV systolic function are ideal candidates for redo surgery.

B. Early postoperative ischemia within the first 30 days usually reflects graft failure (often secondary to thrombosis) or incomplete revascularization, and urgent coronary angiography is indicated. Emergency PCI of the graft, even across suture lines, has been safely performed within days of surgery. Intracoronary thrombolysis should be used with caution. Mechanical thrombectomy is a safer choice. Given that SVG flow is pressure dependent, intra-aortic balloon pump use should be strongly considered in patients that present with hypotension or depressed LV function.

C. Recurrent ischemia 1 to 12 months after CABG surgery usually reflects perianastomotic graft stenosis. Distal anastomotic stenoses respond well to balloon inflation only. Mid-shaft vein graft stenoses are usually due to intimal hyperplasia.

D. Recurrent ischemia >1 year after CABG surgery usually reflects the development of atherosclerosis. SVGs have greater plaque burden than native coronary arteries, and aspirates are composed of atherosclerotic rather than thrombotic elements. This may explain the lack of benefit seen with glycoprotein IIb/IIIa inhibitors (GPIs). Unprotected PCI (i.e.,

no PercuSurge GuardWire or filter device) results in varying degrees of atheroembolization, with 15% of patients having a CK-MB more than five times normal. Therefore, use of distal protection devices during SVG interventions is strongly encouraged when technically feasible. The use of these devices is discussed above in Section XI. In situations of poor reflow after SVG PCI, copious administration of intracoronary adenosine and/or nitroprusside is recommended, with the goal of improving microvascular flow. It should also be noted that poor reflow may be seen due to a plaque-burdened filter, which should resolve with aspiration followed by filter retrieval.

XIII. RESTENOSIS. Restenosis is the most commonly occurring late PTCA complication and typically occurs within 6 months primarily because of vessel contracture, elastic recoil, negative vessel remodeling, and neointimal hyperplasia. **ISR is almost entirely due to neointimal hyperplasia.** Not surprisingly, focal restenosis has a better outcome and response to treatment than does diffuse restenosis. **The predictors of restenosis include diabetes, unstable angina, acute MI, prior restenosis, small vessel diameter, total occlusion, long lesion length, SVG, proximal LAD artery, higher percent stenosis after the procedure, and smaller minimal luminal diameter after the procedure.** Strategies to decrease restenosis include maximizing stent expansion (i.e., bigger is better) and minimizing the distance of arterial injury.

Post-PTCA. Balloon angioplasty alone has a 6-month restenosis rate of 32% to 40%. For restenotic lesions managed with PTCA, the restenosis rate is comparable to de novo lesions. For a third episode of restenosis, PTCA has a restenosis rate approaching 50% (not 100%). With PTCA alone, late patency is 93% after three procedures. Only 1.6% of lesions require four or more procedures. Atheroablative approaches, such as excimer laser and rotational atherectomy, have not proven superior in managing restenosis. However, stents are superior to PTCA, with a 6-month TVR rate of 10% versus 32%.

In-stent restenosis. The risk of recurrent ISR after balloon angioplasty is 10% for focal ISR, 50% for diffuse restenosis, and 80% for total stent occlusion. Atheroablative approaches, such as use of the cutting balloon and rotational atherectomy, have not proven clinically superior to PTCA.

A. ISR occurs in 17% to 32% of patients treated with BMS depending upon such variables as vessel size, lesion length, diabetes mellitus, smaller postprocedure minimal luminal diameter, higher residual percent stenosis, and vessel location. In patients who cannot receive DES but for whom ISR is an issue, consideration may be given to a short course of oral sirolimus therapy. The Oral Rapamycin in ARgentina (studies I to III) investigators have found substantial reduction in TLR for BMS plus sirolimus (10 mg pre-PCI followed by 3 mg daily for 13 days) in comparison with BMS alone (8.3% vs. 38% at 1 year, $p < 0.001$) and equivalence in TLR compared with DES (8.2% vs. 7.0% at 18 months, $p = 0.84$).

B. The observed rate of ISR is significantly lower with DES. As discussed previously, 5-year follow-up from the SIRIUS trial of Cypher SES yielded a 9.1% rate of TLR, similar to the 9.6% TLR rate at 5 years in the TAXUS IV trial of PES. Follow-up data for the EES (Xience V or Promus) have been published up to 2 years in SPIRIT IV and show an ischemia-driven TLR rate of 4.5%. The Intracoronary Stenting or Angioplasty for Restenosis Reduction—Drug-Eluting Stents for In-Stent Restenosis trial compared SES and PES with balloon angioplasty in 300 patients with ISR following BMS and demonstrated a

significant reduction in restenosis at 6-month follow-up in the DES groups as compared with angioplasty alone (8% vs. 33%). A comparison of EES and PES revealed a significant improvement in recurrent TLR with EES (1% vs. 11.5%, $p = 0.0193$) at 1 year, but similar rates of MI, death, and ST. Atheroablative approaches, such as use of the cutting balloon and rotational atherectomy, have not proven clinically superior to PTCA.

Brachytherapy. Brachytherapy damages chromosomes and prevents cell division, thereby **inhibiting neointimal hyperplasia**. Both β and γ brachytherapy catheter-based systems use closed-end lumen catheters that deliver the source and keep it out of contact with the blood, allowing reuse. Both γ (iridium 192) and β (phosphorus 32 and strontium 90) brachytherapy result in approximately 50% reduction in ISR compared with balloon angioplasty alone. It is important to ensure brachytherapy delivery to all balloon-injured segments in the target vessel, or else inadequate radiation to an injured segment can cause neointimal proliferation. Brachytherapy can only be used one or two times in each vessel, and long-term DAPT with aspirin and clopidogrel is essential, given the risk of late in-stent thrombosis. Ultimately, long-term data are disappointing with a high failure rate; brachytherapy has therefore fallen largely out of favor. However, it is seeing a small resurgence in its use at select centers for truly refractory ISR cases.

XIV. PHARMACOLOGIC ADJUNCTIVE THERAPY

A. Antithrombins. Antithrombins prevent the generation of thrombin and/or inhibit the activity of thrombin. An antithrombin such as unfractionated heparin (UFH), bivalirudin (direct thrombin inhibitor [DTI]), or enoxaparin (low-molecular-weight heparin [LMWH]) should be used during all coronary interventions to prevent thrombus formation on the equipment. This principle applies even to patients with a high international normalized ratio (INR). Maintenance of appropriate levels of anticoagulation is imperative to safely navigate the path between thrombosis and bleeding complications. The following provides a brief overview of the anticoagulant agents used during PCI. For specific data regarding their use during ACS, please refer to **Chapter 2**.

B. Unfractionated heparin

1. UFH binds and induces a conformational change in antithrombin, converting it to a more efficient inhibitor of circulating thrombin (factor IIa), factor Xa, factor IXa, factor XIIa, and kallikrein. Initial dosing is weight-based and, at traditional dosing of 50 to 70 units/kg commonly used in PCI, it has a dose-dependent half-life of 30 to 60 minutes. No maintenance infusion is given. A distinct advantage of UFH is that its anticoagulant effect can be followed (and subsequent dosing titrated to achieve) by routine activated partial thromboplastin times or point-of-care ACTs in the catheterization laboratory, with common ACT targets ranging from 250 to 300 seconds for UFH monotherapy or 200 to 250 seconds when used with concurrent GPIs (or if being conservative in the setting of increased bleeding risk or other patient-specific factors). Of note, this ideal ACT range has not been rigorously reexamined with randomized control trials in the era of routine $P2Y_{12}$ receptor blocker use. Additional advantages of UFH include its widespread availability, low cost, rapid clearance after the infusion is discontinued, and the ability to reverse its anticoagulant effects with protamine in urgent situations. Potential disadvantages include the higher incidence of heparin-induced thrombocytopenia with UFH compared with other heparin preparations.

2. In uncomplicated PCI cases, prolonged postprocedural heparin infusions increase bleeding complications and do not lower the likelihood of abrupt vessel closure or the rate of restenosis. The sheath should be removed when the ACT is <180 seconds.

C. Low-molecular-weight heparin

1. LMWHs are a group of agents derived from UFH that act via antithrombin and preferentially inhibit factor Xa more than thrombin. Three LMWH agents have been approved by the FDA for clinical use: enoxaparin, dalteparin, and tinzaparin. Enoxaparin is the most rigorously studied of all the LMWH in the setting of ACS and is the agent typically used in the United States. Enoxaparin exhibits much less binding to plasma proteins and endothelial cells than UFH, giving it a more consistent and predictable factor Xa inhibition and subsequently anticoagulant effect. When given intravenously, enoxaparin has a time to peak effect of 5 to 10 minutes, compared with 3 to 5 hours when administered subcutaneously. Enoxaparin's 5- to 7-hour half-life is dose-independent; however, dose adjustment is required in patients with renal insufficiency.
2. The majority of trials using LMWH in PCI have been in the setting of ACS; the evidence base supporting its use during routine elective PCI is much weaker. Multiple early trials demonstrated a reduction in death and MI among conservatively managed NSTEACS patients (not undergoing routine revascularization) treated with enoxaparin compared with UFH; however, in patients undergoing early invasive management LMWH was noninferior to UFH for composite ischemic end points. Of note, when reviewing the historical evidence base for LMWH use in PCI, it is important to recognize that very few utilized contemporary DAPT (aspirin plus oral $P2Y_{12}$ or GPI). Therefore, in contemporary practice with routine DAPT and the increasing utilization of radial artery access for PCI, LMWH use in the United States has been primarily limited to NSTEACS patients selected for conservative management.
3. If a hospitalized patient has been given subcutaneous enoxaparin, a reasonable strategy is as follows. If PCI is performed within 8 hours of subcutaneous enoxaparin administration, then no additional heparin is required. If PCI is performed within 8 to 12 hours, an additional IV dose of 0.3 mg/kg of enoxaparin should be administered. If PCI is performed >12 hours after enoxaparin injection, standard doses of UFH can be used.
4. When using LMWH, ACT measurement does not reflect the degree of anticoagulation and there is no rapid method for determining factor Xa activity. This inability to confirm adequate antithrombin activity and assess the level of anticoagulation with a bedside test makes some interventional cardiologists uncomfortable. Significant anti–factor Xa activity persists for about 12 hours. LMWH is only partially reversed with protamine.
5. Dosing LMWH in obese patients provides a much less reliable level of anticoagulation. Extreme caution should be exercised in patients with moderate-to-severe renal insufficiency (i.e., creatinine clearance < 30 mL/min), as the renal elimination of LMWH may result in unexpectedly high degrees of anticoagulation for a prolonged period. In these cases, most interventionalists will use an alternative antithrombotic agent.

D. Fondaparinux

1. Fondaparinux is a synthetic pentasaccharide that binds to antithrombin and induces a conformational change that increases its affinity for factor Xa. Fondaparinux has compared favorably with LMWH in both the NSTEMI and STEMI settings, in large part because of a significant decrease in bleeding complications. However, there is an increased

risk of guide-catheter thrombosis during PCI (OASIS-8). Therefore, in contemporary practice, the use of fondaparinux is typically reserved for patients with a high risk of bleeding selected for a conservative management strategy, because it has not been shown to have added benefit over UFH or LMWH in patients undergoing PCI. Because of the unique concerns with catheter thrombosis and fondaparinux, it is not recommended for use as the sole anticoagulant agent during PCI and it is important that patients treated with fondaparinux who go on to have PCI performed do so with the addition of other antithrombotic therapy, such as UFH or bivalirudin.

E. Direct thrombin inhibitors (bivalirudin)

1. The initial DTI was isolated from leech saliva, although now these materials are synthesized using recombinant technology. These agents directly inhibit clot-bound thrombin without requiring an antithrombin cofactor. DTIs are better able to block both fluid-phase and clot-bound thrombin, which may be particularly important in a thrombus' platelet-rich environment.
2. A hirudin analog, **bivalirudin,** is becoming increasingly more common in catheterization laboratories and is an important anticoagulant for patients undergoing PCI. Bivalirudin has several intrinsic advantages over UFH and LMWH in the setting of PCI: It has no known natural inhibitors (such as platelet factor 4), it has a more predictable bioavailability, it does not directly activate platelets, and (unlike UFH) it does not require periprocedural monitoring with ACT levels after it is administered.
3. Bivalirudin has been the focus of multiple randomized clinical trials over a 20-year period, comparing it with various anticoagulation regimens (most notably against UFH and against UFH + GPI) in nearly all PCI settings (elective PCI, NSTEACS, and STEMI). The REPLACE-2 trial compared bivalirudin with the combination of abciximab/UFH in a prospective, randomized, double-blind fashion and found it to be associated with fewer bleeding-associated complications and a statistically noninferior rate of MACEs. Bivalirudin has also shown similar salutary effects in patients with STEMI (HORIZONS-AMI) and NSTEACS (ACUITY). Although a higher incidence of acute ST was observed in patients with STEMI, which may (e.g., EUROMAX trial) or may not (e.g., MATRIX trial) be able to be reduced by prolonging the bivalirudin infusion after PCI, long-term mortality was similar or reduced by bivalirudin compared with heparin + GPI. For several years bivalirudin monotherapy had largely replaced the use of UFH + routine GPI in patients undergoing PCI. However, several concurrent advances in contemporary PCI such as radial artery access, newer thinner stent designs with second-generation antiproliferative drugs, and improved third-generation $P2Y_{12}$ antiplatelet agents have led to the reevaluation of bivalirudin against UFH-only regimens. In several of these recent trials (including NAPLES-III, MATRIX, and HEAT-PPCI), bivalirudin was not found to significantly reduce bleeding, and in one trial in a contemporary STEMI population (HEAT-PPCI), UFH alone reduced composite ischemic events compared with bivalirudin. Another such trial (BRIGHT), again in a contemporary STEMI population, however, found ischemic events and major bleeding reduced by bivalirudin compared with UFH. A high-quality meta-analysis examined 16 bivalirudin trials in nearly 34,000 patients to compare the relative safety and efficacy of bivalirudin to UFH in PCI, stratified according to the use of GPI. In their analyses, ischemic complications were slightly more frequent among patients receiving bivalirudin-based regimens compared with UFH-based regimens (risk ratio [RR] 1.09, 95% CI 1.01 to 1.17),

regardless of the clinical indication for PCI or the GPI strategy used. The impact of bivalirudin on bleeding, however, was significantly impacted by the GPI strategy used. There was no significant difference found in bleeding in comparisons of bivalirudin monotherapy versus UFH monotherapy. Therefore, in the contemporary PCI era where GPIs are not routinely used, the role of bivalirudin over standard dose (70 U/kg) UFH monotherapy with third-generation DAPT is less clear.

4. Please refer to **Chapter 2** for a more detailed discussion of bivalirudin use in STEMI.

5. Bivalirudin is given as a 1 mg/kg bolus followed by a 4-hour maintenance infusion of 2.5 mg/kg/h and by 0.2 mg/kg/h. A given bivalirudin dose provides a more predictable ACT than does UFH. The half-life is 25 minutes in patients with normal renal function, although in dialysis-dependent patients, the half-life may be as long as 3.5 hours. The maintenance infusion can be discontinued after completion of the coronary intervention. If a vascular closure device is not used, the sheath can typically be removed in 1 to 2 hours, given the drug's short half-life. Unfortunately, the effects of bivalirudin cannot be reversed.

F. Warfarin. Routine warfarin is no longer recommended unless a patient has a mechanical prosthetic valve, atrial fibrillation, or intracardiac thrombus. DAPT has proven superior. An INR >1.6 is a strong relative contraindication to elective cardiac catheterization. If emergent cardiac catheterization is required due to ACS or MI, consider accessing the radial artery because hemostasis is rarely an issue with this approach.

G. Antiplatelet therapy

1. Platelets are essential in thrombus formation, and some form of antiplatelet therapy is typically given at the time of PCI.

2. **Thromboxane A2 inhibitor (aspirin).** Aspirin (acetylsalicylic acid [ASA]) is a cornerstone of effective antiplatelet therapy. Aspirin impairs platelet aggregation by irreversibly inhibiting platelet cyclooxygenase, thereby limiting thromboxane A_2 production. A loading dose of 325 mg of aspirin should ideally be given at least 2 hours before PCI and be continued indefinitely at 81 mg daily maintenance therapy following the procedure. Evidence from the CURRENT-OASIS 7 trial, which included a large subgroup of 17,263 patients undergoing PCI, has shown there is no benefit to a higher 325 mg daily maintenance dose, and it is associated with higher rates of bleeding complications. Secondary prevention trials have shown aspirin to reduce death, MI, and stroke by 27%. In PCI patients, aspirin reduces abrupt vessel closure.

3. **Adenosine diphosphate receptor antagonists (ticlopidine, clopidogrel, prasugrel, ticagrelor, and cangrelor)**

a. The addition of a second oral antiplatelet agent to aspirin (DAPT) marked a significant advance in contemporary pharmacotherapy for PCI. In the late 1990s, several landmark trials convincingly demonstrated that combined antiplatelet therapy (aspirin and thienopyridine), as compared with conventional anticoagulant therapy, after PCI reduced the incidence of both thrombotic and bleeding complications.

b. Thienopyridines such as clopidogrel and ticlopidine inhibit adenosine diphosphate–induced platelet aggregation by the $P2Y_{12}$receptor. Clopidogrel is preferred to ticlopidine because of its better safety profile, although both require hepatic metabolism for activation.

c. Ticlopidine is poorly tolerated with prolonged use, resulting in 20% of patients discontinuing the drug because of nausea, diarrhea, and rash. Neutropenia and thrombotic thrombocytopenic purpura (TTP) occur in 1% to 3% and 0.03% of patients, respectively. The complete blood count should be serially examined in the first several months of use (q2wk × 3 months).

d. Clopidogrel is better tolerated than ticlopidine and has largely replaced it in clinical practice in the United States. The risk of TTP with clopidogrel is the same as in the general population (11 in 3 million), and neutropenia is not an issue, making blood count monitoring unnecessary.

e. The ACC/AHA guidelines recommend routine clopidogrel pretreatment with a dose of 600 mg, although this recommendation is made on the basis of studies that included patients with ACS. In patients undergoing elective PCI, a recent study revealed no difference in ischemic or bleeding complications between 300 and 600 mg loading doses. Similarly, in patients on chronic clopidogrel therapy undergoing elective PCI, the ARMYDA-4 RELOAD investigators found no benefit to an additional 600 mg "reloading" dose of clopidogrel; the group of patients with NSTEACS did have a reduction in MACE at 30 days, however.

f. For a discussion of clopidogrel duration after PCI, please refer to Section **XI.F.4**. For details of clopidogrel use after ACS, please refer to **Chapter 2**.

g. The issue of clopidogrel nonresponsiveness, defined as platelet inhibition <20%, is reported to be as high as 40% and is associated with worse clinical outcomes including ST, MI, and death. Mechanisms include genetic predisposition (i.e., CYP2C19 polymorphism that affects clopidogrel metabolism and thus activation) and drug–drug interactions. Unfortunately, recent studies (including OASIS-7 and GRAVITAS) have not shown a benefit to higher maintenance dose clopidogrel (150 vs. 75 mg daily), even in patients with established high platelet reactivity while on clopidogrel. Management of these patients is therefore difficult, and we typically change to a third-generation agent such as prasugrel or ticagrelor in cases of true clopidogrel nonresponse.

h. Prasugrel is a novel "third-generation" thienopyridine prodrug that requires conversion to an active metabolite with high affinity for the platelet $P2Y_{12}$ receptor site, resulting in a potent antiplatelet effect. The TRITON-TIMI 38 trial randomized 13,608 patients with moderate-to-high–risk ACS with scheduled PCI to either prasugrel or clopidogrel therapy and found a significant reduction in the primary efficacy end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke associated with prasugrel therapy. Prasugrel was also associated with a reduction in rates of MI, TVR, and ST. However, of some concern was a significant increase in major (HR 1.32, 95% CI 1.03 to 1.68, $p = 0.03$) and life-threatening (1.4% vs. 0.9%, $p = 0.01$) bleeding observed in the prasugrel group. An important subgroup of patients who had a net negative outcome was those with a prior history of stroke or transient ischemia attack, and prasugrel use in such patients is not recommended. Additional populations in which special caution is advised include patients over 75 years of age and patients weighing <60 kg because increased bleeding complications were noted in these groups. In an important distinction from the CURE trial, NSTEACS patients in TRITON-TIMI 38 only received the prasugrel loading dose after their coronary anatomy was angiographically defined and percutaneous revascularization planned.

i. Ticagrelor is a "third-generation" reversible $P2Y_{12}$ antagonist that is an active drug and does not require hepatic conversion to an active metabolite (unlike the thienopyridines). It exhibits the most rapid onset, greatest inhibition, and least individual variability of the oral $P2Y_{12}$ agents. The foundation of its use was established by the PLATO trial in which ticagrelor demonstrated a lower rate of composite cardiovascular events (death, MI, and stroke; 9.8% vs. 11.7%, $p < 0.001$) with fewer cases of in-stent thrombosis and without a significantly increased risk of major bleeding compared with clopidogrel. There was, however, a higher incidence of non-CABG major bleeding including intracranial hemorrhage in the ticagrelor group (4.5% vs. 3.8%, $p = 0.03$). It is important to recognize several key differences from the PLATO trial design and results when compared with the TRITON-TIMI 38 trial which established prasugrel use. First, in PLATO, ticagrelor was administered "upstream" at the time of randomization and prior to coronary angiography, which more closely fits contemporary patterns of ACS management. In addition, there was a significant benefit from ticagrelor not only among those patients who subsequently received revascularization with PCI, but also in those who were managed medically ("conservative management") as well. In addition to its antiplatelet effects at the $P2Y_{12}$ receptor outlined above, recent studies have suggested possible "pleiotropic" effects of ticagrelor because of its biologic effects on adenosine. Patients with ACS were found to have significantly higher adenosine plasma concentrations 6 hours after ticagrelor loading compared with clopidogrel loading, and ticagrelor-treated patients (but not clopidogrel-treated patients) demonstrate reduced in vitro uptake of exogenous adenosine by erythrocytes. Whereas these early findings are still only hypothesis-generating, a number of reported clinical effects of ticagrelor (e.g., improved endothelial function) could be compatible with an adenosine-mediated effect and this warrants further dedicated investigation. Also in contrast to the other $P2Y_{12}$ agents discussed above, the use of ticagrelor is explicitly contraindicated in patients with severe hepatic dysfunction and another agent should be considered. Similar to clopidogrel and prasugrel, the use of ticagrelor in moderate liver dysfunction has not been well studied.

j. Cangrelor is an IV (nonthienopyridine) adenosine triphosphate analog which reversibly inhibits the $P2Y_{12}$ adenosine diphosphate receptor in a manner similar to ticagrelor. It was approved for use by the FDA in June 2015 as an adjunct to PCI in patients who have not been treated with a $P2Y_{12}$ agent and who are not being given a GPI. Major advantages of cangrelor when compared with other antiplatelet agents are its rapid onset of action and rapid return of platelet function after its discontinuation. Two trials (CHAMPION PLATFORM and CHAMPION PCI) evaluated its use in patients with ACS or stable angina requiring PCI and both failed to show clinical superiority compared to clopidogrel alone for a composite end point of death, MI, or ischemia-driven revascularization. A third trial (CHAMPION PHOENIX) studied patients undergoing urgent or elective PCI and found a composite primary efficacy end point (death, MI, ischemia-driven revascularization, or ST) occurred less often in the cangrelor group, without significant difference in the rate of severe or life-threatening bleeding at 48 hours. The most notable difference in the design of the CHAMPION PHOENIX trial compared with the earlier cangrelor trials was that it used a more sophisticated and detailed definition for PCI-related MI. In a pooled analysis of patient-level data from the three CHAMPION trials (comprised of 12% STEMI, 57% NSTEACS, 31% stable disease), cangrelor lowered the rate of the primary composite efficacy end point of death, MI, ischemia-driven revascularization, or ST at 48 hours compared with control (clopidogrel or placebo) (3.8% vs. 4.7%; OR 0.81; 95% CI 0.71 to 0.91). Mild, but not major, bleeding was increased with cangrelor (16.8% vs. 13.0%).

H. GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban)

1. GPIs are IV medications that inhibit platelet aggregation and thrombus formation by preventing the binding of fibrinogen or circulating von Willebrand factor on the platelet surface. GP IIb/IIIa receptor inhibition prevents these receptors from binding to fibrin and forming the platelet–fibrin cross-linking that is required for thrombus formation. GP IIb/IIIa receptor occupancy >80% prevents the development of thrombus.
2. **Abciximab** is a human–murine chimeric antibody fragment that binds the GP IIb/IIIa receptor with high affinity, resulting in a slow dissociation rate (i.e., noncompetitive inhibition). Although abciximab remains detectable on platelets for the lifetime of the platelet, it is rapidly cleared from plasma, allowing platelet aggregation to return to normal in 12 to 36 hours. Rapid reversal of platelet inhibition in the event of bleeding requires discontinuation of the abciximab infusion, waiting 30 minutes for plasma clearance, and platelet infusion (12 units) so as to provide functional platelets. Profound thrombocytopenia occurs in 0.4% to 1.1% of patients. Platelet counts should be measured within the first 2 to 4 hours and the following day. Abciximab readministration has not been associated with hypersensitivity or anaphylaxis, although the risk of profound thrombocytopenia is somewhat higher (2.2%).
3. **Eptifibatide** is a cyclic heptapeptide and **tirofiban** is a tyrosine derivative nonpeptide mimetic. Both act as competitive inhibitors requiring high levels for adequate inhibition. Both have a short plasma half-life (2.0 to 2.5 hours), with platelet aggregation normalizing in 30 minutes to 4 hours. In the event of bleeding, the infusion should be stopped. Unlike abciximab, the effect cannot be reversed and platelets remain inhibited until plasma drug levels fall. Profound thrombocytopenia is rare (0.0% to 0.3%).
4. The use of GPI versus heparin alone during PCI prevents 65 adverse events per 1,000 treated patients and is arguably beneficial for all types of interventions. These benefits are particularly enhanced for unstable angina, diabetes mellitus, and bail-out stenting.
5. At proper doses, all three GPI agents are very potent inhibitors of platelet aggregation; however, their clinical use has been diminishing because much of their supporting evidence came prior to the contemporary era of routine oral DAPT. Trials reflecting routine use of clopidogrel early in the course of treatment or bivalirudin in PCI did not demonstrate an incremental benefit for ischemic outcomes with the routine addition of GPI. **Therefore, current guidelines for management of patients with ACS call for dual, not triple antiplatelet therapy** (ASA and usually oral $P2Y_{12}$ antagonists rather than GPI), with the addition of GPI reserved for selected patients who remain unstable, have a large thrombus burden on angiography, or have very high-risk clinical features.

For specific recommendations regarding the use of GPIs during ACS, please refer to **Chapter 2**.

I. Intracoronary vasodilators.

PCI can result in no-reflow, which is defined as a reduction in coronary flow without an obstructive lesion. The most probable causes of no-reflow are microvascular spasm and distal embolization. Potent microvascular vasodilators, such as adenosine (36 to 72 µg), nicardipine (100 to 200 µg), nitroprusside (50 to 200 µg), or verapamil (200 µg), often restore normal flow. Nitroglycerin is a logical choice for relieving epicardial spasm but has no effect on the microvasculature. Immediately before SVG intervention, verapamil pretreatment has been shown to prevent no-reflow but has never been shown to reduce the risk of CK-MB elevation.

XV.SUPPORTIVE ADJUNCTIVE THERAPY

A. Please refer to the chapter on mechanical circulatory support devices.

XVI.POST-PCI MANAGEMENT

A. Access site care

1. The groin or arm access site should be examined for hematoma, pseudoaneurysm (systolic bruit), and arteriovenous fistulas (continuous murmur). A pulsatile mass also suggests a pseudoaneurysm. Ultrasound studies can confirm the diagnosis of pseudoaneurysm or arteriovenous fistula. Suprainguinal tenderness, back pain, lower quadrant abdominal pain, or hypotension should make one suspicious for retroperitoneal hemorrhage, which can be confirmed by computed tomography (CT). A hemoglobin level 1 day after PCI should be routine, and a decrease >2 g/dL is concerning. Distal pulses should be examined as well. Pulselessness, pain, pallor, paresthesias, and a cool extremity suggest an acute arterial occlusion.

2. **Pseudoaneurysms** <2 cm often close spontaneously; those 2 to 3 cm can often be closed by external, ultrasound-guided compression (90% success rate); and those >3 cm generally require surgical correction. Another frequently successful option is thrombin injection if the pseudoaneurysm has a thin neck.

3. **Arteriovenous fistulas** are typically small and inconsequential, rarely causing high-output failure. Indications for ultrasound-guided compression (success rate > 80%) or surgical closure include significant shunting, extremity swelling/tenderness, congestive heart failure (CHF), and deep venous thrombosis.

4. A **retroperitoneal hemorrhage** can be treated by supportive care (i.e., transfusions, close observation, and bed rest) in >80% of cases. Anticoagulation must be reversed, and frequent hemodynamic monitoring in an experienced intensive care unit is required. If required, transportation to CT scan should be deferred until the patient is hemodynamically stable. If the bleeding does not spontaneously stop, the patient may require vascular surgery consultation. Other options include balloon tamponade or coil embolization if a small side branch is the culprit.

5. **Acute arterial occlusion** may be due to dissection or thromboembolism. Both typically require angiography of the affected extremity with access from another extremity (e.g., with a cold right leg after right femoral artery access, left femoral access should be obtained and an angiogram of the right lower extremity can be performed by crossing over to the right common iliac artery). Dissection typically requires prolonged balloon inflation and possible stenting or surgery. Stenting at the common femoral artery is discouraged, because it is a flexion point and a frequent site of attaching bypass grafts. Thromboembolism can be treated with surgical (Fogarty catheter) or percutaneous mechanical thrombectomy (Possis AngioJet).

B. Monitoring for myocardial ischemia. A 12-lead electrocardiogram (ECG) should be obtained before and after PCI in order to have a baseline. The patient should be monitored on a cardiac ward that has continuous electrocardiographic monitoring and nurses familiar with routine post-PCI care. The CK and CK-MB levels should be measured 12 hours after the intervention. A procedural MI is presently defined as a CK-MB more than three times the normal (assuming a normal baseline CK-MB). Elevated CK, CK-MB, or electrocardiographic abnormalities occur in 5% to 30% of patients. Mechanisms include

distal embolization, side branch occlusion, dissection, and spasm. Troponin levels are not routinely measured after PCI.

C. **Monitoring for contrast-induced nephropathy.** Nonsteroidal anti-inflammatory drugs, cyclosporine, and metformin should be withheld for 24 to 48 hours beforehand and for 48 hours afterward. Postprocedure saline hydration is continued at 75 to 150 mL/h for a total infusion of 1 to 2 L. Renal function (serum creatinine) should be monitored in patients with diabetes and renal dysfunction.

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CHAPTER 64

Percutaneous Structural Heart Disease Procedures

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I. INTRODUCTION. The last decade witnessed a remarkable rise in the number of novel percutaneous, catheter-based procedures using new concepts and technologies for the treatment of structural heart disease. Most percutaneous therapies have largely evolved from concepts developed by surgeons and often incorporate the lessons learned from established surgical procedures. Currently, percutaneous catheter-based therapy is available for a number of valvular disorders, including aortic stenosis (AS), mitral stenosis (MS), mitral regurgitation (MR), and prosthetic paravalvular leaks (PVLs), as well as other structural cardiac disorders such as hypertrophic obstructive cardiomyopathy, patent foramen ovale (PFO), and atrial septal defects (ASDs). Whereas a comprehensive review of structural cardiac interventions is beyond the scope of this chapter, we provide an overview of the major devices and relevant clinical studies that have been performed.

II. PERCUTANEOUS TRANSCATHETER MITRAL VALVE REPAIR (MVRE)

A. Background. MR is one of the most common valvular disorders, encountered in about 9% of the population aged >75 years. Surgical MVRe, when feasible, produces excellent outcomes, including lower operative mortality, improved long-term survival, and reduced incidence of endocarditis and thromboembolic complications, compared with mitral valve replacement (MVR). A number of percutaneous MVRe techniques have been developed that are analogous to surgical procedures. Percutaneous mitral annuloplasty leverages the close relationship of the coronary sinus (CS) to the posterior mitral annulus. The **Carillon** (Cardiac Dimensions, Kirkland, WA) device, which has been granted Conformité Européenne (CE Mark) approval, is deployed in the CS and serves to "cinch" the annulus, resulting in improved mitral valve (MV) leaflet coaptation. There are also numerous other devices in various stages of preclinical and clinical development.

The **MitraClip** (Abbott Vascular, Santa Clara, CA) remains the most widely tested system in humans and is currently the only device commercially available to treat degenerative MR in the United States. Over 25,000 MitraClips have been implanted worldwide since its inception. The technique is based loosely on the surgical Alfieri stitch, which brings the anterior and posterior leaflets in close apposition using a suture and creates an anatomic "double-orifice" MV. In the United States, transcatheter MVRe is indicated in symptomatic

patients with severe degenerative MR who are considered to have prohibitive surgical risk. Patients with severe functional MR are currently being studied in the COAPT trial, which randomizes patients to MitraClip versus medical therapy. The MitraClip is available commercially for functional MR in Europe where this represents the majority indication of worldwide use.

B. Procedure. The MitraClip system uses a steerable 22F guide catheter that is introduced through the femoral vein and subsequently advanced to the left atrium via transseptal puncture (Fig. 64.1). Through this guiding catheter, a delivery system containing the V-shaped clip is introduced in the left atrium and positioned with the arms of the clip perpendicular to the MV line of coaptation using transesophageal echocardiography (TEE) guidance. The clip is advanced to the left ventricle in an open position and retracted to grasp the anterior and posterior MV leaflets at the desired location. After confirmation by TEE of clip position, the clip can be locked. If satisfactory (by TEE), the clip can be released; otherwise, it can be reopened and the process repeated. If necessary, multiple clips can be deployed to achieve a satisfactory result. Care must be taken in this situation to not impede forward flow across the valve and trade MR for MS.

FIGURE 64.1 Percutaneous transcatheter mitral valve repair. **A:** Right anterior oblique projection of the optimal positioning of the MitraClip device. **B:** Left anterior oblique projection of the optimal positioning of the MitraClip device. **C:** Right anterior oblique projection of MitraClip after its release from the delivery catheter. **D:** Left anterior oblique projection of MitraClip after its release from the delivery catheter.

C. Complications. Routine complications associated with vascular access like major or minor bleeding are the most commonly encountered complications. Recurrent MR and the requirement for MV surgery are the prime limitations of the current technique, especially in ischemic MR or in the presence of a significant annular calcification. Partial clip detachment is the most important mechanical problem encountered with the procedure and treatment with subsequent clip placement or surgical intervention is dependent on the mechanism of leaflet detachment. These are generally not symptomatic and are treatable with MV surgery or placement of an additional clip. Iatrogenic MS is a significant complication that may arise as a result of this procedure.

D. Outcomes. Data from the pivotal EVEREST II trial, which randomized 279 patients to MitraClip versus surgical repair in a 2:1 fashion, demonstrated freedom from the combined end point (death, MV surgery within 90 days, or MR > 2+ at 1 year) of 72.4% and 87.8% in the two groups, respectively, demonstrating noninferiority of the MitraClip to conventional surgical treatment. Nevertheless, the MitraClip arm had a higher incidence of residual significant MR and subsequent need for MV surgery and thus surgical MVRe remains the gold standard for patients able to undergo open heart surgery.

The initial studies of the MitraClip concentrated on patients with degenerative MR. However, the EVEREST II trial and the clinical experience in Europe (where the device received the CE Mark) have shown efficacy in a large number of patients with functional MR as well. Freedom from significant MR was enjoyed by more than 80% of high surgical risk patients, with resultant decreases in left ventricular (LV) volume, New York Heart Association class, congestive heart failure (CHF) hospitalizations, and improved quality of life.

III.PERCUTANEOUS MITRAL BALLOON VALVULOPLASTY (PMBV)

A. Background. Although there has been a significant reduction in the prevalence of rheumatic heart disease in western countries, it still represents a major public health concern in the developing world. MS is one of the most common presentations of rheumatic heart disease. It continues to represent a major clinical problem in the United States primarily because of outmigration from developing countries or the occurrence of restenosis after previous surgical commissurotomy. Stenosis of the valve may occur because of commissural fusion, leaflet thickening, and/or chordal shortening and fusion.

Before the advent of PMBV, symptomatic MS was treated using surgical commissurotomy. Since the introduction of the percutaneous procedure in the early 1980s by Inoue and colleagues, PBMV has evolved to become the first line of therapy for appropriately selected patients with MS. The technique works similarly to commissurotomy, resulting in opening of the fused commissures.

B. Procedure. The Wilkins splitability score is the most widely used echocardiographic parameter to determine the safety and feasibility of PBMV, and this takes into consideration leaflet mobility, leaflet thickening, subvalvular thickening, and valve calcification (each scored 0 to 4 points). Multiple investigators have shown that patients with a score of 8 or less have the greatest freedom from death and valve surgery and the largest improvement in MV area with PMBV.

Selection of the appropriate balloon size is one of the most important steps for accomplishment of a successful PBMV. A good rule of thumb is to use the following formula to determine the maximum balloon dilation size: Balloon size (mm) = patient height (cm)/10 + 10 mm. Transseptal puncture is performed, most commonly with TEE guidance, via a sheath placed in the femoral vein. Once the sheath has entered the left atrium, it is exchanged for the Inoue balloon catheter.

The balloon catheter is slowly advanced into position in the left ventricle. The Inoue balloon consists of three portions with slightly different compliances. As pressure is added to the balloon, the distal portion inflates first followed by the proximal portion. As soon as the distal portion is inflated, the balloon is pulled until resistance is felt. On addition of more pressure, the proximal portion is inflated, which fixes the balloon in the middle waist portion of the valve. The middle waist has the least compliance and dilates only when substantial pressure is added to the balloon, thereby securing the balloon across the valve prior to the dilation of the annulus.

In our institution, we routinely use TEE to guide the valvuloplasty in order to assess the result of balloon inflation (in addition to simultaneous left atrial (LA)–LV gradient measurement) and, more importantly, to evaluate the degree of MR. Substantial increases in MR should preclude further inflation. In addition, the procedure should be aborted in the presence of left atrial appendage (LAA) clot.

C. Complications. The most common serious complications include hemopericardium or severe MR. Perforation of cardiac chambers, which occurs with a rate of 0% to 2%, may happen while manipulating the catheters in the heart. Whereas an increase in MR may routinely be noted after the PMBV, it rarely requires a surgical intervention.

D. Outcomes. Immediate postprocedural success with a final valve area >1.5 cm^2 without moderate or severe MR is the best predictor of long-term outcome. The best results are obtained in young people with favorable anatomic characteristics. Randomized clinical trials have demonstrated that long-term results of PMBV in young patients are as good as open commissurotomy and are better than closed commissurotomy. In patients with optimal morphology, freedom from restenosis has been reported as 92% at 5 years, 85% at 10 years, and 65% at 15 years. Repeat PMBV has been recommended as first-line therapy in patients with symptomatic mitral restenosis after PMBV or commissurotomy in whom the mechanism of restenosis is commissural fusion.

IV.BALLOON AORTIC VALVULOPLASTY (BAV)

A. Background. Degenerative or calcific AS is one of the most common valvular disorders encountered in western countries. Surgical aortic valve replacement (SAVR) is the treatment of choice for patients who are safely able to undergo cardiac surgery, and transcatheter aortic valve replacement (TAVR) is emerging as a favorable option in patients at high risk for surgical complications. Balloon dilation of the calcified aortic valve results in stretching of the fused commissures. Because of rapid reversibility of these effects, there is an early loss of effectiveness in severe degenerative AS, and the valve returns to pre-BAV size in 3 to 6 months.

In patients with severe AS who are hemodynamically unstable and for whom urgent aortic valve replacement (AVR) is not feasible, BAV may serve as a "bridge" to valve replacement. Similarly, we have also seen significant functional improvement in patients after BAV so that patients unable to undergo AVR initially have improved to a point that TAVR or SAVR could be performed safely. In patients with symptomatic severe AS who require urgent noncardiac surgery, BAV may be considered as a temporizing measure in the hope of reducing the risks of perioperative hemodynamic changes associated with anesthesia.

A number of patients with severe AS have other comorbidities, such as chronic obstructive pulmonary disease or liver or kidney disease, that make it difficult to discern the degree to which AS contributes to their symptoms. In such cases, BAV may provide a therapeutic answer; improvement of symptoms points to AS as the driver of symptoms and may push for a more definitive valve replacement option. Finally, in patients without any option for either TAVR or SAVR, BAV may be considered as a palliative measure.

B. Procedure. The femoral retrograde approach is the most commonly utilized method for BAV, although in patients with severe iliofemoral disease, the procedure can be performed in an antegrade fashion via venous access and transseptal puncture. A Swan–Ganz catheter is placed in the pulmonary artery for continuous hemodynamic monitoring and assessment of cardiac output. A temporary pacemaker is placed in the right ventricle to perform rapid pacing (180 beats/min) during balloon inflation to reduce cardiac output and minimize balloon movement in the annulus. After crossing the aortic valve using a 5F AL-1 diagnostic catheter and a straight wire, a stiffer wire is inserted and positioned in the left ventricle. BAV is typically performed using balloons ranging from 18 to 25 mm in diameter. The balloon is sized based on the annulus diameter on transthoracic echocardiography (TTE); the maximum balloon size is 10% larger than the annulus, and we routinely begin dilation at smaller sizes and assess the hemodynamic result prior to

increasing the balloon size. Procedural success with BAV is typically defined as a 50% reduction in mean aortic valve gradient and a 25% increase in aortic valve area (AVA); most patients usually experience almost a 50% increase in AVA.

C. Complications. It should be noted that BAV carries considerable risk. The 30-day mortality associated with the procedure may be up to 10% and as high as 50% at a median follow-up period of 6 months, usually because of either aortic regurgitation (as a complication of the balloon procedure) or persistent heart failure. Other complications (occurring in up to 15% of patients) include stroke, peripheral vascular complications (because of the size of the devices used and concomitant incidence of peripheral arterial disease), coronary occlusion, need for permanent pacemaker implantation, renal failure, cardiac tamponade, and cardiac arrest.

D. Outcomes. Despite a modest improvement in valve area, a significant improvement in functional status may be noted after BAV. However, the benefit of BAV gradually disappears over the course of the next few months. The poor functional status of the patients, as well as only moderate, transient effects of the technique, is primarily responsible for the overall grim long-term results of stand-alone BAV. Extensive data indicate that stand-alone BAV does not change the natural course of AS, even after repeated procedures. Despite this, BAV holds an important place in the treatment of patients with severe AS.

V.TRANSCATHETER AORTIC VALVE REPLACEMENT

A. Background. Up to a third of patients with severe symptomatic AS do not undergo surgical AVR, as they are deemed to have a high surgical risk because of age or multiple comorbidities. The interest in percutaneous aortic valve implantation began in the early 1990s. The first human experience was reported by Cribier et al. in 2002. Since then, rapid advancements in the design of the stented valve and delivery catheters and improved facility in implantation techniques have led to a consistent improvement in the postprocedural outcomes and have heralded a new era in the treatment of valvular AS.

The procedure involves implantation of a tissue pericardial valve that is mounted within a stent. The key to TAVR success is a careful selection of patient population for the procedure and a judicious use of preprocedural and intraprocedural imaging modalities, including fluoroscopy and aortic angiography.

Currently, the indications for TAVR include severe symptomatic AS with a valve area of ≤ 0.8 cm^2, mean aortic valve gradient of ≥ 40 mm Hg, or a peak aortic jet velocity of ≥ 4.0 m/s with one or more of the following:

1. High risk for conventional AVR (Society of Thoracic Surgeons [STS] score > 10 or logistic EuroSCORE > 20%) (https://www.sts.org/resources/risk-calculators)
2. Contraindication to standard thoracotomy including prior multiple thoracotomies or radiation to the chest wall
3. Surgical factors not accounted for by the STS score resulting in high surgical risk (i.e., porcelain aorta, cirrhosis, frailty, etc.)

B. Procedure. There are a number of valves available worldwide for TAVR, but only two are currently available in the United States and have been studied within randomized control trials: the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) and the self-expanding CoreValve ReValving system (Medtronic

Inc., Minneapolis, MN) (Fig. 64.2). The largest human experience is with the Edwards Lifesciences series of balloon-expandable aortic valves. The valve consists of a tubular stainless steel stent with a fabric valve cuff and contains valve leaflets derived from bovine pericardial tissue. This valve is available in four sizes: 20, 23, 26, and 29 mm. Valve sizing takes into consideration the annular area measured using 3D imaging (computed tomography [CT] or TEE) as well as various aortic root characteristics. Although the valve was implanted initially using the transvenous access and subsequent transseptal puncture, it is now routinely implanted using either a retrograde transfemoral approach or an antegrade transapical approach. The newest iteration of the commercially available SAPIEN series, the S3, is delivered via a 14F (20-, 23-, 26-mm valves) or 16F (29-mm valve) expandable sheath.

The preprocedural assessment consists of TTE, iliofemoral contrast angiography or iliofemoral CT, 3D annulus imaging using CT angiography, TEE, or magnetic resonance imaging and coronary angiography. Appropriate patient selection, which includes the anatomic characteristics of the aortic annulus and iliofemoral system, is imperative to procedural success.

FIGURE 64.2 Transcatheter aortic valve replacement. **A:** Proper positioning of various catheters and devices for valve replacement: a transesophageal echocardiography probe in the esophagus, a Swan–Ganz catheter in the pulmonary artery, a pigtail catheter in the aortic root, an AL-1 diagnostic catheter in the ascending aorta (prior to valve crossing), and a temporary pacemaker wire in the right ventricle. **B:** Aortic valvuloplasty being performed using a standard balloon. **C:** Proper positioning of the crimped Edwards SAPIEN prosthesis across the aortic valve. **D:** Deployment of the valve using balloon inflation after initiation of rapid pacing.

1. **Transfemoral TAVR.** Transfemoral TAVR is usually performed under general anesthesia or conscious sedation in a catheterization laboratory or hybrid operating room equipped with multimodality imaging equipment. Vascular sheaths are placed in a standard fashion in both femoral arteries and veins. A transvenous pacing wire is introduced into the right ventricle through the venous access port to enable rapid pacing (180 beats/min) in order to minimize cardiac output and valve movement during valve deployment. A BAV is often performed using standard technique, with a balloon that is slightly smaller than the size of the planned valve prosthesis to facilitate valve crossing.

Once the TAVR prosthesis is suitably positioned, the valve is deployed. This requires rapid pacing for the balloon-expandable valves, but is not necessary for self-expanding valves. The final positions of deployment as well as degree of paravalvular aortic regurgitation are assessed using echocardiography, hemodynamics, and aortography.

Inappropriate positioning may require a second valve deployment. Excessive paravalvular aortic regurgitation may be treated using further balloon dilation or deployment of a second valve. Echo and angiographic assessment for complications (including pericardial effusion, aortic root trauma, and coronary occlusion by the valve) are imperative prior to closure of the femoral access. Similarly, angiography of the iliofemoral system is necessary to evaluate for vascular trauma that might require endovascular or open surgical repair prior to completion of the procedure.

2. **Alternate access for TAVR.** Given the high incidence of peripheral arterial disease in patients with severe AS, several alternative access sites have been investigated and include the **transapical, transcarotid, transsubclavian, transaortic, and transcaval approaches**. The result of TAVR from these access sites is not as well studied as traditional transfemoral TAVR, and outcomes may not be as good.

C. **Complications.** Procedural success has ranged from 86% to 100% across the literature. After an initial learning curve, excellent procedural success rates with minimal intraprocedural mortality have been reported at major tertiary care centers performing TAVR. Vascular access complications are encountered more often (<10%) than with other interventional procedures because of the large sheath sizes used for TAVR. Complications associated with limited thoracotomy are expected after alternate access TAVR. Malposition of the aortic prosthesis may be encountered in about 1% to 3% of cases. Periprocedural strokes have been reported in 2% to 3% of patients undergoing TAVR with the newest generation Edwards S3 valve and about 3% with the CoreValve prosthesis. Major complications following CoreValve implantation include the need for permanent pacemaker implantation in up to one-third of patients.

D. **Outcomes.** The PARTNER 1 trial was the first multicenter randomized controlled trial of TAVR and provided two important randomized comparisons. The PARTNER 1B cohort showed a significant reduction in mortality (30% vs. 50% at 1 year and 72% vs. 94% at 5 years) in 358 inoperable patients with severe symptomatic AS after randomization to TAVR with balloon-expandable valve (Edwards SAPIEN) versus standard therapy including BAV. The PARTNER 1A cohort showed that outcomes of surgical AVR and balloon-expandable TAVR are comparable in high-risk patients, with no difference in 5-year rates of mortality and major clinical outcomes (including stroke, cardiac death, and myocardial infarction [MI]). A randomized control trial of self-expanding valves (CoreValve) showed superiority to surgical AVR in mortality at 1 year (14% vs. 19%), although the STS score was lower in this cohort compared with the PARTNER cohort (7.4% vs. 11.7%). The PARTNER 2 trial showed that balloon-expandable TAVR (Edwards Sapien XT) had comparable primary composite end points of all-cause death or disabling stroke (19% vs. 21%) at 2 years to surgical AVR in intermediate risk patients, with a suggestion that trans-femoral (TF)-TAVR patients fared better than SAVR. The S3 intermediate risk trial compared approximately 1,000 patients at intermediate surgical risk who underwent TAVR (88% TF approach) with a propensity-matched SAVR group from the PIIA trial. At 1 year, the TF-TAVR group demonstrated superiority over surgery with regard to the major end points of death (7.4% vs. 13.0%, $p < 0.001$) and stroke (4.6% vs. 8.2%, $p = 0.004$).

VI.PFO CLOSURE

A. **Background.** PFO is a remnant of fetal cardiac circulation and is found in 27% to 33% of adults. Although generally believed to be an "innocent bystander," PFO has been associated with stroke, migraines, platypnea-orthodeoxia, and decompression sickness among divers. PFO arises when the septum primum and septum secundum fail to fuse despite some degree of overlap. Atrial septal aneurysms and prominent Chiari networks have been associated with PFO. Percutaneous PFO closure is currently recommended in patients with platypnea-orthodeoxia and in divers with decompression sickness. Although several observational studies have shown the benefits of PFO closure in the prevention of

migraine and cryptogenic strokes, these findings have not been confirmed in major randomized trials. Hence, controversy persists regarding definitive indications and settings for PFO closure for migraine and cryptogenic stroke prevention.

FIGURE 64.3 Patent foramen ovale (PFO) closure using Amplatzer device. **A:** Balloon sizing of the PFO tunnel after crossing the PFO using a wire. The intracardiac echocardiography probe is visible next to the balloon. **B:** Deployment of the left atrial disk of the Amplatzer occluder device. **C:** Deployment of the right atrial disk of the Amplatzer occluder device. **D:** Device in place after its release from the delivery catheter.

All PFO closure devices have a similar design, usually consisting of two atrial disks connected by a short neck. Under fluoroscopic and intracardiac echocardiography (ICE) guidance, the device is placed such that the two atrial disks lie on either side of the interatrial septum, with the neck positioned in the PFO tunnel. A large part of the atrial shunt is eliminated as a result of physical obstruction to flow. Most of the residual shunt is eliminated over the course of a few months after the procedure, as the device becomes endothelialized. Dual-antiplatelet therapy is generally recommended for the first 6 months after closure to minimize the risk of thromboembolism prior to device endothelialization.

B. Procedure. Several devices for transcatheter PFO closure have been tested in humans, including the Cardioform Septal Occluder device (WL Gore & Associates, Newark, DE) and the Amplatzer cribriform ASD occluder device (AGA Medical, Golden Valley, MN) (Fig. 64.3). Because these devices are Food and Drug Administration approved only for ASD closure, use for PFO closure is "off-label." Sizing of the devices may vary based on the degree of associated atrial septal aneurysm; significant aneurysm generally requires a larger device.

Briefly, the procedure involves placement of an 8F to 12F vascular sheath (depending on device size) in one femoral vein and a 9F sheath in the contralateral femoral vein for ICE. The ICE catheter is parked in the right atrium for procedural visualization. The PFO is usually crossed using a wire and a Goodale-Lubin (GL) catheter under ICE and fluoroscopic guidance. Through the GL catheter parked in the left superior pulmonary vein, the wire is exchanged for a stiffer wire over which the closure device delivery system is advanced. The LA disk of the device is deployed and the system slowly retracted. This action facilitates apposition of the septum primum to the septum secundum and effectively closes the PFO. The right atrial disk is then deployed. After confirmation of the positioning and stability using ICE and fluoroscopy (and sometimes right atrial angiography), the device is released from the delivery catheter.

C. Complications. Transcatheter PFO closure is generally associated with a high procedural success rate and without significant risk of complication. Rare complications including device migration or embolization, symptomatic air embolism, and atrial fibrillation (AF) or chamber perforation with cardiac tamponade may occur intraprocedurally. Later complications associated with the procedure include thrombus formation (more common with CardioSEAL than Amplatzer), device erosion, or formation of a new ASD.

D. Outcomes. Several large observational studies have demonstrated the benefit of PFO closure in secondary prevention of migraine and prevention of recurrent neurologic thromboembolism in patients with cryptogenic stroke or transient ischemic attack.

However, these findings have not been ratified in randomized clinical trials. The Migraine Intervention with StarFlex Technology study failed to demonstrate any significant difference in migraine cessation between the closure and the "sham" arms. The Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke (RESPECT) trial randomized 980 patients with cryptogenic stroke to PFO closure versus medical therapy alone. The initial results of the RESPECT trial showed no difference in the primary composite end point of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death on the primary intention-to-treat analysis, but there was statistical evidence of benefit to PFO closure in the secondary as-treated and prespecified per-protocol analysis with a reduction in event rate of 0.43 versus 1.38 events per 100 patient-years. Long-term results of the RESPECT study demonstrated a significant decrease in risk of recurrent cryptogenic stroke of 4.3% versus 1.5% with PFO closure.

VII.ASD CLOSURE

A. Background. ASD is one of the most common adult congenital heart diseases encountered in the U.S. population. Although ASDs generally remain asymptomatic till early adulthood, they are associated with several clinical presentations, including right ventricular failure, atrial arrhythmias, pulmonary hypertension, and paradoxical embolism.

Patients with hemodynamically significant ASD should undergo elective closure either surgically or with the transcatheter technique, although in recent years, the transcatheter approach has become the first line of therapy in patients with appropriate secundum ASD anatomy. The hemodynamic significance of an ASD is determined by the presence of right ventricular enlargement in the presence of defect diameter >1 cm or the presence of significant left-to-right shunting with an elevated shunt ratio (Q_p:Q_s > 1.5).

The principle of ASD closure is similar to that of PFO closure, entailing implantation of an occlusion device with atrial disks lying on either side of the interatrial septum and the central waist residing in the ASD. Because of significant variations in size and anatomy of ASD, transcatheter ASD closure is technically more challenging than PFO closure.

B. Procedure. Several devices have been used for percutaneous ASD closure. The Amplatzer atrial septal occluder (AGA Medical, Golden Valley, MN) has the largest reported human experience. The other major device available is the Cardioform (WL Gore & Associates, Newark, DE).

The procedural approach to percutaneous ASD closure is similar to the percutaneous PFO closure approach as described above. A few important differences exist that are worth considering.

1. Because of a significant variation in the size of ASD and the shape of the defect, proper invasive balloon sizing (by ICE and fluoroscopy) is needed. Both oversizing and undersizing of the device may be hazardous and may lead to complications like device erosion or device embolization.
2. Device deployment and orientation during transcatheter ASD closure poses greater technical challenges than during PFO closure. The technical complexities are more frequent when ASDs are associated with other structural anomalies like atrial septal aneurysms or in cases of inadequate rim capture. It is imperative to demonstrate an adequate rim surrounding the defect for percutaneous closure.

3. Multiperforated septa demonstrate a particularly greater challenge to complete closure. In these cases, specific devices like the Amplatzer cribriform occluder or multiple devices may be needed to achieve a good clinical result.

4. The Amplatzer device is sized based on the defect size (i.e., 16-mm device for a 16-mm ASD) and can be used to close defects 2 to 38 mm in diameter. The Cardioform device is sized 1.7 times the size of the defect (i.e., 30-mm device for a 15-mm ASD) and can be used to close defects 2 to 17 mm in diameter.

C. Complications. As in transcatheter PFO closure, procedural success in experienced hands is high and complications are rare. Potential complications include device embolization, perforation as a result of device erosion into the atrial wall, residual shunting, or atrial arrhythmias. ASD device mismatch is encountered in 2% to 5% of cases. Other rare complications include vascular access complications, sizing balloon rupture, and entrapment of right atrial structures. Chest discomfort or new onset of arrhythmia may be clues to device erosion or embolization and should prompt urgent echocardiographic evaluation.

D. Outcomes. Most patients demonstrate improved functional class and exercise capacity after a successful closure. Several observational studies have demonstrated an improvement in overall long-term survival. Timely ASD closure prevents the development of right heart failure and pulmonary hypertension. There has been evidence of reduction in the size of enlarged cardiac chambers with normalization of intracardiac pressures after successful ASD closure.

VIII. VENTRICULAR SEPTAL DEFECT (VSD) CLOSURE

A. Background. Although isolated VSDs are a relatively common form of adult congenital heart disease, congenital VSDs of hemodynamic significance are rare, with a prevalence of 0.03% in the adult U.S. population. More commonly, VSDs are acquired as a result of complication of MI, cardiovascular surgery, or chest trauma. Postinfarction ventricular septal rupture (VSR) is associated with >90% mortality if left untreated. The postinfarction or traumatic VSRs may be located in the posterobasal (inferior infarct) or apical (anterior infarct) portions of the muscular ventricular septum and are typically irregular with multiple ruptures in necrotic myocardium that are prone to rupture or expansion. This presents significant challenges with respect to surgical as well as transcatheter repair.

Percutaneous VSD/VSR closure involves devices that are similar to those described for ASD closure. The device is positioned under fluoroscopy and echocardiographic guidance (TEE and/or ICE as needed) such that the two disks lie on either side of the ventricular septum and the waist lies in the septal defect. The width of the connecting waist determines device sizing.

B. Procedure. The only available device that is approved for closure of congenital muscular VSDs is the Amplatzer muscular VSD occluder device (AGA Medical, Golden Valley, MN). There is a specially designed Amplatzer postinfarction muscular VSR occluder device, which is currently under investigation in the United States. It is similar to its congenital counterpart, except for a longer waist, large disk diameter, and a larger waist diameter. In patients with postinfarct VSR, it may be necessary to use an atrial septal occluder, as the distance between the disks of the VSD occluder device may be too large. Again, this would be considered an “off-label” usage.

VSD closure can be achieved via the retrograde approach from the left ventricle or via the femoral or jugular vein. The VSD is crossed using a diagnostic catheter and wire, with the wire then externalized to the artery (if approached from the right ventricle) or vein (if approached from the left ventricle) to create a continuous arteriovenous (AV) loop. A delivery catheter containing the device is subsequently delivered over the loop. Under fluoroscopic and echocardiographic guidance, proper alignment and position are confirmed and the device is subsequently deployed.

C. Complications. The major complications of transcatheter VSD closure include device embolization, air embolism, residual shunting, defect enlargement, complete heart block requiring pacemaker implantation, arrhythmias, valvular regurgitation because of impingement, and intravascular hemolysis.

D. Outcomes. The results of transcatheter closure of congenital VSDs are encouraging; however, the closure of postinfarction VSR has yielded disappointing results in several studies. Although surgery has been recommended as the gold standard for the repair of postinfarction VSD, emergent surgical repair carries an operative mortality of about 50%. This often leads surgeons to recommend delaying the surgery for at least 2 weeks after the initial ischemic event to improve the tissue integrity for sutures/patches and results in a lesser operative mortality and improves the chance of success. Because of this, several centers have attempted transcatheter VSR closure in patients who are either not surgical candidates or too unstable to survive the "waiting period." Data from observational studies have reported variable success, with mortality rates ranging from 20% to 100%.

IX.LEFT ATRIAL APPENDAGE OCCLUSION (LAAO)

A. Background. AF is associated with 15% of all ischemic strokes. Autopsy studies have shown that up to 90% of the thrombi in nonvalvular AF originate in the LAA. Although warfarin has been demonstrated to reduce the rate of stroke in patients with AF, there are several limitations, including risk of bleeding, pharmacologic interactions, and need for prothrombin time (international normalized ratio) monitoring. In several patients, the use of warfarin may be contraindicated, necessitating another method of stroke prevention.

Surgical amputation and exclusion of the LAA have been demonstrated to reduce the risk of stroke after MV surgery, without any significant impact on the rate of postoperative AF. Given the favorable location of the LAA for percutaneous closure, a number of methods have been developed.

B. Procedure. The two devices with the most significant human experience available for LAAO are the Amplatzer Cardiac Plug (ACP) (AGA Medical, Golden Valley, MN) and the WATCHMAN device (Altritech Inc., Plymouth, MN). The WATCHMAN and ACP devices have CE Mark approval, whereas only the WATCHMAN is commercially available in the United States. The size and the shape of the LAA is most commonly assessed using TEE, although modified discrete cosine transform analysis is often helpful in sizing and understanding the morphology.

The devices are generally implanted using 14F femoral venous access. A transseptal puncture is performed under fluoroscopic and TEE guidance. The device delivery system allows for collapse, repositioning, or removal of the device in case of unsatisfactory result. Adequacy of the LAAO (defined as mild to absent leak) is confirmed using radiopaque contrast injection into the LA cavity.

C. **Complications.** The complications of the procedure include pericardial effusion, cardiac tamponade, residual leakage, or major vascular complications requiring transfusion.

D. **Outcomes.** The two major randomized trials of LAAO versus anticoagulation therapy are the PROTECT-AF and PREVAIL studies. In totality, the trials demonstrate at least equivalence of the two strategies with respect to stroke outcomes. Long-term (4-year) outcomes from PROTECT-AF demonstrated superiority in the primary efficacy outcome of stroke/death/systemic embolism in comparison with warfarin. There have been no major randomized trials of the novel oral anticoagulants compared with the WATCHMAN. In clinical practice, and based on the current trials, the WATCHMAN represents a good alternative to anticoagulation for patients who are intolerant of anticoagulation or at high bleeding risk.

X.ALCOHOL SEPTAL ABLATION (ASA).

Septal myectomy (SM) is considered the historic gold standard for the treatment of symptomatic left ventricular outflow tract (LVOT) obstruction in patients with hypertrophic cardiomyopathy. ASA has emerged as an attractive, less invasive alternative to myectomy that is applicable to those patients with favorable anatomy for ASA who cannot or do not want surgery. Over the last 15 years, the number of ASA procedures done worldwide has surpassed the total number of myectomies performed in the last 50 years. ASA may be considered in patients who have clear evidence of septal hypertrophy (>18 mm) projecting into the LVOT, patients who have dynamic LVOT obstruction (gradient >50 mm Hg at rest or upon provocation), and patients who have been refractory to medical therapy. Patients with coexistent abnormalities of the mitral apparatus are best treated by surgery rather than ASA.

ASA entails creating a controlled myocardial necrosis by injecting alcohol into the septal perforator that perfuses the area of obstruction-inducing hypertrophy. Postablation, the LVOT gradient demonstrates a triphasic response. There is an immediate reduction in the LVOT gradient after a successful procedure, attributable to the loss of septal contractility and associated systolic anterior motion of the MV. Over the next few days, there may be an increase in the LVOT gradient because of recovery of the stunned myocardium and edema of the tissue. The more permanent decrease in LVOT gradient happens over the course of the next few months secondary to myocardial thinning and septal remodeling.

A. **Procedure.** ASA is performed via dual arterial access. Because transient heart block is common during the procedure, an active-fixation temporary pacemaker is inserted via the internal jugular vein and left in place for 48 to 72 hours during inpatient observation for conduction deficits. A pigtail catheter is placed in the LV to allow LV, aorta gradient measurement during the procedure. A guiding catheter is introduced into the left main coronary artery and a guidewire advanced to the septal perforator of interest. Subsequently, a short “over the wire” (OTW) balloon is advanced to the septal perforator and inflated to obstruct backflow of alcohol from the septal to the left anterior descending artery. Angiographic contrast is injected through the balloon to ensure that there is absolutely no backflow into the LAD.

Echocardiographic contrast is then injected through the OTW balloon in order to map the myocardium that would infarct as a result of ASA. This is an important step, because it helps determine the appropriateness of the procedure and helps in selecting the optimal branch for alcohol injection. Subsequently, 1 to 2 mL of alcohol is injected slowly through

the balloon based upon the degree of gradient reduction. The balloon is then deflated and removed.

B. Complications. Besides the routine vascular complications that may arise in any interventional procedure, new-onset right bundle branch block is a significant complication of this procedure and is reported in up to 50% of patients in some series. Complete heart block requiring a need for a permanent pacemaker may occur in about 10% of patients undergoing ASA. The other potential long-term complication includes ventricular arrhythmias, hypothesized to arise as a result of creation of arrhythmogenic myocardial scar. Recent meta-analyses have failed to demonstrate significant differences in ventricular arrhythmias between myectomy and ASA.

C. Outcome. Although there are no randomized comparisons between SM and ASA, large meta-analyses of observational data indicate no significant differences between the two modalities in terms of mortality and improvement in functional status postprocedure. The caveat of ASA is an increased incidence of conduction abnormalities requiring permanent pacemaker implantation, which is necessary in approximately 10% to 15% (a two- to threefold higher rate than patients undergoing SM). Whereas residual gradients are slightly higher with ASA, functional benefit remains similar. Ultimately, patient selection for ASA requires confirmation of appropriate LVOT and coronary anatomy and a conversation among interventionalists, cardiac surgeons, and patients regarding the relative risks and benefit of ASA versus SM for a given patient.

XI.PERCUTANEOUS PARAVALVULAR LEAK CLOSURE

A. Background. PVL is a rare but serious complication that may arise after surgical MVR or more rarely after SAVR. Although most PVLs are small and remain relatively asymptomatic, more than 10% of patients undergoing MVR or SAVR may develop large symptomatic PVLs with serious clinical consequences such as heart failure, endocarditis, or hemolytic anemia. Many PVLs become clinically apparent within 1 year after valve surgery, but a significant proportion may either present later or not require any definitive treatment till later. Several risk factors, including reoperation (on the same valve), extensive annular calcification, evidence of endocarditis, large atria, renal failure, and older age, have been identified that may predispose a valve to develop PVL postsurgery. Unfortunately, reoperation for PVL is associated with increased morbidity and mortality. Transcatheter closure of symptomatic PVL in a relatively small number of high-risk patients has been attempted in several centers over the last two decades. The devices approved for closure of other intracardiac defects have been utilized in an off-label fashion for transcatheter PVL closure.

B. Procedure. In order to deploy an occlusion device across a PVL, it is first necessary to cross the defect with a delivery catheter. Aortic PVLs are generally crossed in a retrograde fashion from the femoral artery. The mitral PVL is most commonly crossed in the antegrade fashion by advancing a catheter from the right atrium into the left atrium via transseptal puncture, sometimes via direct transapical access, and rarely in a retrograde manner via the femoral artery. Similar to percutaneous VSD/VSR closure, creation of an AV loop is helpful to form a supportive rail for the passage of equipment, but may not be necessary if the delivery sheath passes easily with the aid of a stiff wire either in the LV or advanced to the descending aorta. Once the delivery sheath is advanced across the defect,

the plugging device is unsheathed into place. Multiple plugs may be placed until adequate closure is demonstrated by adjunctive ICE and/or TEE imaging.

C. Complications. Immediate and delayed device-related complications have been described as a result of technical failure. The early technical failure happens because of device impingement on nearby critical structures, and the delayed technical failure happens as a result of device embolization. Persistent PVL and/or its associated sequelae (i.e., CHF and hemolytic anemia) may be encountered after PVL closure. Although no procedure-related deaths have been described in any series, rare instances of strokes, dysrhythmias, and cardiac perforation have been described.

D. Outcomes. Transcatheter PVL closure is one of the most challenging structural heart disease interventions. The long-term outcomes after transcatheter PVL closure largely depend upon surmounting the limitations imposed by the current nonspecific devices for PVL closure, as well as challenges in imaging the area of interest. Over the long-term follow-up described in a few relatively large case series, resolution of hemolysis was reported in 60% to 83% of patients, improvement in CHF symptoms was reported in 50% to 100% of the patients, and repeat surgery was required in only 4% to 18% of the individuals. The incidence of long-term mortality has ranged from 25% to 30% over 3- to 36-month of follow-up across various studies.

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CHAPTER 65

Transthoracic Echocardiography

Albree Tower-Rader

I. INTRODUCTION. Transthoracic echocardiography is a reliable and versatile tool for the assessment of cardiac structure, function, and hemodynamics. Compared with other cardiovascular imaging modalities, it is relatively inexpensive, does not expose the patient to radiation, is noninvasive, displays live real-time images, and is widely available.

II. BASIC PRINCIPLES OF ECHOCARDIOGRAPHY. Sound waves consist of mechanical vibrations that produce alternating compressions and rarefactions of the medium through which they travel. **Ultrasound** consists of sound waves in the frequency range that is higher than what is audible to humans (>20,000 Hz). All waves can be described by their frequency (f), wavelength (λ), velocity of propagation (v), and amplitude. The velocity of ultrasound in soft tissue (e.g., myocardium and blood) is 1,540 m/s. Frequency is defined by the number of cycles occurring per second (cycles/second or Hz) and wavelength is measured in meters. Velocity, frequency, and wavelength are described by the following relationship:

$$\text{Velocity} = \text{frequency} \times \text{wavelength or } v = f \times \lambda$$

The typical adult echocardiographic examination uses a transducer with ultrasound frequency between 2.5 and 3.5 million Hertz (MHz). Using the equation above a 3-MHz transducer will have an ultrasound wavelength of approximately 0.50 mm. This has important implications because image resolution cannot be >1 to 2 wavelengths (e.g., 1 mm with a 3-MHz transducer). In addition, the depth of penetration of the ultrasound wave is directly related to the wavelength, with shorter wavelengths penetrating a shorter distance. Therefore, higher frequency transducers result in the use of shorter wavelengths that improve image resolution but at the cost of reduced depth penetration.

Transducers use a piezoelectric crystal to generate and receive ultrasound waves. A piezoelectric substance has the property of changing its size and shape when an electric current is applied to it. An alternating electrical current will result in rapid expansions and compressions of the material and thus produce an ultrasound wave. The piezoelectric crystal also deforms in shape when an ultrasound wave strikes the material, resulting in the production of an electric current. The transducer, and the piezoelectric crystal, thus oscillates between a short burst of transmitting ultrasound waves, with a brief period of no ultrasound transmission when it awaits reception of the reflected signals.

Tissue harmonic imaging has become the standard imaging technique in many laboratories. It utilizes the principle that as ultrasound waves propagate through tissue, the waveform becomes altered by the tissue, with the generation of new waveforms of higher frequency but which are **multiples of the baseline fundamental frequency**. Setting the transducer to receive only harmonic sound waves that are multiples of the fundamental frequency improves image quality significantly. This image quality improvement is based on the fact that weak signals, which tend to be artifacts, create almost no harmonics. In addition, shallow structures, such as the chest wall, generate weak harmonic signals, whereas at depths of 4 to 8 cm, where the heart is located, maximal harmonic frequencies develop. These phenomena result in fewer near-field artifacts and better endocardial definition. One limitation of harmonic imaging is that valve leaflets appear thicker—an artifact generated during image processing that appears to be related to the rapid motion of the leaflets.

The steps involved in creating a final ultrasound image are transmission and reception of waves, conversion to electrical signals, filtering, and extensive computer processing. The details of image processing, formation of artifacts, advanced physics, and technical aspects of echocardiography are beyond the scope of this chapter, but are briefly discussed in Section **VII**.

Patient and probe positioning, electrocardiographic lead placement, and transducer selection are the first steps to beginning the echocardiographic examination.

A. Patient and probe positioning. For the parasternal and apical positions, the patient should be in the left lateral decubitus position, with the left arm extended behind the head, because this brings the heart into contact with the chest wall. The subcostal and suprasternal views require the patient to be in the supine position.

B. Electrocardiographic lead placement. The electrocardiogram (ECG) allows identification of arrhythmias and timing of cardiac events during the echocardiographic examination, and it is used as a timing marker for digital recording of images. Typically, digital "clips" are set to record a predefined number of cardiac cycles (usually one but sometimes two), with timing based on the ECG. It is important that irregular beats be identified and excluded from the analysis. For example, a postectopic beat will falsely increase the two-dimensional (2D) assessment of ejection fraction (EF) and the Doppler assessment of transaortic gradient. In general, any Doppler index requires the average of at least three measurements. For patients in atrial fibrillation, 7 to 10 beats should be averaged. For patients with very high heart rates, or with a noisy electrocardiographic signal, the digital clips can be set to record for a predefined period of time (usually 2 seconds).

C. Transducer selection. The adult echocardiographic examination typically begins with a 2.5- to 3.5-MHz phased array transducer. Transducer frequency is important, because at higher frequencies, spatial resolution improves but at the expense of reduced depth penetration. Higher frequency (3.0 to 5.0 MHz) transducers may be used in thin or pediatric patients or intraoperatively for epiaortic scanning. Therefore, for optimal 2D resolution, select the highest frequency transducer that will provide adequate far-field penetration.

With regard to transducer frequency for the Doppler examination, lower frequency transducers can record higher velocities (see Doppler equation Section **IIIC.1**). The Pedoff probe is a continuous-wave (CW), nonimaging probe (typical frequency being 1.8 MHz)

used mainly to detect higher velocity profiles and confirm velocities obtained by other imaging methods.

III. IMAGING MODALITIES IN STANDARD ECHOCARDIOGRAMS

A. M-mode. Prior to 2D imaging, the echocardiogram was obtained when the transducer sent an ultrasound wave along a **single line** and then displayed the amplitude of reflected signal as well as the depth of that signal on an oscilloscope. This was called an A-mode echocardiography. When these line-of-sight ultrasound images were plotted with respect to time, "motion" mode, or M-mode, was produced. Despite the increasing emphasis on 2D imaging, the M-mode display remains a complementary element of the transthoracic examination. Its **high sampling rate** of up to 2,000 frames/s, compared with 30 frames/s for 2D echocardiography, provides **excellent temporal resolution**, and thus it is very **useful in the timing of subtle cardiac events** that can be missed by the naked eye in 2D imaging. Rapidly moving structures such as the aortic valve, mitral valve, and endocardium have characteristic movements in M-mode. Deviations from these, such as diastolic fluttering of the mitral valve in aortic regurgitation (AR) and systolic aortic valve notching in dynamic left ventricular outflow tract (LVOT) obstruction, may be the only way to detect the underlying dysfunction not appreciated in other imaging modalities. M-mode also has a great spatial resolution along the single line and can be used for precise size measurements such as ventricular dimensions in systole and diastole. The M-mode image is displayed like a graph, with **time on the *x*-axis and distance from the transducer on the *y*-axis**, with the structures closest to the transducer at the top of the image. In order to align the line of sight accurately, **2D imaging should be used to position the M-mode cursor** through the structures of interest.

B. 2D imaging. 2D imaging provides **tomographic views** of various 2D planes of cardiac structures and acts as guide for the M-mode and Doppler portions of the examination. A 2D echocardiographic image is essentially the scan line from M-mode that, instead of having a fixed line of sight, is swept back and forth across an arc. After complex manipulation of the **data received by the transducer from the multiple scan lines**, a 2D tomographic image is generated for display.

Depending on the depth of the image, a finite amount of time is needed for each scan line to be sent and received by the transducer. As opposed to M-mode that has only one scan line and can provide up to 2,000 frames/s, 2D echocardiographic imaging can utilize 128 scan lines but at the expense of a lower rate of 30 frames/s. Faster frame rates can be obtained by electronic manipulation using parallel processing on current ultrasound machines. Doppler overlay of the 2D image tends to slow down the frame rate. This **reduction in temporal resolution** reinforces the need for M-mode to complement 2D imaging in echocardiography, especially for rapidly moving structures and in precise timing of events.

C. Doppler echocardiography. The introduction of Doppler technique to echocardiography not only added new imaging capabilities but also transformed echocardiography into a modality that could provide **hemodynamic assessment** of the heart. Echocardiography has now become the preferred method, and in some cases the gold standard, over cardiac catheterization for certain hemodynamic assessments.

1. Doppler principles. The Doppler principle states that sound frequency increases as the source moves toward the observer and decreases as the source moves away. The change in frequency between the transmitted sound and the reflected sound is termed

the **Doppler shift**. This phenomenon is appreciated daily when an ambulance's siren becomes higher pitched, because of the increase in wave frequency, as it approaches the observer and then lower pitched once it has passed. This Doppler frequency shift directly relates to the velocity of the red blood cell by the following **Doppler equation**:

where v = velocity, f_R = frequency received, f_T = frequency transmitted, c = speed of sound in blood (1,540 m/s), and θ = angle between moving object and ultrasound beam.

The cos θ in the Doppler equation makes the calculation of velocity depend on the angle between the beam and the moving structure (red blood cell). Echocardiography machines do not typically incorporate the angle for calculating the resultant velocity, and thus the goal is to have the angle between the ultrasound beam and the blood flow jet of interest to be as close to zero as possible (cos 0 = 1). When this is not possible, the angle should be <20°, so that the true flow velocity is underestimated by <6% (cos 20 = 0.94). Adhering to this requirement sometimes mandates off-axis or unusual 2D images to align the Doppler ultrasound signal with desired target.

2. **Spectral analysis** is the term used to describe the way in which pulsed-wave (PW) Doppler and CW Doppler are displayed. By convention, the horizontal axis reflects the time and is placed in the middle of the screen with upward deflections representing frequency shifts toward the transducer and downward deflections for frequency shifts away from the transducer. The vertical axis represents the blood flow velocity (or frequency shifts), with the density of pixels on a gray scale reflecting the amplitude of the signal. The final result is that at each time point, the spectral analysis shows blood flow direction, velocity/frequency shift, and signal amplitude.

a. **PW Doppler.** The purpose of PW Doppler mode is to measure the Doppler shift, and thus velocity, at a **specific location of interest within a small sample volume** (e.g., mitral inflow velocity at the mitral valve leaflet tips, systolic velocity at the LVOT, and blood flow within the pulmonary veins). In this mode, a **single crystal** sends short bursts of ultrasound waves at a specific pulse repetition frequency (PRF) to a specific location, which are reflected from moving blood cells at this location and received by the same crystal. The maximal velocity that can be measured is limited by the time required to transmit and receive the ultrasound wave. This is called the **Nyquist limit** (one-half of the PRF). If a velocity greater than the Nyquist limit is measured, the signal appears as a wrap around the baseline, known as **signal aliasing**. Hence, the peak velocity is limited by the depth of the area of interest and also by the transducer frequency (inverse relationship according to the Doppler equation; see previous text). **PW Doppler has excellent spatial/depth resolution, but it has limited capacity to measure high velocities because of the Nyquist limit**. It is, therefore, used primarily to measure low-velocity flow (<2 m/s) at specific sites in the heart.

b. **CW Doppler.** CW Doppler employs **two crystals, one continuously sending ultrasound waves and the other continuously receiving the waves**. It measures Doppler shift **along the entire beam**, rather than at a specific location. Unlike PW Doppler, CW Doppler measures the **maximal velocity along the entire ultrasound beam** but it does not localize the precise position of that peak velocity. However, this is often apparent

anatomically or can be deduced using PW Doppler or color flow Doppler. **In general, CW Doppler is used to assess high-velocity flow and PW Doppler is used to measure low-velocity flow in specific areas**. Clinical applications of PW versus CW Doppler are listed in Table 65.1.

c. Color flow imaging. Although spectral (PW and CW) Doppler imaging is superior for accurate measurement of specific intracardiac blood flow velocities, the best way to visualize the overall pattern of intracardiac blood flow is with color flow imaging. Color flow Doppler is based on the principle of PW Doppler, with multiple sampling volumes at varying depths along a single scan line. A full-color flow map is generated by combining multiple scan lines along the areas of interest. To accurately estimate the velocity along a given scan line, the instrument compares the Doppler shift changes from several successive pulses (typically eight), and this is known as the **burst length**. Where Doppler shifts are detected, color pixels are displayed at that location, with the different colors representing the different degrees of Doppler shift based on a predetermined color spectrum. Tradition has set **blood velocity toward the transducer as shades of red and blood flow away as shades of blue (Blue Away)**. Because this modality uses properties based on PW Doppler technology, color flow Doppler has limitations similar to those of PW Doppler for velocity determination. When the flow velocity is higher than the Nyquist limit (indicated on the color map), color aliasing occurs (depicted as color reversal, red to blue or blue to red transition). The fact that color aliasing occurs can actually provide important hemodynamic information, such as identification of flow acceleration or calculation of the proximal isovelocity surface area (PISA), which is discussed in Section VI.C.6.

TABLE 65.1 Differences and Uses of PW Doppler and CW Doppler

Factor	PW	CW
Transducer crystal	Same transmitting and receiving	Different transmitting and r
Spatial resolution	Excellent—localizes to precise point	Poor—may be anywhere a
Ability to measure high velocity (>2 m/s)	No (limited by Nyquist)	Excellent
Uses	Mitral inflow	Gradients in aortic stenosis
	Pulmonary venous flow and LVOT flow	Gradient and pressure half
	Hepatic vein flow	Peak velocity in mitral reg d*p*/d*t*
	Tricuspid inflow	TR velocity—estimate RV s

CW, continuous wave; LVOT, left ventricular outflow tract; PW, pulsed wave; RV, right ventricular; TR, tricuspid regurgitation.

d. Tissue Doppler imaging (TDI). TDI is based on adjusting standard Doppler to focus primarily on the low-velocity, high-amplitude **motion of the myocardium** (usually <20 cm/s) instead of the high-velocity, low-amplitude motion of red blood

cells. Decreasing the filters (which normally eliminates low-velocity signals) and the Doppler transmit gain (which excludes the low-amplitude blood signals) results in the Doppler focusing primarily on myocardial motion. TDI can be displayed as either PW Doppler, typically at one aspect of the mitral annulus (usually septal or lateral), or color flow TDI mapping of the entire myocardial area of interest (Fig. 65.1). TDI has primarily been used as an adjunct for the evaluation of left ventricular (LV) diastolic function, where the mitral annular TDI pattern shows a systolic (S) wave toward the transducer and two diastolic waves away from the transducer (corresponding to early relaxation and late atrial diastolic myocardial motion, labeled as E′ and A′) (Fig. 65.2 and Table 65.2). With worsening diastolic function, E′ velocity decreases and is directly proportional to the rate of relaxation. TDI annular velocities decrease with age and may be affected by a myocardial infarction in the region adjacent to the annulus or surgery of the mitral valve. Therefore, TDI can be used to help differentiate a normal mitral inflow pattern (normal E′) from a pseudonormal filling pattern (reduced E′) (Fig. 65.2 and Table 65.3). TDI can also be used to assess LV filling pressures, myocardial deformation, and ventricular dyssynchrony.

D. Color M-mode (CMM). This technique, whereby color flow Doppler is imposed on an M-mode image, permits excellent spatiotemporal distribution of velocity (color) data, although it is limited to the defined scan line. It is a valuable adjunct in the timing of cardiac events, which may not be readily appreciated by 2D and color flow imaging alone. Its primary use has been in evaluating diastolic filling pattern where the LV inflow CMM pattern typically has two appreciable waves, the first demonstrating the early passive filling wave and the second later wave resulting from atrial contraction (Fig. 65.2). The slope of the early filling wave (velocity of propagation, V_p) is primarily dependent on the rate of relaxation and is reduced with delayed relaxation. It is useful for differentiating a normal mitral inflow pattern (normal V_p) from a pseudonormal filling pattern (where impaired relaxation results in delayed flow propagation into the left ventricle, slower V_p) (Fig. 65.2 and Table 65.2).

FIGURE 65.1 Tissue Doppler imaging (TDI) for diastolic function recorded from the apical four-chamber window using a 2-mm sample volume positioned in the lateral wall 1 cm from the mitral annulus. The TDI signal is toward the transducer in systole (S) as the myocardium moves toward the apex. In diastole, the myocardial velocity is directed away from the transducer first with early diastolic filling (E′) and then with atrial contraction (A′).

FIGURE 65.2 Diastolic function/dysfunction staging. A, atrial kick mitral inflow velocity; A_m, atrial annular velocity (A′); D, diastolic; E, early mitral inflow velocity; E_m, early diastolic annular velocity (E′); Nl, normal; PV, pulmonary vein; S, systolic; S_m, systolic annular velocity; Tissue Doppler, mitral annular velocity by Tissue Doppler; V_p, velocity of propagation.

Other uses of CMM are the accurate measurement of AR jet diameter in the LVOT in the parasternal views and, with its superior temporal resolution, detection of diastolic mitral regurgitation (MR), which may be seen in certain conditions (severe acute AR, advanced diastolic dysfunction, and complete heart block).

IV. TOMOGRAPHIC VIEWS AND CARDIAC ANATOMY. Most echocardiography laboratories have similar protocols for acquisition of a complete echocardiogram. Each

echocardiographic view is labeled first by the transducer position (parasternal, apical, subcostal, and suprasternal) followed by the tomographic view of the heart (long axis, short axis, four chamber, and two chamber). To acquire these different views, the transducer is placed on different parts of the body and adjusted with rotation and angulation to optimize the final image. Standard imaging planes are illustrated in Figures 65.3 to 65.8; see Table 65.4 for normal echo dimensions, Table 65.3 for standard examination protocol, and Table 65.5 for useful 2D examination tips.

TABLE 65.2 Diastolic Function/Dysfunction Staging

	Normal Young	Normal Adult	Normal Elderly	Delayed Relaxation	Ps
Stage	Normal	Normal	Normal	I	II
E/A ratio	>1 (often >2)	>1	<1	<1	1–
DT (ms)	<220	<220	>220	>220	15
S/D ratio	<1	≥1	>1	>1	<1
Ar (cm/s)	<35	<35	<35	<35	>3
V_p (cm/s)	>55	>55	<55	<55	<4
E′ (cm/s) (E annulus)	>10	>8	<8	<8	<8

V. Ar, atrial reversal; DT, deceleration time.; Vp, propagation velocity from color M-mode; S/D ratio, systolic flow/diastolic flow from

VI. pulmonary vein tracing; E', mitral annular early diastolic velocity; E, peak mitral inflow early diastolic flow velocity; A, peak mitral inflow atrial contraction velocity

TABLE 65.3 Standard Transthoracic Examination

1. PLAX
- Position transducer in third or fourth left intercostal space parasternally (ridge toward right should
- Color Doppler—mitral and aortic valve flow and interventricular septum (in cases of ventricular se
- M-mode—three levels (below mitral leaflets, midmitral leaflets, and aortic valve)
- Move up an intercostal space to get better view of ascending aorta
- Tilt transducer inferomedially to assess RV inflow. Color Doppler to assess tricuspid regurgitation

2. PSAX
- Rotate transducer 90° clockwise from PLAX and tilt transducer from superior to inferior (LV apex aortic valve level)
- Color Doppler at mitral valve level (localize mitral regurgitation if present)
- Color Doppler at aortic valve level (localize aortic regurgitation and assess flow in RVOT/pulmoni
- PW Doppler—RVOT (level of pulmonic valve annulus)
- CW Doppler—RVOT/pulmonic valve and tricuspid valve (estimate RVSP)

3. A4C
- Transducer at apex—ridge toward left (move laterally and inferiorly if necessary to get true apex)
- Color Doppler—mitral flow and tricuspid flow

TABLE 65.3 Standard Transthoracic Examination

- Measure PISA if mitral regurgitation (zoom, decrease Nyquist, and measure radius)
- PW Doppler—mitral inflow—position at level of mitral leaflet tips (gate 1–2 mm)
- PW Doppler—PV (usually right upper PV)—1–2 cm into vein (gate 3–4 mm)
- CW Doppler—across mitral valve (stenosis and/or regurgitation and to calculate PISA)
- CW Doppler—tricuspid flow (estimate RV systolic pressure)
- Tilt transducer anteriorly to obtain "five-chamber view," that is, open up aortic valve/LVOT
- Color Doppler—LVOT/aortic valve
- PW Doppler—LVOT—at the level of the aortic annulus
- CW Doppler—LVOT/aortic valve
- Tilting transducer posteriorly will bring the coronary sinus in view (along AV junction, emptying int

4. A2C

- Rotate transducer approximately 60°–90° anticlockwise
- Tilt posteriorly and rotate clockwise to open out descending aorta

5. Apical long axis (apical three chamber)

- Rotate transducer further 30°–45° anticlockwise
- Color Doppler—LVOT/aortic valve
- Recheck CW Doppler across aortic valve if evaluating for aortic stenosis

6. Subcostal view—patient supine and legs bent at knees

- Subxiphoid, midline, tilt anteriorly under sternum with groove toward patients left for four-chambe
- Color Doppler across interatrial septum to check for a PFO or ASD
- Rotate transducer 90° from four-chamber view until groove is pointing anterosuperiorly
- Same views as PSAX except rotated 90° clockwise
- Sweep from left to right to get apical, midventricular, and aortic valve levels
- IVC should be visualized when scan plane is directed toward the right midclavicular region with out long axis of IVC
- Color Doppler—IVC flow
- PW of hepatic veins (may need to angle posteriorly)

7. Suprasternal view—patient supine and head tilted backward

- Transducer in suprasternal notch, with groove toward left (rotate to about 1 o'clock), parallel to tra
- Color Doppler in arch and upper descending aortas (especially if suspected coarctation)
- PW Doppler in upper descending aorta (if assessing AR severity)

8. Pedoff probe

- Especially for checking maximal aortic valve gradient in aortic stenosis
- Apical position
- Right upper sternal border (aortic stenosis)

VII. A2C, apical two chamber; A4C, apical four chamber; AR, aortic regurgitation; ASD, atrial septal defect; AV, atrioventricular; CW, continuous wave; IVC, inferior vena cava; LV, left ventricular; LVOT, left ventricular outflow tract; PFO, patent foramen ovale; PISA, proximal isovelocity surface area; PLAX, parasternal long axis; PSAX, parasternal short axis; PV,

pulmonary vein; PW, pulsed wave; RV, right ventricular; RVOT, right ventricular outflow tract; RVSP, right ventricular systolic pressure.

A. Parasternal. The parasternal position is typically obtained by placing the transducer at the left of the sternal border in the third or fourth intercostal space. The optimal position for the patient is usually the left lateral decubitus position, but a hybrid between the steep left lateral and supine position may be required to optimize the view. This position allows imaging of the long axis as well as the short axis of the heart.

1. Parasternal long axis (PLAX). The PLAX tomographic view is traditionally the first view of a standard transthoracic echocardiogram. The ultrasound beam is lined up between the patient's right shoulder and the left flank. The right ventricular outflow tract (RVOT) is located at the top of the image, the aorta to the right, the inferolateral (or posterior) wall on the bottom, and the cardiac apex on the left. The anteroseptum is visualized between the RVOT and the LV cavity. Tilting the transducer's tail toward the left shoulder with slight clockwise rotation aims the ultrasound beam inferomedially and brings the right ventricular (RV) inflow into view. This is good for obtaining the tricuspid regurgitation (TR) velocity as well as viewing the tricuspid valve, RV apex, and the right atrium.

FIGURE 65.3 Schematic diagram of the parasternal long-axis view in diastole. AMVL, anterior mitral valve leaflet; Ao, aorta; CS, coronary sinus; DA, descending aorta; LA, left atrium; LV, left ventricle; NCC, noncoronary cusp; PMVL, posterior mitral valve leaflet; post. wall, posterior wall; RCC, right coronary cusp; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; STJ, sinotubular junction. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64. Copyright © 1995 Elsevier. With permission.) **FIGURE 65.4** Schematic diagram of the parasternal short-axis view at the level of papillary muscles. Ant., anterior wall; Ant. septum, anterior septum; Inf., inferior wall; Inf. septum, inferior septum; Lat., lateral wall; Post., posterior wall. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64. Copyright © 1995 Elsevier. With permission.) **FIGURE 65.5** Schematic diagram of the parasternal short-axis view at the aortic valve level. LA, left atrium; LCC, left coronary cusp; LMCA, left main coronary artery; LPA, left pulmonary artery; NCC, noncoronary cusp; PA, pulmonary artery; RA, right atrium; RCA, right coronary artery; RCC, right coronary cusp; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; SVC, superior vena cava. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64. Copyright © 1995 Elsevier. With permission.) **FIGURE 65.6** Schematic diagram of the apical four-chamber view. AMVL, anterior mitral valve leaflet; ATVL, anterior tricuspid valve leaflet; DA, descending aorta; LA, left atrium; LV, left ventricle; MB, moderator band; PMVL, posterior mitral valve leaflet; RA, right atrium; RSPV, right superior pulmonary vein; RV, right ventricle; STVL, septal tricuspid valve leaflet; VAS, ventriculoatrial septum (where communication from LV to RA may occur). (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders;

1995:21–64. Copyright © 1995 Elsevier. With permission.) **FIGURE 65.7** Schematic diagram of the four-chamber view from the subcostal approach. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RV, right ventricle. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64. Copyright © 1995 Elsevier.

With permission.) **FIGURE 65.8** Schematic diagram of the aorta and right pulmonary artery from the suprasternal notch window. Ao, aorta; AV, aortic valve; LA, left atrium; RPA, right pulmonary artery; SVC, superior vena cava. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64. Copyright © 1995 Elsevier. With permission.)

TABLE 65.4 Normal Echo Dimensions in Adults

Factor	Male
Left Ventricle	
LV end-diastolic diameter (cm)	4.2–5.8
LV end-systolic diameter (cm)	2.5–4.0
Septal thickness (ED) (cm)	0.6–1.0
Posterior wall thickness (ED) (cm)	0.6–1.0
LV end-diastolic volume (biplane) (cm^3)	62–150
LV end-systolic volume (biplane) (cm^3)	21–61
Ejection fraction (%)	52–72
Left Atrium	
Left atrium (ES) (cm)	3.0–4.0
LA volume index (biplane-AL) (cm^3/m^2)	16–34
Aorta	
Aortic annulus (cm)	2.3–2.9
Sinuses of Valsalva (cm)	3.1–3.7
Sinotubular junction (cm)	2.6–3.2
Proximal ascending aorta (cm)	2.6–3.4

AL, area length; ED, end diastole; ES, end systole; LA, left atrial; LV, left ventricular.

TABLE 65.5 Tips for Transthoracic 2D Examination

TABLE 65.5 Tips for Transthoracic 2D Examination

1. **Optimize patient position** (left lateral with left hand above head) and **environment** (darkened roo
2. Ensure imaging in **harmonics** mode
3. Consider **contrast** to improve endocardial delineation for technically difficult studies
4. When parasternal and apical images are limited (body habitus, surgical drains, dressings, etc.), t only accessible window
5. Consider **off-axis views** to enhance visualization of specific structures
6. Obtain images at **end of expiration,** as the heart is closer to the transducer
7. **Avoid foreshortening LV apex** (especially in A2C)—true apex may be more inferior and lateral th
8. If there is a **concern of LV thrombus,** zoom and check with low-velocity color Doppler to ensure endocardial contrast if unclear
9. If an object is suspicious for an artifact, reassess in other imaging planes
10. **M-mode** can be useful especially for the accurate timing of cardiac events (especially RV or RA tamponade or assessment of possible systolic anterior motion of the mitral valve)
11. Adjust transducer **frequency** to maximum that permits adequate far-field penetration/depth
12. Set **time gain compensation** in the midrange with lower gain in the near field and higher setting attenuation of the beam with increasing distance from transducer
13. Use the least amount of **depth** that adequately shows the entire area of interest
14. Adjust the **transmit gain/output** to optimize image brightness/quality—too low, everything app "white-out." Initially set it to high and then adjust downward
15. Adjust the **"compress"/dynamic range**. Decrease if image quality is poor to produce high-quality "soften" images. Typically, as compress is increased, the transmit gain should be decreased to r scale
16. Adjust the **focus** (focal zone) to include the area of interest, because the beam is narrowest (imp area, especially when imaging near-field structures (e.g., looking for an apical LV thrombus from th
17. Set the **persistence** to low

A2C, apical two chamber; LV, left ventricular; RA, right atrial; RV, right ventricular.

2. Parasternal short axis (PSAX). While the transducer is in the parasternal position, rotating the transducer clockwise by approximately 90° displays the heart in the short axis. The ultrasound beam in this case is roughly from the left shoulder to the right flank. Using different degrees of transducer tilting, and occasionally moving up or down an intercostal space, results in four traditional views of the heart. On tilting from superior to inferior, the views obtained are aortic valve–RV outflow, mitral valve level, mid-ventricle at the papillary muscles, and the LV apex. The images appear as if viewing the heart from the apex and looking through to the base; therefore, the septum is on the left, lateral wall on the right, the anterior and anteroseptal walls at the top, and the posterior–inferior walls on the bottom of the screen.

B. Apical. The apical position is obtained with the patient in the left lateral position and the probe placed at the apical impulse. This position obtains images of the long axis of the heart.

1. Apical four chamber (A4C). The A4C view is obtained with the ultrasound beam transecting the thorax in a superior–inferior fashion. Most institutions orient the transducer to place the left ventricle on the right side of the screen and the right ventricle

on the left side. The apex is at the top of the image and the atria at the bottom regardless of the orientation. The inferoseptal and anterolateral walls as well as the apex of the left ventricle can be assessed in this view.

2. **Apical five chamber (A5C).** A slight rotation of the transducer introduces a fifth "chamber," the proximal aorta, along with the aortic valve and LVOT. This view allows for qualitative assessment of aortic valve pathology and hemodynamic assessment of the LVOT and aortic valve.

3. **Apical two chamber (A2C).** Further rotation, 90° counterclockwise from the A4C view, obtains the A2C view. In addition to the left atrium, the LV anterior wall, inferior wall, apex, and mitral valve are also well visualized.

4. **Apical three chamber (A3C).** A slightly more counterclockwise rotation (approximately 30°) brings the aorta back into view, resulting in the A3C, or apical long-axis, view. This essentially has the same anatomical structures as those in the PLAX view with a different orientation. The apex is better visualized and the RVOT usually drops out of the image. Additional information on mitral and aortic valve hemodynamics can be obtained in this view, which is not ideally obtained in the PLAX view.

C. **Subcostal.** The subcostal view provides additional views of the ventricles, atria, and atrial septum to those acquired in earlier portions of the examination. In some patients, the subcostal view may be the only way to obtain images of the heart because the parasternal and apical locations may have poor windows (e.g., hyperinflated lungs).

The subcostal position is obtained with the patient in the supine position and the probe located caudal to the xiphoid process. The transducer is placed in the midline nearly parallel to the long axis of the patient's body so that the ultrasound beam slices toward the spine. This shows the right ventricle at the top right, the left ventricle at the bottom right, and their respective atria on the left. Clockwise rotation along with inferior tilting brings the inferior vena cava (IVC) and hepatic veins into view for right-sided hemodynamic assessments.

D. **Suprasternal.** Placing the transducer in the suprasternal notch and pointing inferiorly can assess the ascending aorta, aortic arch, and descending aorta. Hemodynamics from this position can better characterize AR as well as the presence of coarctation.

VIII.ADVANCED ECHOCARDIOGRAPHIC TECHNIQUES

A. **Contrast echocardiography.** Contrast echocardiography is performed by injecting either **agitated saline** or one of the **commercially available contrast agents** into an arm vein. Both are microbubbles that reflect ultrasound waves and opacify intracardiac chambers. The size of the microbubbles relative to the pulmonary capillary diameter determines whether they cross to the left side of the heart or get trapped in the pulmonary circulation. The choice of agitated saline versus commercial contrast agents depends on whether the goal is to visualize the right atrium and ventricle versus the left ventricle and myocardium.

Agitated saline is sterile saline (preferably mixed with some blood), combined with a small quantity of air, which has been exchanged rapidly using a three-way stopcock between two syringes to create small bubbles. These relatively large (and unstable) bubbles are caught in the lung and do not routinely appear in the left side of the heart unless a shunt is present. The appearance of bubbles in the **left atrium within three beats** of the cardiac cycle after they are seen within the right atrium suggests a right-to-left **intracardiac shunt**—typically from a small patent foramen ovale. If bubbles appear in the **left atrium more than four**

beats after they are seen in the right atrium, this more likely signifies an **intrapulmonary shunt**. There is a small risk of embolic complications in the use of agitated saline. Care should be taken to avoid injecting larger air bubbles by inspecting the syringe closely prior to injection and ensuring that the bubbles are very small.

Modern commercial contrast agents consist of either an albumin-based shell containing perfluorocarbon gas (Optison) or a synthetic phospholipid shell containing perfluoropropane gas (Definity). These microbubbles are much smaller (the size of a red blood cell) and more stable; therefore, they can cross the pulmonary capillaries and appear on the left side of the heart, where they opacify the LV cavity for improved endocardial definition and clarify the presence/absence of a suspected LV thrombus/mass. For optimal contrast imaging, it is important to reduce the mechanical index (the output of the machine), typically to 0.4 to 0.6, because higher power ultrasound waves destroy microbubbles.

Contrast enhances Doppler signals. Agitated saline can be used to augment the signal from TR to better estimate peak right ventricular systolic function (RVSP), and commercial microbubble products (Optison and Definity) can be used to enhance the Doppler envelope in patients with aortic stenosis.

Contrast echocardiography was the subject of a black box warning from the Food and Drug Administration (FDA) because of concerns of significant adverse events. More recent data suggest that adverse events following contrast injection are no more common than in those in whom it is not used when appropriate adjustment for severity of illness is made. The FDA has recommended patients with pulmonary hypertension or unstable cardiac conditions such as recent myocardial infarction, unstable angina, decompensated heart failure, ventricular arrhythmia, or respiratory failure should be monitored closely for at least 30 minutes after use. It is contraindicated when a fixed or even transient right-to-left shunt is present or with documented allergy to its components.

B. Three-dimensional (3D) echocardiography is obtained using a transducer that transmits and receives data simultaneously in a 3D volume, in the form of either real-time 3D images or simultaneous biplane (orthogonal) 2D images. The 3D data set can then be manipulated using different software packages to assess function and anatomy. It is of particular benefit for the localization of valvular abnormalities (especially for the complex 3D mitral valve structure), accurate LV volume calculation, improved assessment of the right ventricle, guiding surgical interventions (e.g., mitral valve repair), and complex congenital heart disease. 3D color flow imaging allows for a comprehensive assessment of vena contracta and areas of flow convergence (PISA), which can improve the quantification of valvular regurgitation. It has been documented to allow for a more rapid evaluation of mitral valve area (MVA) in mitral stenosis as compared with conventional 2D planimetry.

C. Myocardial mechanics—tissue strain, strain rate imaging, and speckle tracking. Strain rate imaging allows for the estimation of regional myocardial deformation. Tissue strain, a dimensionless entity, is a measure of the relative deformation of tissue. Myocardial deformation in a segment of interest is assessed with reference to the adjacent segment, avoiding errors introduced by translational motion and tethering. **Strain rate is the rate of the deformation between two adjacent points of interest along a scan line and is expressed in seconds.** A strain rate curve can be derived by analyzing many adjacent segments along a scan line. Doppler techniques for assessing strain are not always ideal because of angle dependence, signal noise, and the need for a high frame rate. Doppler-

independent techniques such as **speckle tracking** use ultrasonic reflectors (speckles) within tissues that can be followed from frame to frame through the cardiac cycle. This method can be used to assess the radial deformation and torsion of the ventricle. Strain rate is a relatively preload-independent measure of regional myocardial function. Clinical applications include assessment of myocardial ischemia, viability, diastolic function, subclinical LV dysfunction in valve disease and in particular in assessing the early effects of cardiotoxic chemotherapeutic agents on LV function, and cardiac involvement in systemic diseases such as diabetes or amyloidosis. For instance, in amyloidosis, strain is often preserved at the apex, but it is diminished in other areas of the heart.

D. Dyssynchrony. Dyssynchrony occurs when different areas of the ventricles contract in an irregular pattern spatially and temporally. It is primarily seen in patients with impaired systolic function and electrophysiologic conduction delays. M-mode, 2D imaging, color Doppler, and tissue Doppler have all been employed to assess the amount of dyssynchrony but no consensus exists on the optimal approach to evaluate ventricular dyssynchrony (see Chapter 56). After the implantation of a resynchronization device, Doppler echocardiography is used for the optimization of programmed timing. Some useful measures include the following:

1. A difference in the time to peak velocity of >65 ms between opposing walls (basal segments in four-chamber, two-chamber, and three-chamber views yielding a total of six segments) using pulsed tissue Doppler
2. A difference of 40 ms in the interval from the QRS complex to the onset of flow in the RVOT versus the LVOT using pulsed tissue Doppler
3. Using M-mode or speckle tracking, a difference of 130 ms in the septal to posterior wall delay

IX.SPECIAL TOPICS

A. Systolic function. 2D imaging is currently the primary echocardiographic means of determining systolic function of the heart. The most utilized measurement is the EF. In the past, EF was based on estimation by visual inspection; however, echocardiographic societies now recommend using standardized objective methods to minimize interobserver differences. LV volume is best measured using the modified Simpson's method (disk summation method). This involves tracing the LV area in two orthogonal views (typically A4C and A2C) and dividing the left ventricle into a number of cylinders of equal height. Total ventricular volume is calculated by adding up all the volumetric cylinders. All modern machines and digital echo reading systems have integrated software to create and combine the volume data after tracing the LV areas in both apical views. Based on the volumes measured in diastole and systole, stroke volume (SV) and EF can be estimated using **Simpson's method**:

Stroke volume (SV) = end-diastolic volume (EDV) − end-systolic volume (ESV)

$$EF = SV/EDV \times 100\%$$

$$\mathbf{EF = EDV - ESV/EDV \times 100\%}$$

Newer semiautomated methods in 3D echocardiography using full matrix-array transducers give accurate, reproducible assessments of LV volume and EF that are superior

to 2D methods when magnetic resonance imaging is used as the gold standard. LV torsion uses speckle tracking to assess LV systolic function by assessing the difference between the clockwise rotation of the base of the heart and the counterclockwise rotation of the apex of the heart (approximately 12°). Global strain also appears to be a robust parameter for assessment of LV function.

B. Diastolic function. Doppler echocardiography remains the primary modality for assessing LV diastolic function and estimating filling pressures. In the **most recent** iteration of the guidelines, information obtained from **PW Doppler of mitral inflow, left atrial (LA) volume index, TDI of the mitral annulus and TR velocity obtained from CW Doppler** are used for staging.

Patients with normal LVEF and diastolic dysfunction can be identified if they have >50% of the following:

1. Average E/e′ > 14,
2. Septal e′ velocity < 7 cm/s or lateral e′ velocity < 10 cm/s,
3. TR velocity > 2.8 m/s, or
4. LA volume index > 34 mL/mm².

Those with <50% have normal diastolic function and those with 50% have indeterminate diastolic function.

For patients with abnormal LVEF or normal LVEF and abnormal diastolic function, grading of diastolic dysfunction relies on examination of the E/A ratio and E velocity in addition to the other variables.

Patients with an E/A ≤0.8 and E ≤50 cm/s have grade I diastolic dysfunction with normal left atrial pressure (LAP).

Those with E/A ≥2 have grade III diastolic dysfunction and increased LAP. For those with an intermediate E/A ratio (>0.8 but <2) or E/A ≤ 0.8 with E > 50 cm/s, the following criteria are taken into account:

5. Average E/e′ >14,
6. TR velocity > 2.8 m/s, and
7. LA volume index > 34 mL/mm².

If two or three of the three are negative, the patient has **grade I** diastolic dysfunction with normal LAP. If two or three of the three are positive, the patient has **grade II** diastolic dysfunction with increased LAP.

In the circumstance that data regarding only two of these variables are available, if both are negative, the patient has grade I diastolic dysfunction with normal LAP; if both are positive, the patient has grade II diastolic dysfunction with increased LAP; and if only one is positive, the grade of diastolic dysfunction and LAP cannot be determined.

Accurate assessment of diastolic dysfunction can be limited by many factors including inadequate views, rhythm (atrial fibrillation or ventricular pacing), and mitral valvular dysfunction (severe annular calcification, severe regurgitation, prior valve replacement or repair).

C. Hemodynamics

1. **Transvalvular pressure gradient.** The **Bernoulli equation** allows measurement of relative pressure differences across valves, shunts, or the LVOT. In its complete form, the Bernoulli equation is too complex for routine clinical use, because it incorporates three main components, namely, convective acceleration, inertial term (flow

acceleration), and viscous friction. In many clinical situations, the latter two components can be ignored, leaving the flow gradient across an orifice to be derived from the convective acceleration term alone:

where V_2 is the velocity distal to an obstruction and V_1 is the velocity proximal to an obstruction.

The flow proximal to a narrowed orifice (V_1) is much lower than the peak flow velocity (V_2) and can be frequently ignored, leaving a **simplified Bernoulli equation**:

The simplified Bernoulli equation is unreliable when

a. V_1 is > 1 m/s, which occurs in serial lesions (subvalvular and valvular stenoses) and mixed stenosis with regurgitation.

b. Viscous resistance becomes significant such as in the evaluation of long stenoses (e.g., coarctation or a tunnel-like ventricular septal defect).

c. The inertial term (flow acceleration) is not negligible (flow through normal valves).

It is important to realize that in aortic stenosis, the Bernoulli equation represents the **maximal instantaneous gradient** across the valve, which is always higher than the customary peak-to-peak gradient measured in the catheterization laboratory because the LV systolic peak and aortic peak pressures do not occur at the same time and therefore are not instantaneous.

The flow within the heart is pulsatile; hence, mean gradients are an important measure and are obtained by integrating the velocity profile over the ejection time. This can be readily obtained with the software available on all modern echocardiography machines by simply tracing the area of the velocity profile. The mean pressure gradient is then derived from the mean velocity data using the Bernoulli equation.

2. Intracardiac pressure measurement

a. **Estimated right atrial (RA) pressure** can be derived from the size of the IVC and its response to changes in respiration or a sniff (Table 65.6). Using a dilated IVC to assess elevated RA pressures is not accurate in mechanically ventilated patients; however, a small IVC of size <1.2 cm in a mechanically ventilated patient is 100% specific for an RA pressure <10 mm Hg.

b. **Pulmonary artery systolic pressure (PASP)** is estimated from the TR peak velocity. Provided that there is no tricuspid valve obstruction, peak TR velocity will depend on the pressure gradient between the right ventricle and the right atrium. Estimated RVSP is equal to this pressure difference, determined from the peak TR velocity, plus the estimated RA pressure. In the absence of pulmonic stenosis, the RVSP is similar to the **PASP**:

PASP = 4 × (peak TR velocity)2 + estimated RA pressure

c. **Pulmonary artery diastolic pressure (PADP).** Pulmonary regurgitation represents the pressure difference between the pulmonary artery (PA) and the right ventricle at end systole. Hence, the end pulmonary regurgitation velocity can be utilized to

measure the end-diastolic pressure difference between the PA and the right ventricle. The RV end-diastolic pressure should be similar to the RA pressure; therefore, addition of estimated RA pressure to the end-diastolic pressure difference between the PA and the right ventricle will estimate the PADP:

TABLE 65.6 Estimation of RA Pressure

IVC Diameter	Change with Respiration/Sniff	Estimated RA Pressu
Normal (<2.1 cm)	Decrease >50%	0–5
Dilated (>2.1 cm)	Decrease >50%	6–10
Dilated (>2.1 cm)	Decrease <50%	10–15
Dilated (>2.1 cm)	No change	>15

IVC, inferior vena cava; RA, right atrial.

d.

e. **PADP = 4 × (end pulmonary regurgitant velocity)^2 + estimated RA pressure**

f. **Estimated LAP or left ventricular end-diastolic pressure (LVEDP).** Provided that there is no mitral stenosis, LVEDP and LAP should be the same. This important measure of LV diastolic function can be estimated by several methods.

1. **1 Deceleration time (DT) of mitral inflow.** A DT of <150 ms is strongly suggestive of an elevated LVEDP/LAP. In very young patients, a DT <150 ms may be normal because of rapid equalization of pressures secondary to vigorous early diastolic relaxation.
2. **2 Difference between pulmonary venous atrial duration and mitral atrial duration (Ar–A).** Normally, mitral A-wave duration is greater than pulmonary venous atrial reversal (Ar) duration. When LVEDP is increased, the velocity and duration of the mitral A-wave decrease, whereas pulmonary vein Ar velocity and duration increase. The difference between the duration of the Ar-wave and the mitral A-wave correlates with LVEDP. An Ar–A duration of >50 ms is specific for an elevated LVEDP >20 mm Hg. This is reliable in patients with reduced EF but not in patients with normal EF. The primary limitation with this method is the difficulty in accurately measuring the duration of Ar.
3. **3 Combined mitral inflow/CMM index (E/V_p ratio).** This index has been demonstrated to correlate with LAP/LVEDP, especially when these filling pressures are elevated. A ratio of >2 is suggestive of elevated filling pressures. In patients with normal EFs, especially with small ventricles and hyperdynamic function, the flow propagation velocities are not accurate.
4. **4 Combined mitral inflow/TDI index (E/E= ratio).** This index has been shown to be a semiquantitative measure of LVEDP. A ratio of >10 (using the lateral annulus) or >15 (using the septal annulus) correlates with a wedge pressure of >20 mm Hg. A ratio of <8 (using the lateral annulus) correlates well with normal filling pressures. For intermediate values, other information such as LA size should be incorporated to assess whether filling pressures are elevated.

3. **d*P*/d*t***. This index of LV contractility is the rate of pressure increase during isovolumic contraction and is traditionally obtained using invasive pressure transducers. It can be estimated from the CW Doppler of the MR jet. During isovolumic contraction, there is no change in LAP; therefore, MR velocity changes reflect d*P*/d*t*, with more rapid increases in MR velocity being associated with increased contractility. The pressure change between 1 and 3

m/s = 4 ($V_2^2 - V_1^2$) = 32 mm Hg. The time it takes the ventricle to accelerate an MR jet velocity from 1 to 3 m/s is measured and then the d*P*/d*t* is calculated as follows:

d*P*/d*t* = 32 mm Hg/time (in seconds)

This has been demonstrated to correlate well with invasively measured d*P*/d*t*. It is considered normal when the calculated value is >1,200 mm Hg/s.

4. **Continuity equation** is an application of the principle of conservation of mass, which states that flow across a conduit of varying diameter is equal at all points. This equation is useful in quantifying a stenotic aortic valve area (AVA) that cannot be accurately measured using planimetry from the transthoracic window. Flow at any point in the heart is the product of the cross-sectional area (CSA) and the flow velocity. As flow velocity varies during ejection in a pulsatile system, individual velocities must be integrated to measure the total volume of flow (velocity time integral [VTI]). This is determined by tracing the spectral Doppler profile, using standard measurement software built into all echocardiography machines.

Flow at any point = CSA × VTI

Based on the continuity equation, flow through the LVOT must be equal to the flow through the aortic valve; therefore, AVA can be calculated following these steps:

The assumption is that the LVOT cross-section is a circle. The greatest source of error in this equation is in the measurement of the LVOT diameter because the value is squared, resulting in magnification of any initial measurement error. The appropriate place to measure the LVOT can be difficult to define accurately in some calcified valves. The **dimensionless index** (DI) is the ratio of the VTI of LVOT to the VTI of aortic valve. It is preferable to use this to assess aortic stenosis when accurate measurement of the LVOT diameter is not possible or in those patients with history of previous aortic valve replacement. A DI <0.25 suggests severe aortic stenosis.

Of note, the flow across the LVOT per beat is the SV, which can thus be calculated from the product of the LVOT diameter and flow velocity (VTI_{LVOT}):

5. **Volumetric method to assess regurgitant volume/regurgitant fraction.** This is based on the conservation of flow, with total flow across a regurgitant valve being equal to the sum of the forward flow and the regurgitant flow. For example, for MR:

Total transmitral flow volume = forward flow volume + regurgitant volume

(LVOT flow can be assumed to equal the forward flow provided there is no AR)

Regurgitant volume = mitral forward flow – LVOT flow

Regurgitant fraction = regurgitant volume/total mitral flow

Because of the multiple assumptions and calculations performed, this method is prone to error and is rarely used clinically.

6. The **PISA** method is another application of the principle of conservation of mass. It is based on the phenomenon that flow accelerates proximal to a narrowed orifice. Using color Doppler, as flow accelerates, its velocity may exceed the Nyquist limit which results in color reversal because of aliasing. This is seen as a series of colored ("isovelocity") hemispheres with color flow imaging, with the velocity of flow at the surface of this hemisphere being the aliasing velocity (Nyquist limit) of color flow in that direction. Decreasing the aliasing velocity will increase the size of the hemisphere, because the velocity at which color changes is reduced. In keeping with conservation of mass, blood flow at the surface of this hemisphere is the same as flow through the regurgitant orifice, and this is the basis of using the PISA method to estimate the regurgitant orifice area (ROA) of a valve. PISA has been most extensively used to estimate the mitral ROA to quantify MR.

Flow at surface of hemisphere = flow through regurgitant orifice

Surface area of hemisphere × velocity at hemisphere = ROA × peak velocity of regurgitation [using CW Doppler through the mitral valve]

$2 \times \pi (\text{radius})^2 \times$ aliasing velocity = ROA × peak MR velocity

$\text{ROA} = 2 \times \pi (\text{radius})^2 \times \text{aliasing velocity}/\text{MR}_{\text{CW}}$ peak velocity

The greatest source of error is in defining the precise location of the ROA, so as to accurately calculate the radius.

This method can also be used to measure MVA in mitral stenosis (where forward flow convergence is seen and measured) and the aortic ROA in AR, although it may be difficult to obtain satisfactory visualization of the aortic PISA for quantification from the apical long-axis view (best view to appropriately line up AR jet with the Doppler). When the jet is eccentric, and a full hemisphere is not visible, an angle correction should be considered. The PISA equation for MR can be simplified if the aliasing velocity is set to 40 cm/s and it is assumed that peak MR velocity will be 5 m/s (equates to a normal LV-to-LA pressure gradient of 100 mm Hg). Using these two constants, the PISA equation is simplified to

$\text{ROA} = (\text{radius})^2/2$

Peak MR velocity will increase or decrease depending on the changes in LV systolic pressure and LAP, and it cannot always be assumed to be 5 m/s. However, this method is useful for semiquantification and rapid assessment. Regurgitant volume can be calculated as follows:

Regurgitant volume = ROA × $\text{VTI}_{\text{MRjet}}$

7. **Pressure half-time ($P½$)** is used to estimate the MVA, because the time for the pressure to fall by half across a stenotic valve is proportional to the degree of stenosis. It is the time interval for the peak pressure gradient to fall by half. Using the Bernoulli equation to convert pressure to velocity, there is a constant relationship between peak velocity and the velocity at $P½$.

Pressure at half the peak pressure = 1/2 peak pressure

In addition, the $P½$ has a constant relationship with the DT of the early mitral filling wave, and it is usually estimated from the following:

$$P½ = 0.29 \times DT$$

Hence, $P½$ can be easily measured by using the DT or by simply measuring the time interval from peak to ½ peak pressure (which is determined from the V_{max}). Most echocardiographic measurement software packages automatically calculate $P½$ when the slope of the CW Doppler of the mitral inflow jet is measured. For mitral stenosis, an empirical constant has been validated to correlate $P½$ and MVA:

$$MVA = 220/(P½)$$

This has only been validated for native valves and will overestimate valve areas for prosthetic valves.

The other primary use of $P½$ is to help quantify AR. The $P½$ of the AR Doppler velocity jet becomes shorter when the pressures in the aorta and the left ventricle equilibrate more quickly. This can occur with increasing severity, especially in acute AR. A $P½$ <250 ms suggests severe AR. There are many limitations to this because of the fact that aortic and LV compliance and systemic vascular resistance affect $P½$.

X.TECHNICAL ASPECTS AND ADVANCED IMAGE ACQUISITION

A. Machine settings. To obtain the best images and accurate Doppler information, it is important to optimize the machine settings during different parts of the examination (Tables 66.3 and 66.5).

1. **Time gain compensation.** These controls differentially amplify the echo signals returning from different depths to compensate for attenuation of the ultrasound beam with increasing distance from the transducer. This function is useful with higher frequency transducers, because they are associated with more attenuation at greater depths.
2. **Depth.** Start with the greatest depth to get an overview and then decrease the depth to include all of the target structure. A depth of 16 cm is usually adequate for the apical window and 12 cm for parasternal imaging. Increasing the depth decreases the frame rate, reducing temporal resolution.
3. **Transmit gain.** This adjusts the displayed amplitude (power) of all received signals and, therefore, affects the brightness of echoes displayed. Setting the power too low results in inadequate returning signals and poor image quality, whereas setting it too high results in image white-out.
4. **Compress.** The compress setting is also known as a **dynamic range**. It converts the range of returning echo intensities, which may vary a billion-fold in intensity, into 100 to 200 visual shades of brightness or the "gray scale." Increasing the compress will "soften" the image and allow identification of lower level signals. Decreasing the compress results in the production of high-quality contrast images such that weaker signals are eliminated, noise is reduced, and the strongest echo signals are enhanced. Therefore, the compress/dynamic range is decreased when image quality is poor.
5. **Focus (or position).** The focal zone of the transducer indicates the region of the image at which the ultrasound beam is narrowest, and hence where spatial resolution is maximal. Therefore, it is important to reposition the focus to the area of greatest

attention/importance, especially those in the near field. When adjusted proximally, however, distal structures may appear blurred as the ultrasound beams scatter.

6. **Persistence.** Persistence is the temporal averaging of the latest frame with the previous frames to produce a smooth or less noisy display. Fast-moving cardiac structures (e.g., valve leaflets) may appear blurred if the persistence is set above low.

B. Imaging artifacts

1. **Acoustic shadowing.** Highly reflective structures block transmission of ultrasound to distal structures, causing poor imaging of these far-field structures. For instance, a mechanical mitral prosthesis prevents good visualization of the left atrium from the apical window.

2. **Reverberation.** This occurs when multiple linear echo signals are generated from a back-and-forth reflection between two strong reflectors of the ultrasound signal, before the signal returns to the transducer. These appear as multiple parallel irregular dense lines extending from the structure into the far field (e.g., linear echodensity in the ascending aorta in the PLAX view simulating a dissection flap, which is a reverberation from a more anteriorly lying structure, such as a rib). Reverberation artifacts will be present at a multiple of the distance between the two strong reflectors—usually at twice the distance between the strong reflectors. Careful analysis of the artifact in multiple views and with color Doppler should be performed. Color flow signals will be seen to pass through the artifact.

3. **Refraction.** Refraction of the ultrasound beam as it passes through a tissue layer can result in a side-by-side double image. This artifact is often seen in PSAX views of the aortic valve where the image appears to show two aortic valves overlapping.

4. **Beam width artifact.** Ultrasound beams are 3D and are reflected from 3D structures, but they are displayed in a 2D tomographic plane. Strong reflectors at the edge of a central beam, especially outside the narrow proximal focal zone, can be superimposed on a structure in the central zone, with the resulting appearance of a structure within the image, that is, outside the 2D tomographic plane (e.g., an aortic valve in the left atrium in the A4C view).

5. **Range ambiguity.** Echo signals from earlier pulse cycles reach the transducer on the next receiving cycle because of re-reflection, resulting in deep structures that appear closer to the transducer than their actual location, and are manifested as the appearance of an anatomically unexpected echo. This can be confirmed by the disappearance of the artifact when the depth setting is changed.

6. **Side lobe artifacts.** In addition to the central beam, transducers produce side lobes 10° to 30° off axis. All echoes returning from structures in these peripheral beams are displayed, as if they arose from targets within the main beam. Therefore, strong reflectors may be imaged by these low-intensity side lobes and displayed in an erroneous position on the screen. This is a major source of "clutter" in cardiac cavities. Harmonic echoes have much lower intensity side lobes, with a resulting reduction in side lobe artifacts in the image.

C. Factors affecting color Doppler image. Many factors affect spectral Doppler and color flow Doppler, and it is important to consider these. They can be broadly divided into three groups: machine settings, imaging factors, and hemodynamic factors (see Table 65.7 for tips to optimize Doppler settings).

TABLE 65.7 Tips for the Transthoracic Doppler Examination

TABLE 65.7 Tips for the Transthoracic Doppler Examination

1. Doppler (all modalities) is very **angle-dependent**—angle between the ultrasound beam and th <20°. In order to achieve this, off-axis views are often required

PW and CW Doppler

2. Shifting the **Doppler baseline** up or down can double the maximal velocity detected (still <2 m/s
3. Increasing the **depth** decreases the Nyquist limit and reduces the maximal ve with PW
4. Recheck high-velocity jets with the **Pedoff (CW)** probe to confirm peak velocity (include right trying to obtain peak aortic stenosis velocity)
5. Start with **high-gain setting** and reduce until noise and clutter are adequately suppressed
6. Set **wall filter** to low to avoid overestimation of low velocities
7. Decreasing the **compress** enhances the edges of the spectral envelope; increasing it enhan within the Doppler envelope
8. Initially set **"reject"** at low (20%–40%) to allow the display of a wide range of signals, then incr the image (i.e., to reduce noise)
9. Adjust **gate width**—1–2 mm for mitral inflow and LVOT, 3–4 mm for pulmonary venous flow, an

Color flow Doppler

10. **Narrow** the sector and minimize the **depth** to maximize color resolution (increase frame rate)
11. Spatial resolution is higher **axial** to the beam than lateral
12. Higher **transducer frequencies** result in an increased area of flow disturbance (reduces t visualize lower velocities)
13. Adjust **color gain** until just before noise appears in the color
14. Minimize **wall filters** during analysis of PISA/flow convergence, to avoid overestimating low velo
15. Decreasing the **Nyquist limit** increases the size of any regurgitant jet as lower velocities are d higher Nyquist velocities); therefore, set at 50–60 cm/s initially
16. Be careful not to miss or underestimate very **eccentric jets** of mitral regurgitation or aortic regur
17. Remember that **chamber constraint** reduces the size of a jet —wall jets tend to underes compared to a jet that is not constrained by a wall

CW, continuous wave; LVOT, left ventricular outflow tract; PISA, proximal isovelocity surface area; PW, pulsed wave.

D.

1. **Machine settings**

a. **Nyquist limit.** At any given depth, in color Doppler imaging, the Nyquist or aliasing velocity (which is related to the PRF) can be adjusted. Typically, it is set to 50 to 60 cm/s. The lowest velocity that is displayed on the color map is related to the Nyquist

(minimal displayed velocity = Nyquist × 2/32). Therefore, decreasing the Nyquist increases the lowest velocity displayed, which has the effect of increasing the size of the jet area.

b. **Transducer frequency.** In color flow imaging, higher transducer frequency reduces the peak velocity (Nyquist limit) that can be measured (see Doppler equation above). Lower Nyquist results in an increased color flow jet area. Therefore, higher frequency transesophageal echocardiography generally produces larger areas of flow disturbance than transthoracic echocardiography. In spectral Doppler imaging, lower frequency transducers can measure higher velocities.

c. **Depth setting.** Minimizing the depth setting to encompass only the region of interest maximizes the PRF and frame rate.

d. **Gain.** Adjust the color gain until just before random noise appears in the color. Increased color gain increases the size of color flow disturbance. 2D gain should be decreased during the color Doppler examination to maximize color flow disturbance because each pixel is assigned to either 2D or color. In PW and CW Doppler, start with a high-gain setting until the desired signal is appreciated. The gain is decreased until noise and clutter are adequately suppressed.

e. **Baseline.** Used primarily for unwrapping aliased signals. Generally leave it in the middle of the color bar, but it can be adjusted to maximize the velocity that can be displayed with PW or color Doppler. This is also useful for highlighting a specific velocity as in proximal convergence analysis.

f. **Wall filter.** Excludes low-velocity, high-amplitude signals from myocardial motion. If set too high, it tends to decrease the color flow disturbance. A typical initial setting is 400 Hz. The setting of the wall filter should be minimized during analysis of the proximal flow convergence region to avoid overestimation of low velocities (i.e., set low for PW Doppler and high for CW Doppler).

g. **Beam width.** Beam width is especially important with PW and CW Doppler. As the ultrasound beam propagates, it spreads out. For example, when sampling pulmonary venous flow with pulse Doppler from the apical view, the sample volume may be at 16-cm depth and the ultrasound beam may be >1 cm in width. This can lead to the detection of aortic flow, which is displayed as if it arose along the beam axis (from the pulmonary vein) leading to beam width artifact.

h. **Gate length or sample size.** This is the size of the PW Doppler sampling region. It is usually set at 3 to 5 mm. Narrowing the gate focuses the velocity data to a smaller spatial area and can help improve image quality, but it requires very accurate positioning to prevent missing of the appropriate sample area during cardiac motion.

i. **Scale.** Controls the range of Doppler velocities displayed. As the velocity scale increases, the velocity limits increase and the displayed waveform size decreases.

j. **Compress.** In spectral (PW and CW) Doppler, the compress setting adjusts the gray scale, which controls image softness. Decrease the compress to enhance the edges of the spectral envelope. Increase the compress to enhance the various velocities displayed within the Doppler spectrum. Set at 30 dB or higher initially.

k. **Reject.** In spectral Doppler, the reject control removes low-amplitude signals (“noise”) from the spectral display. The reject control is initially set at a low level (20% to 40% maximum) to allow the display of a wide range of signals. The reject is then increased to remove signals that obscure the image.

2. **Imaging factors**

a. **Interrogation angle.** Color flow imaging measures only the component of flow that is parallel to the ultrasound beam. This is related to the true flow velocity by the cosine of the angle between the blood flow and the interrogating ultrasound beam. Satisfactory alignment (as parallel to the flow as possible) is vital to record the full and maximal velocity jet with spectral (both PW and CW) Doppler.

b. **Attenuation.** Loss of signal strength caused by too high a transducer frequency for the required depth results in a reduced area of color flow disturbance.

c. **Acoustic shadowing.** Loss of signal strength caused by a proximal reflector of ultrasound (e.g., a mechanical prosthetic valve preventing apical imaging of MR jet in the left atrium).

3. **Hemodynamic factors**

a. **Flow volume.** Increasing regurgitant volume results in an increased area of color flow disturbance, and this is the basis for the common practice of judging the severity of valvular regurgitation by the size of the color jet. However, as outlined in this chapter, many factors affect the size of the color flow jet area. Therefore, it is important to include other factors in the assessment of regurgitation, such as ventricular and atrial sizes, the morphologic appearance of the valve, the width of the color jet at its narrowest point (vena contracta), and, in particular, more quantitative analysis using the proximal flow convergence region (PISA). Several cardiac cycles should be inspected with minor adjustments in the angle of interrogation to ensure that the largest jet is visualized.

b. **Driving pressure.** Increased pressure gradient across a regurgitant orifice results in an increased color flow disturbance in the receiving chamber. Color jet size is closely related to jet momentum, given by flow rate multiplied by jet velocity.

c. **Chamber constraint in eccentric jets.** Impingement of a regurgitant jet against walls of the receiving chamber will decrease the size of the color disturbance. For example, severe but eccentric MR may have a very small area of color flow disturbance because the jet loses momentum to the constraining LA wall and appears narrower in a 2D view as it is splayed out over a larger surface area of the wall.

4. **Doppler artifact.** Mirror image artifact can be seen occasionally when the Doppler signal is duplicated on the other side of the baseline.

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CHAPTER 66

Transesophageal Echocardiography

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I.INDICATIONS. In general, transesophageal echocardiography (TEE) is performed when there is a clinical question for which the information obtained using transthoracic echocardiography (TTE) is insufficient. This may be to better define pathology that has been identified by TTE or to obtain better images when transthoracic images are inadequate. The close proximity of the esophagus to the heart allows for improved visualization of many cardiac structures, particularly those that are posteriorly located. In addition, higher frequency probes can be used, given the shorter distance between the probe and the heart, further enhancing the resolution. However, imaging planes are somewhat constrained by the relative position of the esophagus and heart, which in turn makes transthoracic imaging superior in the assessment of certain structures (i.e., pulmonic valve) and Doppler measurements.

Indications for TEE in various conditions and clinical situations are listed in Table 66.1. Very common indications include examination to rule out a cardiac source of embolus and assessment of valves, prosthesis, and intracardiac device for endocarditis or its accompanying complications, such as abscess. The assessment of native and prosthetic valvular function, in terms of degree and mechanism of regurgitation or stenosis, is a frequent indication for TEE. Acoustic shadowing by prosthetic valves, particularly in the mitral position, poses less of a problem for TEE than it does for TTE. Given the increasing prevalence of atrial fibrillation, another frequent indication for TEE is to assess left atrial and left atrial appendage pathology and function, particularly prior to cardioversion. Congenital cardiovascular abnormalities, intracardiac shunts, as well as intracardiac tumors and masses can also be well delineated by TEE. Because of its ability to assess the ascending aorta, arch, and descending aorta, TEE also has an important role in the diagnosis of aortic dissection, aneurysms, and atheroma. In extremely technically difficult/limited transthoracic study such as in postoperative and mechanically ventilated patients, TEE may be used for usual TTE indications such as the assessment of left ventricular function.

TEE is a useful imaging modality in both the operating room and the cardiac catheterization laboratory. In cardiothoracic surgery, TEE is used to assess the mechanism of valvular abnormalities and subsequently evaluate the efficacy of valve repair or replacement. TEE can be used to guide the location of the aortic cross-clamp so that segments with severe atheromatous involvement can be avoided, thereby reducing

the risk of embolization. In addition, TEE can provide an assessment of left ventricular function and regional wall motion. As newer transcatheter procedures have become widespread, TEE has been increasingly utilized to help guide catheter position, transseptal punctures, implantation of percutaneous valves, placement of left atrial appendage occluding devices, as well as closure of paraprosthetic leaks, atrial septal defects, ventricular septal defects, and patent foramen ovale. Prevention and early recognition of complications achieved by TEE imaging is often crucial for periprocedural success.

TABLE 66.1 Indications for TEE in Various Conditions and Clinical Situations

Condition	Indication
Infective endocarditis	Patients with at least moderate pretest probability such as *Staphylococcus* or intracardiac device
	Detection of complications of endocarditis: abscesses and fistula
Cardioembolic source	Identification of left atrial and left atrial appendage thrombus or spontaneou
	Identification of PFO, ASD, or atrial septal aneurysm
	Identification of aortic atheroma
	Evaluation of mitral and aortic valve for vegetation, tumors, and valve stran
Valvular heart disease	Evaluation of mechanism and severity of mitral regurgitation
	Characterization of valvular pathology such as aortic morphology
Prosthetic valves	Evaluation of suspected prosthetic dysfunction (stenosis, thrombosis, or reg
Atrial fibrillation/flutter	Assessment of left atrial and left atrial appendage thrombus prior to cardio ablation
	Follow-up for resolution of thrombus after anticoagulation prior to cardiovers
Aortic disease	Evaluation for suspected acute aortic pathology: dissection, aortic trauma, a
	Characterization of aortic aneurysm and atheroma
Interventional procedures	Guiding performance of interventional cardiac procedures (e.g., p valvuloplasty, closure of paraprosthetic leak, ASD, VSD, or PFO)
Intraoperative	Assessment of valve repair/replacement and evaluation of systolic function
Intracardiac masses	Detection of characterized masses such as tumors and thrombus
Critical care	Assessment of suspected papillary muscle rupture
	Assessment of mechanical complications of acute myocardial infarction or r
	Evaluation of unexplained hypotension, especially in the ICU

TABLE 66.1 Indications for TEE in Various Conditions and Clinical Situations		
		Assessment of early postoperative bleeding, which may result in localize posteriorly)
Congenital disease	heart	Identification of site of origin and initial course of coronary arteries
		Detection of intracardiac shunts

ASD, atrial septal defect; ICU, intensive care unit; PFO, patent foramen ovale; TEE, transesophageal echocardiography; VSD, ventricular septal defect.

II.CONTRAINDICATIONS

A. There are few **absolute** contraindications to the performance of TEE (Table 66.2). These include the **presence of pharyngeal or esophageal obstruction, active upper gastrointestinal bleeding, recent esophageal or gastric surgery, and suspected or known perforated viscus**. If there is instability of the cervical vertebrae, then the examination cannot be performed.

B. **Relative** contraindications include the **presence of esophageal varices** and **suspected esophageal diverticulum**. In these cases, it is prudent to obtain gastrointestinal evaluation before proceeding, if the study must be performed. Severe cervical arthritis, in which patients may have difficulty with neck flexion, may make it difficult to pass the probe. Oropharyngeal pathology, anatomic distortion, or extreme muscle weakness can likewise make it difficult to proceed with the examination.

TABLE 66.2 TEE Contraindications
Absolute
Esophageal or pharyngeal obstruction
Suspected or known perforated viscus
Gastrointestinal bleeding that has not been evaluated
Instability of cervical vertebrae
Relative
Esophageal varices or diverticula
Cervical arthritis
Oropharyngeal distortion
Bleeding diathesis or overanticoagulation
Uncooperative patient

C. TEE, transesophageal echocardiography.

D. **Severe cardiopulmonary disease** is not a contraindication to evaluation by TEE (on the contrary, TEE can often provide critical information when used in these patients), but the operator must be particularly careful to minimize any stress on the patient. This is

particularly true in **suspected aortic dissection**, where any sudden increase in blood pressure caused by patient discomfort could result in extension of the dissection. In cases where there is **respiratory instability**, endotracheal intubation with assisted ventilation should be considered prior to the procedure. Patients who are **hypotensive** may not be able to receive sedative agents, as these agents could lead to further hemodynamic compromise. In such patients, the examination may have to be performed with topical anesthesia alone. This is obviously much more difficult for the patient, and TEE should be done only if critical information is not obtainable by other methods.

E. Given the invasive nature of the procedure, prudence must be observed in patients who are prone to **bleeding**. The procedure is commonly performed on patients who are anticoagulated, such as in those with atrial arrhythmias prior to cardioversion. However, there is increased risk in those who are overanticoagulated. Although no set guidelines exist, it would seem advisable to **delay the examination if possible in patients with an international normalized ratio >5 or a partial thromboplastin time >100 seconds**. **Thrombocytopenia** may also increase the risk, particularly with platelet counts <50,000 per cubic millimeter. TEE can still be performed if needed, as the absolute risk remains low, but meticulous attention must be given to nontraumatic esophageal intubation.

F. **Esophageal infections**, such as those that occur in the context of human immunodeficiency virus (HIV), do not necessarily represent contraindications to the procedure. **Patient discomfort** caused by the presence of the probe in the esophagus may preclude the examination. Universal precautions should be followed (as they should for any patient). The standard disinfectants used to clean the probe will inactivate HIV.

G. A patient who is very uncooperative is at significant risk for complications from the procedure. In such a case, consideration should be given to aborting the TEE or to increase the level of sedation and prophylactic endotracheal intubation if required.

III. PERSONNEL. The American Society of Echocardiography has proposed the following guidelines for operators who wish to perform TEE: as background, attainment of at least level 2 experience in transthoracic echocardiogram; a minimum of 25 esophageal intubations under guidance; and a minimum of 50 supervised TEE examinations during training. Furthermore, operators should perform a minimum of 25 to 50 TEE examinations yearly to maintain competency.

TABLE 66.3 Equipment for TEE

1. Echo machine and probe (calibrate prior to intubation)
2. Sphygmomanometer
3. ECG rhythm monitor
4. Pulse oximeter
5. Supplemental oxygen
6. Wall suction with Yankauer
7. Intravenous lines and tubing
8. Topical anesthetic agents
9. Sedative medications
10. Bite block
11. Gloves and goggles

TABLE 66.3 Equipment for TEE

12. Emergency equipment
- **a.** Drugs (e.g., atropine, epinephrine, naloxone, flumazenil, and lidocaine)
- **b.** Defibrillator
- **c.** Intubation supplies

IV. ECG, electrocardiogram; TEE, transesophageal echocardiography.

V. The presence of a skilled assistant is invaluable during the procedure. The assistant should be either a sonographer or a registered nurse. The role of the assistant is to monitor vital signs during the procedure, ensure proper suctioning of oropharyngeal secretions, and administer medications.

VI. EQUIPMENT. Necessary equipment is listed in Table 66.3.

VII. THE TRANSESOPHAGEAL PROBE. The probe is a modification of the standard gastroscope, with transducers in place of fiber optics. The conventional rotary controls with inner and outer dials are present. The inner dial typically guides anteflexion and retroflexion, whereas the outer dial controls medial and lateral movement of the tip. A locking mechanism is present, which must not be in effect when the probe is advanced or withdrawn, because esophageal trauma may result. The multiplane probe also has a lever control to guide rotation. Advancement and withdrawal of the probe, rotation of the probe about its long axis, and the manipulations available using the above rotary controls constitute the means by which specific images can be obtained (Fig. 66.1). Most current generation probes are also equipped for 3D imaging.

VIII. PATIENT PREPARATION (Table 66.4). The patient should have had nothing by mouth (NPO) for at least 4 to 6 hours before the procedure. Water is allowed up to 2 hours before the test. The clinician can rule out possible contraindications by asking for a history of odynophagia or dysphagia. It is important to be aware of any history of radiation therapy to the mediastinum or cervical region that may have resulted in stricture formation.

The extent of previous workup for any history of gastrointestinal bleeding must be reviewed. The clinician should review recent laboratory studies, paying particular attention to platelet count, hemoglobin level, and coagulation profile. Appropriate inquiries should be made with regard to allergies and former tolerance of sedative medications. The clinician should ensure that the patient understands the procedure, including risks and benefits, and that proper informed consent is obtained and documented before proceeding.

IX. STEP-BY-STEP GUIDE TO THE EXAMINATION

A. The patient's **dentures** should be removed.

B. **An intravenous (IV) line** should be inserted to allow for administration of medications and saline contrast for study.

FIGURE 66.1 Specific images can be obtained by advancement and withdrawal of the probe, by rotation of the probe about its long axis, and by the manipulations that are possible using rotary controls.

C. The American Heart Association does not recommend **antibiotic prophylaxis** for patients undergoing endoscopic procedures. The reported incidence of transient bacteremia with endoscopy is no higher than the contamination rates reported with blood cultures.

D. A **blood pressure cuff** should be placed on the patient's arm.

E. **Electrocardiographic leads** should be applied and connected to the telemetry monitor.

F. A **pulse oximeter** should be applied to the patient's finger or ear.

G. A **nasal cannula** should be used so that supplemental oxygen can be given as needed. Capnography is encouraged as well, to monitor respiratory effort.

H. While sitting up, the patient should be asked to gargle **viscous 2% lidocaine** for 1 minute and then swallow it for topical anesthesia. **Lidocaine (xylocaine) spray (4%) or Cetacaine spray (10%)** is then sprayed on to the posterior tongue and upper pharynx. These procedures normally suppress the **gag reflex**, but if necessary, this can be verified using a tongue depressor or gloved finger; additional **topical anesthesia** is then applied until the reflex is dulled. By visualizing the area being sprayed, inadvertent spraying of the vocal cord and resultant laryngospasm can be avoided. Methemoglobinemia has been reported with the use of benzocaine-containing product (e.g., Cetacaine), which is usually manifested as central cyanosis and desaturation and can be treated with supplemental oxygen and methylene blue. Some operators advocate the use of drying agents to minimize oropharyngeal secretions (e.g., glycopyrrolate). We generally have not found a need for the use of such agents, which can cause an increase in heart rate.

TABLE 66.4 Preparation for TEE

Patient must have had nothing by mouth for at least 4 h prior to the procedure
Assess for possible contraindications:
History of odynophagia or dysphagia
History of mediastinal or cervical radiation that might have resulted in stricture formation
History of and workup for gastrointestinal bleeding
Allergies to and previous tolerance of sedative medications
Patient understanding of procedure and indications
Informed consent of patient

I. TEE, transesophageal echocardiography.

J. Have the patient lie down on the left side (left lateral decubitus position), facing the echo machine (alternatively, the patient can lie on the right side, with the machine on the right), with neck flexed. TEE can be performed with the patient sitting, but is easier in the lateral position.

K. **Midazolam**, a benzodiazepine, is the preferred agent for sedation, having the benefit of a short half-life. It also produces an antegrade amnesic effect and has anxiolytic properties. Typically, administer IV doses of 0.5 to 1 mg every 3 to 5 minutes until adequate sedation is achieved. The goal is to reduce anxiety without compromising

respiratory drive and while maintaining the patient's ability to follow simple commands, such as swallowing when necessary. Check pulse oximetry and blood pressure before each dose. **Fentanyl**, a short-acting opioid analgesic, can be used for sedation (typically 25 µg IV per dose) in conjunction with midazolam and may be better tolerated in patients with poor left ventricular function or renal impairment. An alternative sedative is **meperidine**, which is typically given in 12.5 to 25 mg IV doses. Meperidine and fentanyl possess an analgesic effect and help to suppress the gag reflex as well. Again, **check vital signs before and after each dose**. Additional doses of these sedatives and anxiolytics may be administered during the procedure if necessary. Sedation can lead to potential respiratory suppression; therefore, a benzodiazepine antagonist (e.g., flumazenil 0.2 to 0.6 mg IV) and an opiate antagonist (e.g., naloxone, increments of 0.1 to 0.2 mg IV doses) should be available if required.

L. With adequate sedation and topical anesthesia (diminution of gag reflex), **begin probe insertion**. There are two approaches that are generally used.

1. The first is the **digital technique**, which is especially useful with larger profile probes. With this method, the bite guard is inserted onto the shaft of the probe such that after esophageal intubation the bite guard can be moved into place. The distal end of the probe is lubricated. The imaging surface of the transducer is placed toward the tongue. The tip of the transducer is placed under the index finger, and it is slowly guided downward and posterior to the hypopharynx. At this point, the patient is asked to swallow, and gentle pressure is applied with the other hand to guide the probe down. Swallowing results in relaxation of the upper esophageal sphincter. If resistance is met, stop; let the patient relax, and reattempt or redirect as needed. Using the finger as a guide will help center the probe in the region of the hypopharynx over the esophagus and avoid the lateral recesses.

2. An **alternative method is to use the rotary controls on the TEE probe** to guide the intubation. The bite guard is inserted first. The probe is inserted through the bite guard, and gentle anteflexion is applied as the probe is passed over the back of the tongue. The probe is then returned to the neutral position, or with slight retroflexion, as it is passed down into the esophagus. The patient is asked to swallow as the probe is advanced past the upper esophageal sphincter. The operator is still able to guide the probe if needed by insertion of a finger around the side of the bite guard.

Patients often gag as the probe enters the upper esophagus (even with adequate anesthesia); however, patients generally find it more comfortable once the probe has passed beyond this point (usually at 25 cm, past the level of the carina). The probe should be advanced to approximately 30 to 40 cm (mid-esophageal level).

In intubated patients, it is important to **secure the endotracheal tube firmly to one side of the mouth** to prevent dislodgment and inadvertent extubation. Direct visualization with a laryngoscope may be needed. **Sedation** is equally important in these patients, and given the tendency for partially sedated patients to bite on their tubes, a **paralyzing agent** is often required. Intubation in the supine position is not a problem because the airway is protected. Other catheters in the esophagus, such as feeding tubes or nasogastric tubes, often have to be removed prior to the procedure; they may become interposed between the esophagus and the TEE probe, interfering with the images. If left in, these tubes may become dislodged by the TEE probe, and tube position should be reconfirmed after the echocardiographic examination. For patients with tracheostomies, some operators will carefully and gently deflate the cuff to facilitate probe insertion.

X. IMAGING. TEE technology has undergone much evolution, from the initial monoplane views to the current multiplane views and three-dimensional views. Monoplane TEE provides for images in the horizontal plane only, perpendicular to the shaft of the endoscope. Longitudinal relationships among cardiac structures are difficult to appreciate. With biplane TEE, the orthogonal longitudinal plane can also be obtained. Both monoplane and biplane systems required additional manipulation to obtain off-axis views, making the examination more difficult and more uncomfortable for the patient. With **multiplane TEE**, the transducer has a single array of crystals that can be rotated 180° around the long axis, producing a continuum of transverse and longitudinal images from a single probe position. This minimizes the probe manipulation necessary to obtain intermediate and off-axis images. Consequently, multiplane TEE has increased sensitivity for the detection of sometimes subtle abnormalities, including vegetations, periprosthetic leaks, left atrial appendage thrombi, and aortic dissection. The development of **real-time three-dimensional (3D) TEE** (see Section VIII.C) offers the possibility of assessing cardiac structures volumetrically. It has emerged as a clinically relevant modality by providing relatively high image quality, which may enhance clinical decision making, especially in regard to structures with a complex anatomy such as the mitral valve. However, this technology is still evolving, particularly with regard to its incremental value in routine clinical practice.

A. Basic views. The TEE examination tends to be more goal directed than the transthoracic examination, because there may be time constraints imposed by how long the patient can tolerate the esophageal probe. Initial views should focus on the question at hand, but it is still important to perform a comprehensive and thorough examination. Most operators prefer to begin with upper esophageal views before proceeding to transgastric views. The order of views obtained is not important, provided the operator develops a consistent and comprehensive approach.

B. The **probe may inadvertently rotate** during insertion and may require initial manipulation before starting the examination. The left atrium should be seen at the center of the screen. If the aorta is seen (which is posterior to the esophagus), then the probe must be rotated anteriorly. Slight retroflexion of the probe may be necessary to maintain adequate contact between the probe and the esophagus. Air in the esophagus, which is interposed between the probe and the heart, may affect image quality. This generally lessens as the examination progresses (from ongoing peristaltic activity in the esophagus). Similarly, the presence of a hiatal hernia may compromise image quality.

C. Multiplane TEE is now universal. Multiplane views are described in terms of degrees of rotation required to obtain particular images. At each transducer location, start array at 0° and rotate to 180° at 5° to 15° increments to obtain a complete sweep. The standard horizontal plane is designated as 0°. At approximately 45°, short-axis views are obtained. Ninety degrees is defined as the longitudinal plane, whereas at around 135°, the true long-axis cardiac views are obtained. At 180°, a mirror image view of the standard horizontal plane is obtained. Given the variable anatomic relationships between structures, the degree of probe manipulation required to obtain the standard views will vary from patient to patient.

1. Upper esophagus (30 cm)—base of the heart (Fig. 66.2). With the array at 0°, a five-chamber cross-sectional view of the left atrium, left ventricle, right atrium, right

ventricle, and aortic valve is obtained. At 40° to 60°, the three leaflets of the aortic valve become visible (right coronary cusp at the bottom of the screen, noncoronary cusp on the top and to the left, and left coronary cusp on the right). Planimetry of the aortic valve orifice is often possible in this view. Subtle in-and-out movements allow for visualization of the proximal coronaries. The left atrial appendage is also seen in this view (zooming in on the atrial appendage, with subsequent rotation of the array, facilitates inspection for thrombus). At 60° to 100°, the tricuspid valve and right ventricular outflow tract/pulmonic valve become visible. At 120°, long-axis images of the left ventricular outflow tract (LVOT), aortic valve (noncoronary and right coronary cusps), and proximal ascending aorta are seen. Slight withdrawal of the probe at 110° to 120° permits visualization of the ascending aorta. With the probe withdrawn further into the upper esophagus (Fig. 66.3), the pulmonary artery and its bifurcation can be visualized (from 0° to 45°).

FIGURE 66.2 Schematic representation of selected multiplane transesophageal echocardiography views of the aorta and aortic valve from the upper esophagus. Ao, aorta; AV, atrioventricular; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; PV, pulmonary valve; RA, right atrium; RV, right ventricle. (Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68. Copyright © 1996 Elsevier. With permission.)

2. **Lower and middle esophagus** (Fig. 66.4 A and B). With the array at 0°, a four-chamber view is obtained (some retroflexion of the probe is needed for a true four-chamber view, because with anteflexion one will see portions of the LVOT and aortic valve). This view is similar to an inverted transthoracic apical four-chamber view. With the left atrium and left ventricle kept in the center of the view field, rotation of the array allows for a thorough evaluation of the left-sided structures. Doppler interrogation of mitral inflow is generally performed with the array at 0° to 30°. Skillful maneuvers as the array is rotated to 90° allow for interrogation of both leaflets of the mitral valve, including the specific scallops of the leaflet. Rotation of the array to 90° to 110° reveals the two-chamber view (left atrium/left ventricle), with the anterior and inferior walls of the left ventricle visualized. The left atrial appendage and the left upper pulmonary vein are also seen. Long-axis views of the LVOT, aortic valve (right and noncoronary cusps), and proximal ascending aorta are obtained by rotation to 120° to 140°. The anterior mitral leaflet is particularly well visualized in these views. This complete sweep permits full delineation of the extent of mitral regurgitation.
Similar views of right-sided structures and the interatrial septum can also be obtained from this position. At 0° (in the four-chamber view as described previously), the septal and anterior leaflets of the tricuspid valve can be seen. The endoscope is then rotated to bring the interatrial septum and the right atrium to the center of view (some withdrawal or advancement of the probe may be necessary to optimize visualization of the interatrial septum). By rotation of the multiplane array, the interatrial septum and fossa ovalis can be thoroughly examined for evidence of a patent foramen ovale or atrial septal defect. Agitated saline contrast can be given intravenously at this time to expose evidence of shunting; asking the patient to perform Valsalva maneuver or to cough can help identify right-to-left shunting. At approximately 100°, the superior vena cava (SVC) and inferior vena cava can be seen entering the right atrium, and the right atrial appendage can also be seen. This is a good view to identify

anomalous pulmonary venous drainage into the right atrium or SVC or a sinus venosus atrial septal defect. Further rotation will allow for assessment of the right pulmonary veins.

FIGURE 66.3 Schematic of some of the multiplane transesophageal echocardiography views of the aorta and pulmonary artery that can be obtained from the upper esophagus. Ao, aorta; LA, left atrium; LPA, left pulmonary artery; MPA, main pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle. (Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:

15–68. Copyright © 1996 Elsevier. With permission.) **FIGURE 66.4 A:** Schematic diagram showing some representative sections of the left heart that can be obtained with multiplane transesophageal echocardiography from the lower and middle esophagus. Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. **B:** Schematic diagram showing representative multiplane transesophageal echocardiography sections of the atria and interatrial septum that can be obtained from the lower middle esophagus. Ao, aorta; IAS, interatrial septum; IVC, inferior vena cava; LA, left atrium; RA, right atrium; SVC, superior vena cava. (A and B, Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68. Copyright © 1996 Elsevier. With permission.)

3. Transgastric views

a. Proximal (Fig. 66.5 A). These are images obtained from the fundus of the stomach. A cross-sectional view of the left and right ventricles is obtained at 0°. By rotating the shaft of the endoscope to center with the left ventricle in the field of view, serial short-axis ("doughnut") views of the left ventricle can be obtained. Anteflexion of the probe will give rise to basal views, with the mitral and tricuspid valves seen in cross section. With the transducer in a more neutral position, middle and apical short-axis views will be obtained.

At 80° to 100°, a two-chamber view of the left atrium (with appendage) and left ventricle (anterior and inferior walls of the left ventricle, mitral leaflets, and papillary muscles) will be obtained. At ≥120°, a long-axis outflow tract view with aortic valve and ascending aorta will be visualized. The anteroseptal and posterior walls of the left ventricle are seen. Depending on the alignment with the transducer, this view may be useful in obtaining velocities across the aortic valve.

Bringing the array back to 0° and rotating the shaft of the endoscope to center the right ventricle in view will allow for interrogation of the right-sided structures (Fig. 66.5B). At 30° to 60°, the three leaflets of the tricuspid valve are visualized (anterior leaflet at the bottom, posterior leaflet on the top, and septal leaflet to the right). At around 70° to 80°, the right ventricular inflow tract view (SVC and tricuspid valve with anterior and posterior leaflets) is obtained. At 90° to 100°, the right ventricular outflow tract and pulmonary valve become visible as well. At 110° to 130°, the two-chamber view of the right ventricle and right atrium can be seen. By rotating to 130° to 150°, the papillary muscles and chordae supporting the tricuspid valve are further delineated.

b. Deep transgastric. The probe is advanced further into the stomach with the tip anteflexed. At 0°, a foreshortened five-chamber view is obtained. This view allows for Doppler interrogation of the aortic valve and LVOT. By rotating the multiplane array,

different segments of the left ventricle apex can be visualized in the search for thrombus or aneurysm.

D. Aorta. Counterclockwise rotation of the endoscope brings the aorta into view. Typically, the probe is advanced beyond the diaphragm and then slowly pulled back, following the aorta back to the arch. Rotation of the probe is required to keep the aorta in view in the center of the screen. At the level of the diaphragm, the aorta is posterior to the esophagus. In the mid-esophagus, the aorta is medial, whereas the ascending aorta and arch lie anterior to the esophagus. At 0°, the aorta is seen as a circular structure. Long-axis images (at 100° to 130°) provide additional information as needed at selected intervals. At the arch, the aorta is curved in front of the esophagus, presenting a sausage-shaped structure with the probe at 0°. Gentle clockwise rotation will follow the arch back to the ascending aorta. The ascending aorta is visualized in the longitudinal planes as discussed with the other views. The distal ascending aorta may be difficult to image fully, given the interposition of the trachea between the esophagus and aorta in this region and the greater likelihood of encountering a gag reflex the closer the probe is to the pharyngoesophageal junction.

E. Three-dimensional probe. The current 3D TEE probes use fully sampled matrix array transducers, allowing a pyramidal volume of data to be acquired. Besides standard 2D imaging modalities, this transducer is able to perform 3D imaging in several modes: live X-plane imaging, live 3D echo, live 3D zoom, triggered full volume, and triggered 3D color. Real-time X-plane imaging allows simultaneous biplane imaging from the same heartbeat. Live 3D mode displays real-time 3D images with a small pyramidal segment; 3D zoom mode displays the region of interest with a larger pyramidal segment in real time. Full-volume mode acquires a wider segment over several cardiac cycles, and color Doppler can also be added in this mode. The 3D TEE is useful in the evaluation of native valves, prosthetic valves, interatrial septum, and left atrial appendage, as well as in the guidance of percutaneous interventional procedures such as mitral valve repair, mitral or aortic valve implantation, closure of atrial septal defect, paraprosthetic leaks, and left atrial appendage. By convention, the 3D imaging acquisition and presentation of each cardiac valve follows individual rules. The acquisition of the mitral valve should be performed in 3D zoom (not full volume) from the mid-esophageal 90° (two-chamber view) and 120° (long-axis view). Once acquired, the image volume should first be rotated 90° counterclockwise around the *x*-axis, which results in en face view of the mitral valve; followed by a 90° counterclockwise rotation in the *z*-plane, which results in the conventional display of the aortic valve superiorly on the screen, regardless of whether it is viewed from the left atrium (surgeon's view) or the left ventricle. The tricuspid valve should be imaged from the 0° to 30° mid-esophageal or the 40° transgastric (with anteflexion) views. Off-axis four-chamber views would result in two adequately centered orthogonal images for 3D zoom acquisition (not full volume). The tricuspid valve should be displayed in superior orientation to the interatrial septum or interventricular septum, regardless of whether the valve is viewed from the right atrium or the right ventricle. Thus, the image volume should first be rotated 90° counterclockwise around the *x*-axis to allow en face view of the tricuspid valve from the right atrium; followed by a 45° rotation in the *z*-plane to allow the septal leaflet to appear inferiorly at 6 o'clock. The aortic valve should be imaged from the mid-esophageal view, either in short axis (60°) or long axis (120°), using 3D zoom or full volume. The imaged

aortic valve should be rotated (usually, 90° clockwise around the *y*-axis), in order to be displayed with the right coronary cusp oriented inferiorly (6-o'clock position), independent of whether it is viewed from the aorta or the LVOT. Images of the pulmonic valve should be acquired either from the 90° high-esophageal view (3D zoom) or the 120° mid-esophageal view (3D zoom also). The image volume should be rotated 90° counterclockwise around the *x*-axis, which results in en face view of the pulmonary valve. The image should then be conventionally rotated 180° in the *z*-plane so that the anterior cusp is oriented superiorly (12-o'clock position), regardless of whether the valve is viewed from the pulmonary artery or the right ventricular outflow tract. Images of left and right ventricles should performed individually by using full-volume acquisitions, from 0° to 120° mid-esophageal views with the index ventricle in the center of the screen. By convention, the left ventricular apex is oriented superiorly (12 o'clock) and right-sided structures are displayed on the left-hand side. The right ventricle is displayed with the left atrium oriented superiorly (12-o'clock position). The interatrial septum should be acquired at 0° while in 3D zoom or full volume. When viewed from the right atrium, the interatrial septum should be displayed with the SVC oriented superiorly (11-o'clock position), whereas if viewed from the left atrium, the right upper pulmonary vein should be oriented superiorly at the 1-o'clock position. The left atrial appendage should be from the left atrium and displayed en face with the pulmonary veins oriented superiorly and longitudinally. 3D echo has the potential to acquire quantitative data on valve area (aortic and mitral valve stenosis) and on the size of the LVOT and aortic annulus, which may be important in aortic valve procedures such as TAVR where accurate prosthesis size selection is vital.

FIGURE 66.5 A: Schematic diagram showing representative multiplane transesophageal echocardiography sections of the left heart from the proximal transgastric location. Ao, aorta; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MV, mitral valve; RV, right ventricle. **B:** Schematic images from a transgastric, multiplane sweep through the right ventricle. Ao, aorta; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve. (A and B, Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68. Copyright © 1996 Elsevier. With permission.)

XI.PATIENT RECOVERY. The patient's NPO status should be maintained until the gag reflex has returned. The patient should be instructed to avoid oral intake for at least 1 to 2 hours after the test. When the patient commences oral intake, he or she should initially take a small sip of cold water. If the water does not feel cold in the back of the throat, then some topical anesthetic effect is still present. The patient should wait for another half an hour and test the throat again. Until this has dissipated, the patient should avoid any hot drinks so as to avoid scalding. Appropriate precautions should be followed if sedatives were used, because the effects persist for several hours. Patients may have dizziness and orthostatic symptoms for up to several hours and should be instructed to sit or lie down if this occurs. Patients should not drive or operate heavy equipment until the next day. If the **esophageal intubation is traumatic** or there is evidence of significant blood staining of the saliva at the end of the TEE procedure, fluid should be withheld pending a full evaluation of the pharynx and neck seeking evidence of injury or of

subcutaneous emphysema in the neck region which may suggest esophageal perforation. A low threshold for referral for cervical neck x-ray to detect air in the mediastinum is indicated in this situation. Any concern about potential esophageal or pharyngeal perforation should lead to an immediate surgical consultation.

XII. PROBE CARE. Following use, the nonimmersible parts of the probe, such as the handle and rotary controls, should be cleaned with a bactericidal solution. The probe should be cleaned with soap, and water first, followed by the application of a proteolytic enzymatic detergent for at least 1 minute. It should then be rinsed for approximately 1 minute, and then leak tested by connecting the probe to a vendor-dependent Ultrasound Transducer Leakage Tester. Afterward, the probe should be soaked for at least 12 minutes in a ready-to-use high-level disinfecting solution (glutaraldehyde free), with a fast onset of action, long-lasting efficacy, and minimal vapor pressure to avoid inhalation exposure risk (i.e., *ortho*-phthalaldehyde). The probe should not be soaked in this solution overnight. Rinsing should then take place for at least 3 minutes to minimize the risk of allergic reaction, as well as mucosal, and skin or clothes staining. It should then be dried with a lint-free absorbent tray liner. Date of probe cleaning should be documented, and repeated weekly to avoid bacterial overgrowth.

XIII. COMPLICATIONS. In reported series, the incidence of major and minor complications is 2% to 3%, with most being minor complications. Major complications (death, esophageal perforation, significant arrhythmias, congestive heart failure, and aspiration) occur with a frequency of 0.3%, with a reported mortality of <0.01%. Reported minor complications include transient hypotension, hypertension (particularly with agitation), transient hypoxia, transient bronchospasm, and arrhythmias (such as supraventricular tachycardia, nonsustained ventricular tachycardia, and transient atrioventricular block). Methemoglobinemia has been rarely reported because of the anesthetic spray and should be considered if cyanosis occurs. Other complications of intubation include tracheal intubation, laryngospasm, and vocal cord paralysis. Sore throat is not uncommon after the procedure and may persist for a day. Anaphylaxis and other allergic reactions can occur because of the medications used.

XIV. PITFALLS. The improved resolution and anatomic detail provided by TEE, as compared with TTE, is what makes it such a powerful diagnostic tool. However, this can also lead to misinterpretation of normal structures. Trabeculations in the atrial appendage can be mistaken for thrombi, and lipomatous hypertrophy of the interatrial septum can be incorrectly labeled as a mass, as can the eustachian valve. The transverse and oblique sinuses can be mistaken for abscess cavities. Off-axis images may create the appearance of a mass on the aortic valve when one of the cusps is cut obliquely. The lungs can give rise to reverberation artifacts, which can erroneously be diagnosed as dissection flaps (presence in nonanatomic planes, lack of disruption of color Doppler of blood flow, and crossing of normal anatomy all favor diagnosis of artifact). Abnormal findings should be visualized and verified in several views to ensure that they do not represent imaging artifacts.

These pitfalls are best minimized by the experience of the operator, but variations in anatomy may provide diagnostic dilemmas for even the most skilled echocardiographer.

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CHAPTER 67

Pericardiocentesis

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I. INTRODUCTION. Pericardiocentesis is an important therapeutic and diagnostic procedure in cardiology. The most common indications are to relieve tamponade and to identify causes of pericardial effusions. When performed correctly by experienced operators, pericardiocentesis has proven to be an effective and safe procedure.

II. INDICATIONS. As of this date, there are no published guidelines by the American Heart Association or the American College of Cardiology for the management of pericardial disease. However, the European Society of Cardiology published their most recent guidelines on the topic in 2015. Most of their recommendations are level of evidence C, as they are based on case reports, retrospective series, and expert opinion. From a broad perspective, they recommend considering pericardiocentesis in patients with pericardial effusion who become symptomatic from the effusion, in patients with pericardial effusions measuring more than 20 mm, in patients with chronic (more than 3 months) pericardial effusions, or in whom the effusion progresses despite empiric treatment with nonsteroidal anti-inflammatory drugs. In this chapter, we provide a more specific approach, summarizing the most common indications for pericardiocentesis in different clinical scenarios in the following section.

A. Alleviation of cardiac tamponade. Cardiac tamponade is a clinical diagnosis characterized by hypotension, tachycardia, distended neck veins, pulsus paradoxus, and distant heart sounds. Echocardiographic evaluation provides confirmatory evidence demonstrating the presence of pericardial effusion (regional or circumferential), inferior vena cava plethora, diastolic collapse of the right atrium and right ventricle, and increased respiratory variation of blood flow through the tricuspid and mitral valves. The normal pericardial cavity typically contains 15 to 50 mL of fluid. **The additional volume of fluid required to cause hemodynamic compromise is variable** and is dependent upon several factors, including the patient's volume status, the rapidity of fluid accumulation, and intrathoracic pressure (positive end-expiratory pressure increases intrathoracic pressure, impairing right heart filling and exacerbating tamponade physiology). Therefore, a relatively small but rapidly accumulating effusion can cause tamponade, particularly in the intravascularly depleted patient or in intubated subjects receiving positive end-expiratory pressure.

B. Evaluation of and therapy for pericardial effusion

1. **After open heart surgery.** Effusions after open heart surgery are common, but they rarely lead to hemodynamic impairment. Data from the Mayo Clinic suggest that the incidence of significant effusion in patients 18 years of age or older up to 30 days after cardiac surgery with cardiopulmonary bypass is 1.5%. The risk of effusion is highest in patients after heart transplant and lowest in patients post coronary artery bypass grafting. Renal failure, immunosuppression, pulmonary thromboembolism, prolonged cardiopulmonary bypass, and high body surface area are all independent risk factors for significant effusion. The role of anticoagulation in effusion formation is less clear, but it has been proposed to be an additional risk factor.
2. **Idiopathic.** In patients presenting with large, idiopathic effusions, evaluation of pericardial fluid with cytology, culture, cell counts, and chemistries frequently assists in diagnosis. The cause of most effusions can be diagnosed with history, physical examination, laboratory evaluation, and pericardial fluid analysis. Fluid analysis has been shown to be more helpful than pericardial tissue biopsy for culture of viral and bacterial pathogens, and cytology is positive in 65% to 85% of cases of malignant effusion. It is recommended that large pericardial effusions (>20 mm) be drained if the effusion persists for more than 1 to 3 months because **up to one-third of patients with large idiopathic pericardial effusions develop cardiac tamponade unexpectedly**.
3. **Malignant.** Malignant pericardial effusions are a rare manifestation of metastatic disease. Fluid cytology can be of value if the primary tumor is unknown. The most common neoplasms associated with malignant pericardial effusion include those of lung, breast, and hematologic malignancy. Controversy exists regarding the most appropriate management of malignant effusions. There are no prospective, definitive studies comparing surgical management with pericardial window and pericardiocentesis, but surgery is commonly used because of the risk of reaccumulation. Large malignant effusions treated with simple pericardiocentesis without prolonged catheter drainage reaccumulate in as many as 60% of cases. However, several studies have indicated that when a pericardial drain is left in place for several days until drainage is <25 mL/d (average 4.8 days), the risk of reaccumulation decreases to about 12%. Sclerotherapy has a similar failure rate. Surgical treatment with pericardial window is usually effective in decreasing the risk of reaccumulation but it carries a 30-day mortality of approximately 8%. Therefore, pericardiocentesis with drain placement is a very reasonable initial procedure for the diagnosis and management of malignant effusions.

III.CONTRAINDICATIONS

A. **Absolute.** In emergent scenarios of cardiac tamponade, when circulatory collapse is imminent, there are no absolute contraindications. In these instances, pericardiocentesis is often a life-saving intervention.

B. **Relative**

1. **Anticoagulation.** The risk of bleeding is low with pericardiocentesis; however, if time permits, prothrombin time and partial thromboplastin time (PTT) should be obtained in all patients undergoing pericardiocentesis. An international normalized ratio >1.8 or PTT greater than twice the normal should be corrected with fresh frozen plasma before intervention. It should also be noted that **tamponade physiology, by leading to hepatic congestion, may produce or exacerbate coagulation abnormalities**. Of note, if the patient is

coagulopathic, the subxiphoid approach is best avoided, because perforation of the hepatic vessels could lead to life-threatening bleeding.

2. **Thrombocytopenia.** Platelet counts should be >50,000.
3. **Traumatic hemopericardium.** A patient with traumatic hemopericardium should be treated surgically.
4. **Type A aortic dissection.** Typically, hemorrhagic effusions secondary to type A dissections are treated emergently with surgery. However, in situations where tamponade and circulatory collapse are imminent, small volume pericardiocentesis, with removal of the minimal amount of fluid necessary to maintain hemodynamic stability (about 10 to 25 mL) is indicated to stabilize patients before surgery. Data suggest that larger volume taps may be detrimental.
5. **Subacute free wall rupture.** As with dissections, free wall ruptures are best addressed surgically. However, as in pericardial effusions caused by type A dissection, draining a small volume of fluid may be necessary to stabilize patients in preparation for operative repair of the free wall rupture.
6. **Small, loculated, or posteriorly located effusions** are technically more difficult to tap and have increased risk of complication. Echocardiographic guidance is paramount if pericardiocentesis is attempted, and in some cases echocardiography combined with fluoroscopy might be necessary. Another possibility is to use a computed tomography–guided approach with the help of interventional radiology.
7. **Purulent effusions.** Whereas suspected purulent or tuberculous effusions are considered an indication for pericardiocentesis, grossly infected pericardial fluid should be managed surgically. If fluid is obtained, a way to differentiate purulent from tuberculous effusions is by measuring glucose and white count. In purulent effusions, there is a low glucose ratio (mean of about 0.3) and high white cell count (mean of 2.8 per milliliter) with neutrophilic predominance (mean of 92%). On the contrary, a tuberculous effusion has a higher glucose ratio (mean of 0.7) and a lower white cell count (mean of 1.7 per milliliter) with less neutrophilic shift (mean of 50%). In neoplastic effusions, the glucose ratio is even higher (about 0.8), with an average white cell count of about 3.3 per milliliter and 55% neutrophils.
8. **Malignant effusion.** As stated previously, management of malignant effusions is controversial. Although pericardiocentesis is an effective and proven first-line therapy, recurrent effusions should be considered for pericardial window. The European Guidelines for pericardial disease recommend pericardiocentesis in the absence of tamponade in large effusions based on a recurrence rate of 40% to 70%. They also recommend considering intrapericardial instillation of cytostatic/sclerosing agents in addition to the treatment of the primary tumor, in order to prevent recurrences. However, this approach should be tailored to each type of tumor and has not been validated in prospective trials.

IV. PERICARDIOCENTESIS VERSUS SURGICAL MANAGEMENT

(Table 67.1) The preferred procedural approach for pericardial drainage varies depending on the underlying etiology of the effusion, chronicity, size, hemodynamic impact, and suspected recurrence rate.

V. PATIENT PREPARATION.

Ideally, pericardiocentesis is performed in a laboratory equipped for fluoroscopy and invasive hemodynamic monitoring. In our institution, we routinely notify the cardiothoracic surgery service when a percutaneous

pericardiocentesis is planned, so if any complication requiring surgical intervention occurs during the procedure, the patient can be intervened upon promptly.

A. Informed consent. Patients should receive a clear explanation of the risks and benefits of pericardiocentesis, including the rationale for performing the procedure.

B. Monitoring. Patients should have heart rate, blood pressure, and oxygen saturations measured throughout the procedure. In addition, electrocardiographic monitoring is necessary. Worsening hemodynamics or falling oxygenation should alert the operator to the possibility of a procedural complication. Frequent ectopy (premature ventricular contractions, premature atrial contractions [PACs], or nonsustained ventricular tachycardia) may result from irritation of the myocardium, indicating impending perforation of a cardiac chamber.

C. Sedation. Pericardiocentesis is an anxiety-producing procedure for the patient. Appropriate pain relief and sedation should be administered prophylactically when this is clinically indicated, keeping in mind its potential impact on a patient with an already tenuous hemodynamic or respiratory state.

D. Intubation. The decision to intubate a patient with tamponade is challenging and controversial, and it is usually reserved for patients who develop severe respiratory insufficiency and is best avoided as it may worsen the hemodynamic situation.

TABLE 67.1 Approach to Pericardial Drainage

Pericardiocentesis	Surgical Management
Most cases of cardiac tamponade	Cardiac tamponade because of aort tamponade
Large or symptomatic effusions refractory to medical treatment	Recurrence of large chronic effusions
High suspicion of tuberculous, purulent, or neoplastic pericarditis	Purulent effusion
	Loculated effusion
	Need for pericardial biopsy
	Coagulopathy

VI. TECHNIQUES

A. Echo guided. Currently, ultrasound-guided pericardiocentesis is the standard approach at most institutions. It is feasible in over 95% of patients with pericardial effusions, especially when anterior or large. Patients are placed supine or in a slightly left lateral decubitus position. Echo guidance allows the selection of the most appropriate window to access the effusion and to ascertain the depth to which the needle should be inserted to obtain pericardial fluid.

1. Identifying the best window. The head is elevated approximately 30°, and a complete echocardiographic evaluation is performed with standard parasternal, apical, and subcostal views. In addition to these, it may also be necessary to obtain off-axis views with the purpose of identifying where the pericardial fluid is nearest and most accessible to the

skin without any interposing structure. In general, there are three different approaches, apical, subcostal, and parasternal, with the first two being the most commonly used. The subcostal approach has the lowest risk of causing pneumothorax, but the greatest risk of injuring the liver, or gastrointestinal tract, especially in obese patients. Moreover, the distance from the skin to the effusion is the longest with the subcostal approach. The apical approach has the lowest risk of pneumothorax or injury to major vascular structures (coronary arteries or internal thoracic artery), but has the highest risk of injuring the left ventricle and triggering ventricular arrhythmias. The parasternal approach has the advantage of small distance between the thoracic wall and the pericardium, but has a higher risk of causing pneumothorax or puncture of an internal thoracic artery. These three approaches are summarized in Table 67.2. The apical approach is most commonly used followed by the subcostal, with the remaining performed in off-axis views. When planning an apical approach, it is useful to obtain extreme apical views, with displacement of the probe laterally and posteriorly, close to the midaxillary or posterior axillary line, and if needed with inferior displacement of the probe until the largest pocket of fluid with the greatest distance to the myocardium is identified. When planning a subcostal approach, the liver should be identified to avoid accidental laceration during the procedure. See Section **VI.B** for appropriate positioning for subxiphoid approach. Because it is air filled, lung tissue will block ultrasound waves and preclude imaging of the heart; consequently, the risk of pneumothorax is low if a good echocardiographic window is selected for the tap. While imaging, it is imperative to take note of the **distance to the fluid pocket** as well as ***the probe trajectory***. Failure to maintain an appropriate trajectory is a common cause of failure in accessing a pericardial effusion percutaneously. Because real-time imaging of the needle tip accessing the pericardial fluid is not always possible, it is of vital importance to maintain the trajectory of the needle during the pericardiocentesis identical to the trajectory of the echocardiographic probe when imaging.

2. **Prepping the patient.** Once the best window is selected, the probe's location is marked with a permanent marker and scrubbed with sterile chlorhexidine–alcohol or povidone–iodine solution. The entire torso is draped with sterile towels or a full-body sterile field if available. The patient should not move between the echocardiographic examination and the procedure.
3. **Echo probe.** We use a sterile sleeve over the echo probe so that the operator has it to hand when performing the pericardiocentesis.
4. **Marking the needle.** Using a sterile pen, a mark can be made on the pericardiocentesis needle at the approximate distance between the skin and effusion that was noted on the echocardiogram. The needle used should be 5 to 8 cm in length, with a short bevel to lessen the risk of lacerating structures at the needle's tip. In some instances, particularly in obese patients, longer needles will be needed.
5. **Anesthetic.** Local anesthetic (e.g., 1% lidocaine) is applied to the skin over the mark. Then deeper anesthetic is given over the superior aspect of the rib (if a chest wall approach is used). Occasionally, in a relatively superficial pericardial effusion, the pericardial space will be entered with the anesthetic needle and pericardial fluid may be aspirated. Care should be taken when using an apical or intercostal approach to avoid damaging the neurovascular bundle at the lower rim of the rib at the superior aspect of the rib space.

6. **Entering the pericardium.** Using a three-way stopcock, an 18G Cook needle is attached to a syringe that contains a few more milliliters of local anesthetic. The needle is advanced through the anesthetized tract while maintaining negative pressure in the syringe, over the rib, along the same trajectory as the echocardiographic probe, until the fluid is aspirated. Alternatively, a sheathed catheter may be used instead of the Cook needle. Upon aspiration of the fluid, the catheter is advanced over the needle, and the needle is withdrawn. If no fluid is retrieved at the depth calculated from the echo images, it is recommended to withdraw the needle and reassess the trajectory with the ultrasound probe as it may need to be redirected.

TABLE 67.2 Advantages and Disadvantage of Different Access Sites in Performing Pericardiocen

Approach	Technical Details	Advantages	Disad
Apical	• Find the largest fluid pocket closest to the skin • Trajectory of the needle should be same as that of echo probe • Use with echo guidance	• Less possibility of injuring adjacent organs or vascular structures • Easiest to perform	• Hig wa fibr • situ the
Subcostal	• Place the needle in the subcostal space at a 45° angle relative to the transverse plane and direct it toward left shoulder • Blind, echo-guided, or fluoroscopic approach	• Less risk of pleural puncture or pneumothorax • It is the safest approach in emergent situation, when ultrasound is not available	• Hi co • If th les su • Hig
Parasternal	• The needle is inserted proximal to the sternum, close to the fifth left intercostal space • Preferred approach is echo-guided	• Less likelihood of puncturing the pleura or the lung than apical approach	• Hig tho • Hig sub

7. **Confirming catheter/needle placement.** Once fluid is obtained during aspiration, it does not necessarily confirm access to the pericardial space, because pleural and peritoneal collections may be traversed during pericardiocentesis. When confirmation that the needle is in the pericardial sac is needed, agitated saline contrast may be injected through the stopcock while imaging the heart from a remote location. **The appearance of bubbles in the pericardial space confirms an appropriate location.** Bubbles appearing within a cardiac chamber suggest that the heart has been perforated and that the needle or catheter should be withdrawn. If agitated saline cannot be visualized, one should reconsider the needle position. If the effusion is large, the contrast may not be visible from all echocardiographic windows; occasionally, it may be necessary to reinject saline and image from an alternative location. Of note, it is recommended to inject agitated saline when the needle is in the pericardial fluid and before using the dilator and inserting the catheter. With this approach, it is possible to avoid dilating the myocardium with a larger bore device in case of perforation of the ventricular wall.

8. **Placing the pericardial catheter.** Once the intrapericardial position is confirmed, a floppy-tipped, 0.035-in. guidewire is inserted through the needle into the pericardial space. A scalpel blade is then used to nick the skin over the needle, the needle is withdrawn, and a 6F dilator is used to broaden the tract into the pericardium. Finally, the dilator is removed and a 6F to 8F pigtail angiocatheter with side holes is threaded over the wire well into the pericardial space, ensuring at all times that the end of the wire is controlled. The wire is removed, and catheter placement can again be confirmed with agitated saline injection if needed. With a three-way stopcock, fluid for laboratory analysis should be collected with a large syringe upon initial drainage; the catheter is then attached to a 30-cm length of plastic tubing, which in turn may be connected to a vacuum bottle or drainage bag. If the catheter is being left to drain for some time, it should be sutured in place.

9. **Bloody pericardial fluid or frank blood?** Occasionally, very bloody fluid may be aspirated during pericardiocentesis, and confirmation of the needle placement may be difficult. Therefore, differentiating between blood (chamber perforation) and bloody effusion can be challenging. A few milliliters of the aspirate can be placed on a gauze pad; classical teaching suggests that if the fluid coagulates, it is blood from chamber perforation. Conversely, fluid that spreads out on the gauze forming a pinkish halo suggests an intrapericardial origin. In reality, effusions caused by cardiac rupture, dissection, or ongoing bleeding into the pericardial space may clot upon aspiration; this fluid should be sent for hematocrit (to confirm that it is blood), and cardiothoracic surgery consultation should take place emergently.

B. **Electrocardiographic guidance via subxiphoid approach.** Electrocardiography (ECG)-guided pericardiocentesis is an alternative approach in which ECG monitoring is performed as the needle is advanced, while carefully watching for the presence of current of injury that would suggest the myocardium has been reached. This approach may be used if echocardiography is unavailable or it may be used in conjunction with echocardiography. However, most experts agree that electrocardiographic guidance adds little to the safety of a carefully performed echocardiographically guided procedure. If ECG guidance is used instead of echocardiography, a subxiphoid approach is typically preferred:

1. The patient is positioned at a 45° incline. Electrocardiographic limb leads are attached to the patient in the usual fashion.

2. The xiphoid process is identified, and a point just inferior and to one side of the process is marked. The region is prepared and draped sterilely, and local anesthetic is given around the mark with a 25G needle. A 21G steel spinal needle is attached to a syringe filled with local anesthetic. The needle should be approximately 10 cm long. With a sterile alligator clip, the V lead of the ECG monitor is attached to the metal hub of the spinal needle.

3. The needle should be directed posteriorly at approximately 90° to the patient until the tip is below the costal margin. Then the hub of the needle should be depressed toward the patient's skin and advanced toward the left shoulder at an angle of 15° to 30° to the patient. Local anesthetic is injected as needed, and gentle suction should be applied to the syringe when advancing.

4. ST-elevations or premature ventricular contractions on the ECG monitor indicate that the needle is encountering the right ventricle. PR-segment elevation or frequent PACs indicate that the needle is penetrating the right atrium. In the average adult, the distance from skin to pericardium is approximately 6 to 8 cm (1).

5. Once in the pericardial space, a catheter may be placed as described previously.

C. **Fluoroscopic guidance.** Fluoroscopy was previously the most common method used as to guide pericardiocentesis, but this approach has largely been supplanted by echocardiography. With fluoroscopy, a subxiphoid approach is also used. Patient positioning and anatomical approach is the same as described above for ECG guidance. For this approach, either a polytef-sheathed needle with an attached saline-filled syringe or a Tuohy-17, blunt-tip introducer needle can be used. The needle is directed to the left shoulder and toward the anterior diaphragmatic border of the right ventricle, at about 30° angle to the skin. The purpose is to avoid the coronary, pericardial, and internal mammary arteries with this direction and angulation. Upon penetration into the pericardial space, needle position may be confirmed with injection of radiopaque contrast media. The left lateral with a slight left anterior angiographic view, or an anteroposterior view, provides the best visualization of the puncturing needle in relation to the diaphragm and the pericardium. As the needle is advanced, the operator should perform moderate suction, and once fluid is obtained, it is advised to inject very small amounts of contrast until the pericardial silhouette is demarcated on the fluoroscope, a phenomenon known as the "halo sign." Once the wire is advanced over the needle, it should be imaged to verify that it is in the intrapericardial space and not in a cardiac chamber. The soft J-tip wire may be confirmed to be in the pericardium by identifying how it crosses from the right to the left chambers, because a wire in the right ventricle would not cross to the left side unless a ventricular septal defect is present. A drainage catheter may then be placed as described earlier.

D. **Blind approach.** In emergent conditions, blind pericardiocentesis may be necessary. A subxiphoid approach is used as described above, aiming the needle toward the left shoulder. However, because of the significantly higher rates of complications and because of the increased availability of bedside ultrasound, blind taps should be avoided unless absolutely necessary.

VII. DIAGNOSTIC STUDIES.

If the cause of the pericardial effusion is not clear, the fluid should be sent for analysis. The primary causes of idiopathic effusions depend somewhat on the patient population but include tuberculosis (TB), viral infection, uremia, collagen vascular disease, neoplasia, surgery, and myocardial infarction. Therefore, all fluid from idiopathic effusions should be sent for bacterial, mycobacterial, and viral cultures; cytologic examination; acid-fast bacillus smear; cell count; protein; glucose; and lactate dehydrogenase. If TB is suspected, evaluate for adenosine deaminase, interferon gamma, pericardial lysozyme, and polymerase chain reaction. If malignancy is suspected, tumor markers including CEA, CA 72-4, and CA 19-9 may be sent for evaluation. Blood samples should be sent for chemistry, complete blood count, blood cultures (if bacterial infection is likely), thyroid-stimulating hormone, erythrocyte sedimentation rate/C-reactive protein, antinuclear antibody, and rheumatoid factor (if connective tissue disease is suspected). Consideration should also be given to conducting a tuberculin purified protein derivative skin test.

VIII. COMPLICATIONS.

Using echocardiographic guidance, the rate of complications is low. The largest series of echo-guided pericardiocenteses comes from the Mayo Clinic. Among the 1,127 procedures studied, major complications occurred in 1.2% of cases, and these included one death from right ventricular perforation, five nonfatal perforations that

required surgery, one intercostal artery laceration, five pneumothoraces, one episode of sustained ventricular tachycardia, and one episode of bacteremia. Minor complications occurred 3.5% of the time and included 11 chamber perforations that sealed spontaneously, 8 self-limited pneumothoraces, 9 pleuropericardial fistulas, and 2 episodes of nonsustained ventricular tachycardia.

Fluoroscopy appears to be associated with higher rates of complications. In one series of 352 procedures, complications included 2 (0.6%) deaths, 23 (5.6%) chamber perforations (3 requiring surgery), 5 (1.4%) arterial bleeds (3 diaphragmatic, 1 posterior descending artery, and 1 left internal mammary artery), and 2 pneumothoraces (2).

Blind pericardiocentesis has been associated with morbidity rates as high as 20% and mortality rates as high as 6%.

Therefore, complications are relatively rare in experienced centers, although one must be mindful of the following:

A. Pneumothorax. This is usually effectively avoided with echocardiographic imaging. If the parasternal approach is used, remaining close to the sternum decreases the risk of pneumothorax.

B. Myocardial perforation and chamber entry. This is usually asymptomatic and self-sealing, particularly if the left ventricle is entered. Right ventricular perforations have a somewhat higher likelihood of bleeding when perforated, but right atrial lacerations carry the highest risk. If laceration is suspected, the needle or catheter should be withdrawn and the patient should be observed overnight in an intensive care setting. Serial echocardiograms are indicated to assess for changes in effusion size.

C. Arterial laceration. The left internal thoracic/mammary artery runs down the chest wall about 1 to 2 cm lateral to the sternum, with the vein running slightly more medial. Left chest wall and subxiphoid approaches must take this anatomy into consideration. The posterior descending artery may be lacerated on subxiphoid approaches if the needle is aimed too medially. On a chest wall approach, the intercostal arteries and nerves are avoided by passing the catheter just superior to the rib.

D. Infection. Sterile technique during the procedure and meticulous catheter care afterward if a drain is left in place minimize this risk. As the Mayo series suggests, the risk of catheter-related infection is very low, even among cancer patients.

E. Death. This is exceptionally rare when procedures are performed by experienced operators with echocardiographic guidance.

IX.POSTPROCEDURE CARE

A. Chest radiography. A postprocedure chest film should be obtained in all patients to exclude pneumothorax.

B. Monitoring. Patients should be observed for 1 to 2 hours following the pericardiocentesis. Patients without significant comorbidities who have uncomplicated diagnostic taps do not require inpatient care following the procedure.

C. Drain care. Care of an indwelling pericardial catheter is similar to that for any central line. After the catheter is sutured in place, the site is treated with an antibacterial ointment and then dressed sterilely. The dressing should be changed every 2 or 3 days.

1. The drain should be aspirated every 6 hours. Continuous drainage can also be used, but the risk of catheter obstruction is higher. Following aspiration, the catheter is flushed with sterile or heparinized saline.

2. If the fluid becomes purulent or the patient becomes septic, the catheter must be removed.
3. Strict record of the volume of fluid draining from the catheter must be kept. The catheter is typically left in place for 1 to 2 days, but extended drainage has been associated with lower rates of effusion recurrence. When the drainage is <25 to 50 mL/d, the catheter can be removed.

D. Follow-up echocardiography. Before pulling the drain, an echocardiogram should be obtained to ensure resolution of the effusion. Sometimes, when the drainage volume is minimal, it may be useful to clamp the catheter for few hours and observe the patient for clinical signs of tamponade. Alternatively, an echocardiogram can also be performed in order to assess for reaccumulation once the drain is clamped.

E. Patient care. Patients may be ambulatory, with the drain securely in place. Pericardial pain is best managed with nonsteroidal anti-inflammatory medications.

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CHAPTER 68

Commonly Used Cardiovascular Formulae

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GENERAL HEMODYNAMICS

Stroke volume (mL) = End-diastolic volume − End-systolic volume

Cardiac output (L/min) = Heart rate × Stroke volume

Ohm's law $V = IR$
V = Pressure difference across the system

I = Cardiac output or flow

R = Resistance across the system

PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure;

1 Wood unit = 80 dynes/s/cm^5

RVOT, right ventricular outflow tract; VTI, velocity time integral

Transpulmonary gradient (mm Hg) = Mean PAP − PCWP
PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure

Fick equation

VO_2 (oxygen consumption); SaO_2, systemic arterial oxygen saturation; SvO_2, systemic venous oxygen saturation; Hgb, hemoglobin

Body surface area (m^2) = [Height (cm) + Weight (kg) − 60]/100

Stroke work (g-m/beat) = Stroke volume × Mean arterial pressure × 0.0144

VALVULAR DISEASE AND LEFT VENTRICULAR (LV) FUNCTION

Gorlin equation

Simplified Bernoulli equation

Pressure difference = $4v^2$

VTI, velocity time integral; LVOT, left ventricular outflow tract

Proximal isovelocity surface area (PISA) method in mitral regurgitation

r, radius of PISA

Simplified PISA when aliasing velocity ~40 cm/s and peak continuous wave mitral regurgitation velocity ~5 m/s

r, radius of PISA

LVED, left ventricular end diastole; LVES, left ventricular end systole

Estimated pulmonary artery systolic pressure (mm Hg) = RA pressure + 4 × (Peak tricuspid regurgitation velocity)^2
RA, right atrium

Estimated pulmonary artery end-diastolic pressure (mm Hg) = RA pressure + 4 × (Pulmonary regurgitation end-diastolic velocity)^2
RA, right atrium

Assessment of right atrial pressure (by echo)

IVC Diameter (cm)	IVC Collapse	Estimated RA Pressure (mm Hg)
≤2.1	>50%	3 (range 0–5)
≤2.1	<50%	8 (range 5–10)
>2.1	>50%	8 (range 5–10)
>2.1	<50%	15 (range 10–20)

IVC, inferior vena cava; RA, right atrial.

Left atrial (LA) pressure (mm Hg) = Systolic blood pressure − 4 × (Mitral regurgitation velocity)^2

D*t*, time it takes velocity to go from 1 to 3 m/s

Tei index (myocardial performance index) =

SHUNTS

SaO_2, systemic arterial oxygen saturation

SVO_2, systemic venous oxygen saturation

PVO_2, pulmonary venous oxygen saturation

PaO_2, pulmonary arterial oxygen saturation

MVO_2, mixed venous saturation

SVC, superior vena cava

IVC, inferior vena cava

TVI, time velocity integral

LVOT, left ventricular outflow tract

RVOT, right ventricular outflow tract

VTI, velocity time integral

ELECTROPHYSIOLOGY/ECG

Left ventricular hypertrophy

Limb lead criteria

1. **R-wave in lead I + S-wave in lead III > 2.5 mV**
2. **R-wave in aVL > 1.1 mV**
3. **R-wave in aVF > 2.0 mV**
4. **S-wave in aVR > 1.4 mV**

Precordial lead criteria

1. **R-wave in V_5 or V_6 > 2.6 mV**
2. **R-wave in V_6 + S-wave in V_1 > 3.5 mV**
3. **Largest R-wave + largest S-wave in precordial leads > 4.5 mV**

Cornell criteria

R-wave in aVL + S-wave in V_3 > 2.0 mV for females and 2.8 mV for males

Duke treadmill score (DTS)

DTS = Exercise time (minutes) − (5 × Maximal ST deviation) − (4 × Angina score)
0 = No angina

1 = Nonlimiting angina

2 = Angina limiting further testing

DTS ≤ −11 = High risk

DTS − 10 to 4 = Moderate risk

DTS ≥ 5 = Low risk

Age-predicted maximal heart rate (beats/min) = 220 − Age

PHARMACODYNAMICS

MISCELLANEOUS

Cockcroft–Gault

If female, multiply by 0.85

Central perfusion pressure = Mean arterial pressure − Intracranial pressure

Assessment of appropriateness of ascending aorta size to height

If ratio > 10, consider repair of aorta

Cholesterol mg/dL to mmol/L

1 mg/dL = 0.02586 mmol/L; 1 mmol/L = 38.7 mg/dL

Thus, 130 mg/dL = 3.45 mmol/L

Total cholesterol = LDL cholesterol + HDL cholesterol + 0.20 (Triglyceride level)
HDL, high-density lipoprotein; LDL, low-density lipoprotein

STATISTICS

	Disease Present	Diseas
Test result positive	a (True positive)	b (False
Tests result negative	c (False negative)	d (True

	Outcome Positive	Outcome Negat
Treated group	a	b
Control group	c	d

Absolute risk reduction = Difference in risk of outcome between control group and treated group