Ragavendra R. Baliga
Kim A. Eagle
Editors

Practical Cardiology

Evaluation and Treatment of Common Cardiovascular Disorders

Third Edition

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Chest Pain

1

Sharon Roble

Definition and Scope of Problem

Chest pain can be broadly defined as any discomfort in the anterior thorax occurring above the epigastrium and below the mandible. However, pain of cardiac origin may be felt primarily in the arms or jaw regions. Of the 110 million patients who presented to U.S. hospital emergency departments in 2004 over six million were for the evaluation of chest pain syndromes [1].

Principal Causes

The principal causes of chest pain can be grouped as life-threatening and non–life-threatening (Table 1.1). The principal life-threatening causes of chest pain include: acute coronary syndromes, aortic dissection, pulmonary embolism, and esophageal perforation. The principal non–life-threatening causes are stable angina, pericarditis, gastrointestinal reflux disease (GERD), esophageal spasm, musculoskeletal disorders, valvular heart disease, and hypertrophic cardiomyopathy. When the patient with chest pain arrives in a medical facility, it is the responsibility of the medical personel to assess the risk and to embark on an apprpriate treatment program.

Acute coronary syndromes comprise a broad range of clinical manifestations from acute myocardial infarction with cardiogenic shock to relatively "low-risk" unstable angina. The common pathophysiologic process involves myocardial oxygen supply-demand mismatch. This can be due to rupture of an atherosclerotic plaque in an epicardial coronary artery with resultant platelet aggregation, activation of the coagulation cascade, and thrombus formation or progressive narrowing and obstruction to coronary blood flow. Thus, treatment and management strategies are similar.

Table 1.1 Principal causes of chest pain

Life-threatening	Non–life-threatening
Acute coronary syndromes	Stable angina Pericarditis
Aortic dissection	GERD/esophageal spasm
Pulmonary embolism	Musculoskeletal
Esophageal rupture	Valvular heart disease
	Hypertrophic cardiomyopathy

GERD gastroesophageal reflux disease

History

The history is the most important component of the evaluation of chest pain. The history can be documented expeditiously for most patients and will guide further diagnostic testing. In addition to detailed questioning about the nature of the chest pain, the physician should elicit a history of prior myocardial infarction, coronary revascularization [coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA)], and congestive heart failure (CHF) symptoms. All patients should be queried about the major cardiovascular risk factors [diabetes, smoking, hypercholesterolemia, family history of premature coronary artery disease (CAD), and hypertension] and for a history or symptoms of peripheral vascular disease. Illicit drugs such as cocaine may cause chest pain and myocardial infarction more commonly in the younger population. All patients should be asked about the associated symptoms of dyspnea, diaphoresis, and nausea, as well as the response to nitroglycerin although esophageal pathology may also respond to nitroglycerin (i.e., esophageal spasm).

The interviewer should elicit the location, onset, duration, character, intensity, and radiation of the chest pain. When questioning the patient, the interviewer should use the term *chest "discomfort"* rather than *chest "pain,"* because many patients deny having "pain." In fact, many patients emphatically point out to the interviewer that the discomfort is not a "pain." For the purposes of discussion, this chapter retains the traditional term *chest "pain."*

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Cardiac

Chest pain that is cardiac in etiology is termed *angina pectoris*. Angina is defined as a clinical syndrome "characterized by discomfort in the chest, jaw, shoulder, back or arm" [2, 3]. Angina usually is provoked by physical exertion or emotional stress and is relieved with rest or nitroglycerin. Patients typically describe angina with adjectives such as "heavy," "dull," "pressure-like," "suffocating," or "squeezing," or they use phrases such as "like a heavy weight on my chest." Angina is classically substernal in location but can occur in the arm, shoulder, jaw, mandible, or upper back with or without radiation. Pain above the mandible, below the epigastrium, localized to an area less than one fingertip in size, or that radiates into the lower extremities is rarely angina. Angina usually lasts for a few minutes and is relieved by nitroglycerin within 5 min or less. Continuous pain that lasts for several hours or fleeting pain that last for only a few seconds suggests an alternative diagnosis. Angina typically does not vary with respiration, position, or palpation.

Angina is termed *stable* when it occurs only with provocation, has been occurring for at least 2 months, and is symptomatically stable. According to the Canadian Cardiovascular Society Classification system [4], angina can be graded on the basis of the history (Table 1.2). Class I angina occurs only with strenuous exertion, Class II results in a slight limitation of ordinary activity and occurs only during moderate levels of exertion, Class III is associated with a marked reduction in ordinary activity and can occur with mild exertion, and Class IV angina causes limitations on activities of daily living and can occur even at rest.

Unstable angina, which is an acute coronary syndrome, can be classified as rest angina, new-onset angina, or increasing angina [5] (Table 1.3). Rest angina occurs at rest without provocation for longer than 20 min within 1 week of presentation. New-onset angina is angina that is at least Class III in severity and presents within 2 months of initial presentation. Increasing angina is stable angina that is increasing in frequency or duration, has a decreasing threshold for provocation, or has increasing intensity.

Table 1.2 Grading of angina pectoris by the Canadian Cardiovascular Society Classification system

Class I
Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina (occurs) with strenuous, rapid, or prolonged exertion at work or recreation
Class II
Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening
Class III
Marked limitations of ordinary physical activity. Angina occurs on walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace
Class IV
Inability to carry on any physical activity without discomfort—Anginal symptoms may be present at rest

Adapted from Campeau [4]

Table 1.3 Principal presentations of unstable angina

Rest angina	Angina occurring at rest and usually prolonged >20 min occurring within a week of presentation
New-onset angina	Angina of at least CCSC III severity with onset within 2 months of initial presentation
Increasing angina	Previously diagnosed angina that is distinctly more frequent, longer in duration or lower in threshold (i.e., increased by at least one CCSC class within 2 months of initial presentation to at least CCSC III severity)

CCSC Canadian Cardiovascular Society Classification system

Anginal pain from myocardial infarction classically is often described as "crushing" or "as if an elephant were standing on my chest" and is usually severe and unrelenting. For many patients, it is the sentinel episode of chest pain. Others may have a history of stable angina, unstable angina, or both in the preceding 2 weeks. It is not uncommon for patients to present several days after a myocardial infarction with congestive heart failure symptoms or postinfarction angina. Some patients are completely asymptomatic or are able to recall only vague "gas pains."

Cardiac pain does not always present as typical angina pectoris. This may be particularly the case in women, the elderly and in those with diabetes mellitus. Patients may present with pain limited to the shoulder, arm, throat or jaw. Occassionally patients with ACS will present predominantly with sweating, shortness of breath, or GI symptoms such as nausea or vomiting (more common with inferior infarctions).

Angina pectoris is most frequenly caused by CAD resulting in reduced blood supply to the myocardium, but can also be due to increased demand. Conditions include hypertension, aortic valve stenosis, hypertrophic cardiomyopathy, tachycardia, and other systemic conditions such as anemia/acute blood loss or conditions resulting in increased cardiac output such as sepsis. Chest pain may be the presenting manifestation of severe valvular heart disease or hypertrophic cardiomyopathy. When present, it manifests as typical angina caused by a supply/demand imbalance in coronary blood flow that leads to myocardial ischemia or as chest discomfort caused by pulmonary congestion resulting from left atrial hypertension or volume overload. The symptoms are usually chronic and may be associated with CHF symptoms (dyspnea, fatigue, orthopnea, edema). If either valvular heart disease or hypertrophic cardiomyopathy is suspected, a history of syncope or aborted sudden cardiac death and a family history of sudden cardiac death should be sought. A history of rheumatic fever raises the possibility of rheumatic valvular disease.

These conditions can be distinguished by the physical examination and other diagnostic testing.

Pericarditis

Chest pain is a primary complaint in acute pericarditis. The pain is typically located over the precordium with radiation to the trapezius ridge and neck. The pain is often "sharp" or "knifelike," is exacerbated by respiration and thoracic motion, is relieved by leaning forward, and is aggravated by recumbency. It is not related to exertion and can last for hours on end. Patients may complain of dyspnea, and will often take shallow respirations to avoid the pleuritic pain. Pericarditis is more common in men and younger patients. Dyspnea on exertion and other symptoms of congestive heart failure should raise the suspicion for concomitant myocarditis.

Aortic Dissection

Aortic dissection is characterized by separation of intima and media and consequent propagation as blood enters the intima/media space. The separation of the layers of the aorta with formation of a dissection flap can lead to ischemia of any of the branches of the aortic trunk, including the coronary arteries. Although much less common than acute coronary syndromes, dissection should be considered early in the evaluation of chest pain, in view of its divergent management and exceedingly high short-term mortality rate. Aortic dissection has classically been described as a severe and sudden "ripping" or "tearing" chest or back pain that radiates in a migratory fashion [6]. A multicenter registry of almost 500 patients diagnosed with acute aortic dissection revealed that the pain of aortic dissection is more often sharp and typically of sudden and severe onset. The clinical manifestations of aortic dissection are quite varied, and thus the physician must have a high clinical index of suspicion in order to make the diagnosis.

Pulmonary Embolus (PE)

Pulmonary embolus is a frequent cause of death. It generally results from the embolization of thrombotic material from lower extremity and deep pelvic veins. The thrombotic material can occlude any of the branches of the pulmonary artery and lead to hypoxia, pulmonary infarction, and acute right ventricular dysfunction. It is also critical to consider this diagnosis early in the evaluation of chest pain, because a recurrent pulmonary embolus may be fatal.

The chest pain of PE can be pleuritic in nature and is associated with abrupt-onset dyspnea and apprehension. Many affected patients have risk factors for PE, such as previous deep vein thrombosis, recent surgery, prolonged immobilization, malignancy, hypercoagulability syndromes, advanced age, congestive heart failure, oral contraceptive use, or pregnancy.

Pleuritic chest pain may be a sign of pulmonary embolus, infection or inflamation of the pleura or lungs or result from a pneumothorax. If due to pneumonia, the pain may be accompanied by cough, sputum production and fever.

Gastrointestinal Pathology

Chest pain associated with GERD and esophagitis is often described as a "burning" sensation or simply as "heartburn" and occurs after meals or upon recumbency. The pain usually starts in the epigastric region, radiates superiorly across the entire chest, and usually does not radiate into the arms. However, the pain can also be retrosternal. The patient may also complain of hoarseness, a need to repeatedly clear the throat, or a deep pressure in the throat. A history of regurgitation or water brash supports the diagnosis. The chest pain of GERD is frequently exacerbated by maneuvers that increase intraabdominal pressure, such as bending, squatting, and coughing. Many patients have risk factors for GERD, such as excessive caffeine or alcohol use, cigarette smoking, and heavy meal consumption. The pain of esophageal spasm can be very severe, may last seconds to hours, radiates to the back, and is frequently indistinguishable from angina. It is important to query the patient about associated dysphagia, weight loss, or hematemesis. Of note, the pain of esophageal spasm and esophagitis may respond to nitroglycerin.

Cholecystitis may present with a pain radiating into the anterior chest. It is usually associated with nausea, vomiting and tenderness in the right hypochondrium.

Musculoskeletal Etiologies

Musculoskeletal chest pain is commonly associated with a history of coughing, trauma, injury, or strenuous muscular exertion. The patient may relate a history of the pain varying with physical position and being exacerbated by specific thoracic or limb movements. The pain usually is of low intensity and has a duration of several hours or days.

Chest pain may also be classified as atypical or typical on the basis of the presence of three features: (a) substernal location, (b) provocation with exertion or emotional stress, and (c) relief with nitroglycerin or rest. If all three features are present, the chest pain is termed *typical angina;* if two are present, it is termed *atypical angina;* and if only one is present, it is considered *noncardiac chest pain.*

The great majority of patients with chest pain do not have a life-threatening cause. It is important to identify these patients early to provide effective treatment, allay patient concerns, and utilize health care resources appropriately.

Physical Examination

A focused physical examination should be performed expeditiously to rule out life-threatening causes. Bilateral arm blood pressures, heart rate, respiratory rate, and oxygenation saturation should ideally be measured in every patient with acute chest pain.

The physical examination of patients with acute coronary syndrome is particularly important. Both myocardial infarc-

tion and unstable angina can cause severe myocardial ischemia that manifests as acute left ventricular dysfunction. Patients may present with a low cardiac output state (e.g., hypotension, tachycardia, poor urine output, mental status changes, cool extremities), acute pulmonary edema (tachypnea, hypoxia, rales, elevated jugular venous pressure), or both. The cardiac examination may reveal a soft S1, an S3 gallop, or a displaced and/or enlarged apical impulse. A low-output state or pulmonary edema greatly increases the short-term mortality rate in patients with acute coronary syndrome, and physical examination findings are used to guide therapeutic decisions.

The classic findings of aortic dissection include hypertension, pulse deficits, and the murmur of aortic insufficiency. However, these findings occur in the minority of patients, and the physical examination is most often unhelpful in the diagnosis of aortic dissection [7]. The murmur of aortic insufficiency is best heard at the lower left sternal border with the patient in the upright position, leaning forward, and at maximal expiration. Peripheral pulses should be evaluated and documented.

The most common physical examination finding in patients with PE is tachypnea (more than 16 respirations per minute) and is found in more than 90% of patients [8]. With large pulmonary emboli, findings of acute cor pulmonale may be present (acute hypotension, accentuated pulmonic component of S2, elevated jugular venous pressures, and a right ventricular lift). Pulmonic auscultation findings, if present, include rales and evidence of consolidation or pleural effusion. As with aortic dissection, the physical examination is usually unrevealing; thus, clinical suspicion must be heightened in order to make the diagnosis.

The results of a characteristic physical examination of patients with chronic, stable angina are usually normal. There are no specific physical examination findings for chronic CAD. However, the findings of diminished peripheral pulses or carotid and femoral bruits greatly increase the probability of coexisting CAD. If the patient is examined during an episode of acute ischemia, it may be noted that the S1 is diminished and a soft mitral regurgitation murmur may be present. Both these findings are presumably caused by transient, ischemia-mediated left ventricular dysfunction. Patients with chronic CAD and left ventricular systolic dysfunction or those with a recent untreated myocardial infarction may have enlargement and displacement of the apical impulse, elevated jugular venous pressures, a soft S1, or an abnormal S3.

The pathognomonic sign of pericarditis is the friction rub. The friction rub has been classically described as a "scratchy," three-component (though frequently only one- or two-component) sound that is related to the cardiac motion. It is best heard when the patient is sitting upright at full expiration. Friction rubs are well known to be evanescent and vary from examination to examination. The most common physical examination finding in pericarditis is tachycardia. If a coexisting pericardial effusion is present, the heart sounds may be distant or muffled. If the patient is markedly dyspneic or distressed, pericardial tamponade should be considered, the jugular venous pressure inspected, and pulsus paradoxus measured.

The physical examination in patients with GERD or esophageal spasm is unrevealing. Patients with underlying scleroderma may present with calcinosis, sclerodactyly, and telangiectasias. The diagnosis is usually suspected from history alone or response to antacid therapy.

Reproduction of pain with palpation or with thoracic or extremity movement and costochondral joint tenderness or swelling are characteristic findings of patients with musculoskeletal chest pain. Prevesicular herpes zoster may produce intense chest pain and may be difficult to distinguish from angina; however, it usually has a dermatomal distribution and is constant in nature.

The physical examination of patients with chest pain is most useful in those with significant valvular heart disease or hypertrophic cardiomyopathy. Significant aortic stenosis is characterized by a loud, late-peaking, crescendo-decrescendo systolic ejection murmur, heard best over the base of the heart, which may radiate into the neck or carotid arteries. An S4 may be prominent. The S2 may become single, because of an inaudible A2 component, or paradoxically split. Carotid pulses may be slow to rise and small in amplitude (parvus and tardus) [9]. Hypertrophic cardiomyopathy may also manifest with a systolic murmur and an S4. The murmur is typically harsh in nature and heard best between the left sternal border and the apex without radiation to the carotid arteries. It is mostly midsystolic at the left sternal border and holosystolic at the apex (as a result of concomitant mitral regurgitation). In contrast to aortic stenosis, the murmur increases with Valsalva maneuvers (during strain) and with rising from squatting to standing (and other maneuvers that decrease preload); the carotid upstroke is brisk; and the S2 is normal [10].

Diagnostic Testing

In all patients with chest pain where a cardiac etiology is suspected, a 12-lead electrocardiogram (ECG) should be obtained. It may show evidence of acute ischemia or injury, previous myocardial infarction, left ventricular hypertrophy, left bundle branch block, pericarditis, acute right ventricular strain, or a variety of other disorders. The ECG should be obtained within 5–10 min of the patient's presentation.

Acute Coronary Syndromes

In patients suspected of having chest pain. as a result of epicardial CAD, the physician should determine whether the patient is having an acute coronary syndrome with concomitant myocardial ischemia. The ECG should be compared with a previous ECG obtained during a pain-free episode. If significant changes from the baseline ECG are present (ST segment elevation/depression (Figs. 1.1 and 1.2), T wave abnormalities, Q waves, new left bundle branch block), myocardial ischemia is suggested. Unfortunately, a normal ECG or an ECG unchanged from baseline does not necessarily exclude an acute coronary syndrome.

Chest radiographs are generally not a necessary diagnostic test for myocardial ischemia. However, if the patient is complaining of dyspnea or if the pulmonary examination findings are abnormal, a radiograph should be ordered. Occasionally, the chest radiograph may reveal uncommon causes of chest pain such as pneumothorax or chest masses.

Simple bedside maneuvers may be tried if cautiously interpreted. Anginal pain typically abates completely less than 5 min after nitroglycerin administration. However, the

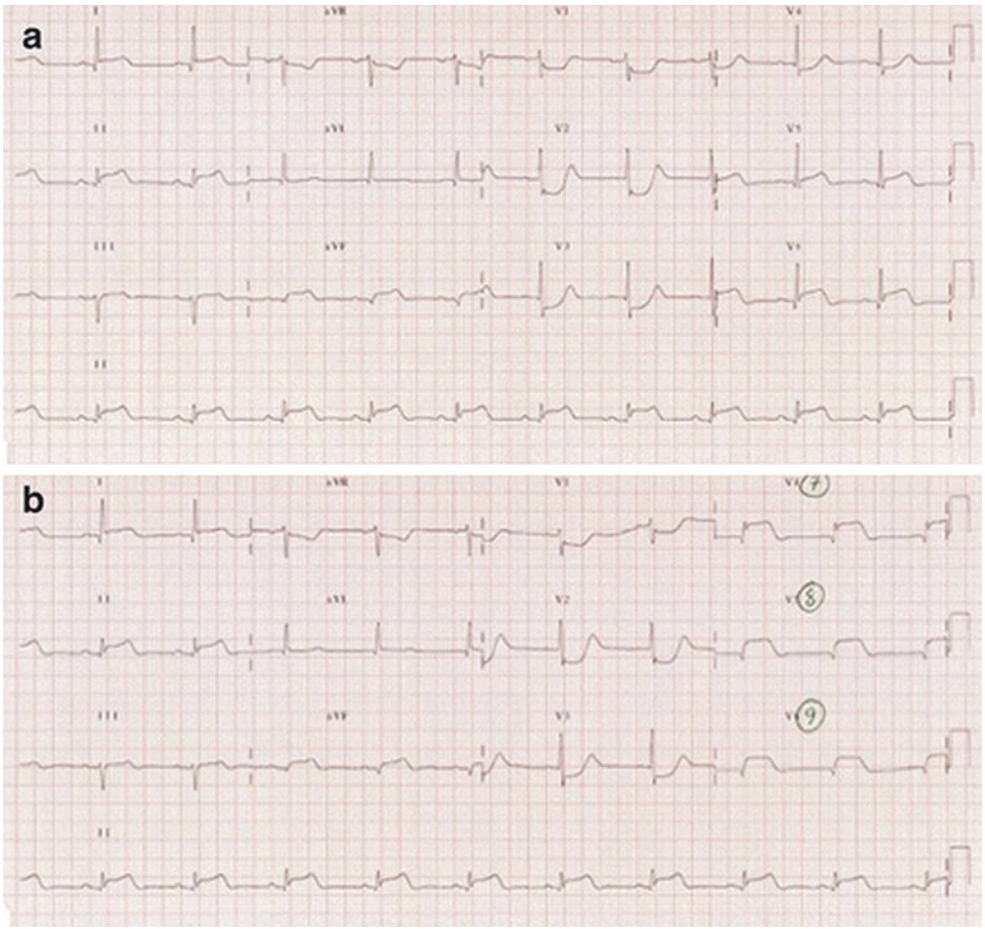

Fig. 1.1 (**a**) ECG demonstrating an infero-postero-lateral STEMI in a patient with acute chest pain. Note the presence of ST-depression in leads V1-V3 with associated dominant R-wave. (**b**) Placing leads V4-V6 posteriorly (V7-V9) unmasks the posterior ST-elevation. (From Zacharias and Makan [25]; with permission)

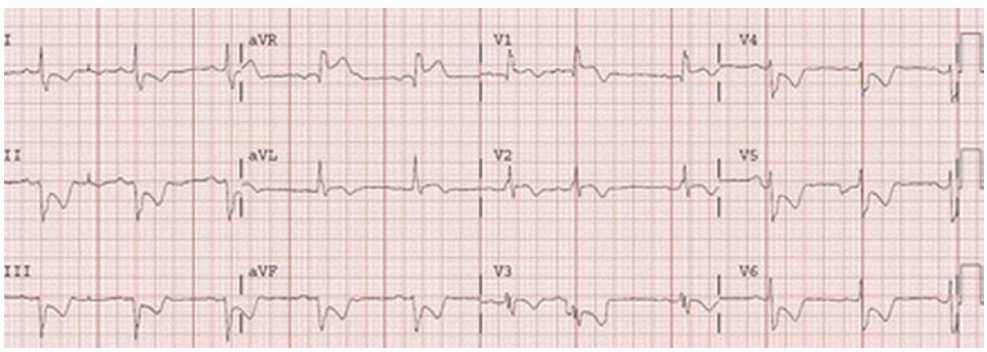

Fig. 1.2 ECG demonstrating ST-segment elevation in lead aVR, with associated ST depression in the precordial leads, suggestive of left main stem ischaemia. (From Zacharias and Makan [25]; with permission)

pain of esophageal spasm and esophagitis is also relieved with nitroglycerin but may not completely resolve; there may be a residual dull ache in contrast to ischemic chest pain. A gastrointestinal (GI) "cocktail," a mixture of antacids and viscous lidocaine, is often employed as a diagnostic maneuver. Because of the variety of medications given with the "cocktail," the possibility of spontaneous, coincidental resolution of ischemic chest pain, and the lack of good data to support this maneuver, it cannot be recommended for the routine evaluation of chest pain. However, if a patient presents with symptoms that are strongly suggestive of gastrointestinal origin, relief of pain with antacids or a "GI cocktail" may support the clinical diagnosis.

Biochemical cardiac markers are used to diagnose acute myocardial infarction and provide prognosis in unstable angina [11]. The commonly available cardiac markers are creatine kinase (CK) and myocardial band (MB) fraction, myoglobin, and troponin I or T (TnI or TnT). Myoglobin is the enzyme most rapidly released after an acute coronary syndrome, its levels peaking within 4–6 h and normalizing within 24 h, but it is not very specific. CK-MB has traditionally been used to diagnose myocardial infarction; its levels become elevated within 12 h of infarction, peak at 24 h, and normalize by 72 h. However, elevated levels of CK-MB can be found in normal individuals and in those with severe skeletal muscle. injury. Troponin levels become elevated within 6–12 h, peak by 48 h, and can remain elevated for 10 to 14 days after the initial event. Because of their high cardiac specificity, troponins have become the biochemical cardiac markers of choice for diagnosing acute myocardial infarction. However, caution must be used in the interpretation of an elevated troponin level because it may represent a cardiac event that occurred in the preceding 14 days. In these cases, a myoglobin level can be checked. If it is elevated, the troponin elevation is probably a result of a recent cardiac event. However, normal troponin. levels do not definitely rule out adverse cardiac outcomes in patients with chest pain. Patients with normal biochemical markers may be presenting without injury but may still have ischemia and thus will not have biochemical evidence of myocardial necrosis. When an acute coronary syndrome is suspected, acute myocardial infarction should be ruled out by serial troponin or CK-MB measurements. The first troponin measurement should be drawn upon initial presentation, and a second test should be repeated 8–12 h after the original symptom onset. If the patient has recurrent chest pain after the initial episode, or if the first two troponin measurements are indeterminate, further measurements of cardiac enzymes should be considered. More recently, there has been an interest in the "delta troponin" or change in troponin over time, suggesting that an increase in troponin levels although still within the normal range, may be suggestive of ischemia. in the appropriate clinical setting and may warrant further clinical evaluation.

Aortic Dissection

When aortic dissection is suspected, diagnostic imaging should be performed without delay. There are no specific ECG findings for aortic dissection. The ECG may be normal, show nonspecific ST segment or T wave changes, or show evidence of acute myocardial ischemia if the dissection involves the coronary arteries. Chest radiography has a low sensitivity for aortic dissection, and at least 20% of patients with suspected aortic dissections do not have a widened mediastinum or altered aortic contours [7].

The most widely available and reliable imaging modalities for aortic dissection are contrast-enhanced computed tomography (CT) and transesophageal echocardiography (TEE). CT is generally more widely available than TEE, allows for visualization of the entire aorta, and provides information about extraaortic structures. The CT should be performed according to specific aortic dissection protocols that involve thinner tomographic slices to improve resolution and boluses of intravenous contrast instead of slow infusions to delineate the aortic lumen. TEE may be preferred because it can be performed quickly at the patient's bedside with minimal risk to the patient. Overall, both tests have similar sensitivities and specificities, and the choice of test usually depends on availability and local expertise. If a strong clinical suspicion for aortic dissection exists even after a negative test result, a second modality should be utilized. Gadolinium-enhanced magnetic resonance imaging (MRI) is an excellent test for aortic dissection; however, fewer centers may be able to provide this service for emergency diagnostic purposes.

Pulmonary Embolism

The ECG in PE is rarely diagnostic and is most likely to be normal or shows nonspecific changes. When present, ECG changes can be helpful. If a significant PE occurs, transient right bundle branch block, $S_I\,Q_{III}\,T_{III}$ pattern, right axis deviation, or T-wave inversion in leads V_1 to V_3 can appear [12]. The chest radiograph typically shows nonspecific findings. Specific findings on chest radiographs are exceedingly rare.

Most patients with PE have reduced arterial partial pressures of oxygen, an increased alveolar-arterial oxygen pressure gradient, or both. However, these findings are nonspecific and cannot be used alone to initiate therapy.

The most commonly available and widely used initial diagnostic test for PE is the CT pulmonary embolus (PE) study. Another possibility for testing includes a ventilation/perfusion (V/Q) scan in patients who cannot undergo a CT scan for various reasons. CTPE studies are both highly specific and sensitive for the diagnosis of acute pulmonary emboli to the level of the subsegmental pulmonary arteries and has become the gold standard for the diagnosis of acute

pulmonary embolism. The test can be performed quickly with just a peripheral IV; however, it does require IV contrast. V/Q scanning is less frequently used nowadays given the potential need for further diagnostic testing. V/Q scans are reported out as normal, indeterminate probability, low probability, intermediate probability, or high probability. If the result is normal, PE can almost always be ruled out. A high-probability result confirms the diagnosis. Patients with an intermediate- or indeterminate-probability result and those with a low-probability result and a high clinical suspicion should undergo pulmonary arteriography, or CT pulmonary angiography to exclude the diagnosis.

D-Dimer levels have been shown to be elevated in patients with PE and are now rapidly available by enzyme-linked immunosorbent assay (ELISA) testing. One review [13] revealed that the ELISA D-dimer assay has an overall sensitivity of 90% to 95% but is not specific for the diagnosis of PE. However, negative D-dimer findings in a stable outpatient with a low clinical suspicion of PE can be used to exclude the diagnosis [14].

Echocardiography does not play a role in the diagnosis of pulmonary emboli; however, it can be useful to assess for right heart strain which is one criteria for catheter based lytic therapy, a relatively new technology in which thrombolytic therapy is delivered directly to the clot to decrease clot burden while decreasing bleeding risk.

Stable Angina

If, on the basis of the history and physical examination, the physician determines that the patient is clinically stable and unlikely to be having an acute coronary syndrome, then an evaluation for chronic epicardial CAD should be undertaken. The ECG in chronic stable angina can be normal, can show evidence of prior myocardial infarction, or can show nonspecific ST segment and T wave changes. The chest radiograph is usually unrevealing and only rarely shows coronary artery calcifications. The definitive diagnostic test for epicardial coronary stenoses is coronary angiography. However, because of cost and safety considerations, it is not feasible to perform this test in every patient with chest pain and suspected CAD.

Therefore, stress testing is routinely performed in the evaluation of the patient with chest pain as a decision aid in estimating the probability of significant coronary artery disease [15]. It is important to realize the principles of Bayes' theorem [16] when interpreting the results of stress testing. Briefly stated, the posttest probability of CAD is a function of the pretest probability of disease. In patients with a very low pretest probability of CAD, an abnormal stress test result can just as likely be a false-positive as a true-positive finding. Similarly, in a patient with a very high pretest probability of CAD, a negative test result does not rule out significant CAD. Patients with an intermediate pretest probability of CAD have the greatest benefit from stress testing, because a positive or negative result will result in a posttest probability that is significantly different from the pretest probability.

Table 1.4 Pretest likelihood of CAD in symptomatic patients according to age and sex[a] (combined Diamond/Forrester [17] and CASS [18] data)

	Nonanginal chest pain		Atypical angina		Typical angina	
Age (years)	Men	Women	Men	Women	Men	Women
30–39	4	2	34	12	76	26
40–49	13	3	51	22	87	55
50–59	20	7	65	31	93	73
60–69	27	14	72	51	94	86

CAD coronary artery disease, *CASS* coronary artery surgery study
[a]Each value represents the percent with significant CAD on catheterization

In a landmark study, Diamond and Forrester [17] showed that the pretest probability of CAD can be estimated solely on the basis of the patient's age, gender, and type of chest pain (noncardiac, atypical, and typical), as shown in Table 1.4 [data combined with the CASS [18] trial]. In view of the pretest probability and the sensitivity and specificity of the specific stress employed, the posttest probability of significant CAD can be determined with reasonable accuracy.

Stress testing can be performed with either exercise or pharmacological stimulation. Electocardiographic monitoring is used in all tests and imaging of the myocardium can be utilized with either echocardiography or nuclear scintigraphy. The relative characteristics of the various stress tests are summarized in Table 1.5.

In general, exercise tests are preferred over pharmacologic stress testing (e.g., dobutamine, adenosine, dipyridamole), because exercise is physiologic and provides important prognostic information. Furthermore, exercise testing objectively demonstrates whether the chest pain is exercise induced and at what level of exertion the chest pain is provoked. However, in order for an exercise test to have acceptable sensitivity for detecting significant CAD, the patient should be able to exercise to a workload of 6 metabolic equivalents of oxygen consumption (METS) and attain 85% of the maximum age-predicted heart rate. Exercise tests are further divided into nonimaging (ETT) and imaging (ETT-echocardiography, ETT-nuclear, ETT-MRI). Imaging is generally indicated when the patient has an abnormal baseline ECG (resting ST segment depression, left bundle branch block, preexcitation, paced rhythm, and/or left ventricular hypertrophy), is taking digoxin, or has a history of previous coronary revascularization.

Pharmacologic stress testing is indicated for the evaluation of chest pain when the patient is unable to exercise adequately. The choices for pharmacologic stress testing are

Table 1.5 Relative characteristics of various stress test modalities

Test	Sensitivity	Specificity	Sensitivity in single vessel disease	Sensitivity in multivessel disease	Relative cost	Assessment of LV ejection fraction	Assessment of cardiac anatomy and function	Feasibility in outpatient	Feasibility in obese patient	Feasibility in severe pulmonary disease	Accuracy in women	Accuracy with hypertension	Appropriate with abnormal baseline ECG	Appropriate with concomitant digoxin therapy
ETT	67	72	+	++	+++	No	No	+++	+++	+++	+	+	No	No
ETT SPECT	89	76	++++	+++	–	Yes[a]	No	+	+++	+++	++	++	Yes	Yes
Adenosine SPECT	90	70	++++	+++	–	Yes[a]	No	+	+++	++	++	++	Yes	Yes
ETT echocardiography	85	86	+++	++++	++	Yes	Yes	+++	+	+	+++	+++	Yes	Yes
Dobutamine echocardiography	82	85	+++	++++	++	Yes	Yes	++	++	++	+++	+++	Yes	Yes

ECG electrocardiogram, *ETT* exercise treadmill testing, *LV* left ventricular, *SPECT* single photon emission computed tomography
[a]Only if gated acquisitions available

either dobutamine echocardiography or vasodilator (adenosine or dipyridamole) nuclear scintigraphy. In general, the two tests have comparable sensitivities and specificities when performed in experienced laboratories. The choice of which type of test to order (echocardiography vs. nuclear scintigraphy) is largely a matter of physician's preference. However, each test has its own unique advantages and disadvantages. Echocardiography has the advantage of better specificity in hypertensive patients, better accuracy in women, lower cost, greater feasibility in the outpatient setting, faster turnaround time, no radiation exposure, and the ability to obtain concomitant anatomic and hemodynamic cardiovascular information. The disadvantages are the reduced feasibility and sensitivity in patients with poor echocardiographic image quality (caused by obesity and pulmonary disease) and reduced sensitivity for left circumflex artery disease. Nuclear scintigraphy has superior resolution in predicting the location of a coronary artery stenosis and greater availability and collective experience. The main disadvantage of nuclear scintigraphy is the decreased sensitivity for detecting balanced three-vessel and left main coronary artery disease, significant radiation exposure, and lower specificity, especially in women. Ultimately, the decision of which type of imaging stress test to order (echocardiography vs. nuclear scintigraphy) is based on local expertise, test availability, and the patient's characteristics.

The evaluation of chest pain with stress testing requires the physician to temper the results of the stress test with the pretest probability of CAD. In patients with a high pretest probability of CAD, a negative stress test result should not lead the physician to falsely conclude that the patient does not have significant CAD. Instead, an alternative stress testing strategy or cardiac catheterization should be considered. Likewise, in patients with a very low pretest probability of CAD who have positive stress tests, the results should be interpreted in light of the known disadvantages of the particular stress test ordered and the overall cardiovascular status of the patient.

A newer imaging modality, coronary artery CT angiography allows for anatomic evaluation of the coronaries arteries non-invasively using ECG gated multidector CT scanning. CT coronary angiography has a very high negative predictive value, in other words, it is very helpful in ruling out coronary disease. However, it does not provide any functional data as does stress testing.

Pericarditis

The most important diagnostic test for pericarditis is the ECG. The diagnosis can be confirmed by serial ECGs demonstrating four classical stages. In Stage I, the ECG demonstrates ST segment elevation (Fig. 1.3), which is concave upward and usually present in all leads except V_1 and aV_R. The T waves are usually upright. The ST segment changes of acute pericarditis differ from acute myocardial infarction in that the ST segment elevation is concave upward, does not fit any particular coronary artery distribution, and lacks associated reciprocal ST segment depression. The first stage typically lasts for a few days before the Stage II changes evolve. In Stage II, the ST segments return to baseline and the T waves flatten. In contrast to acute myocardial infarction, the ST segments return to baseline before the T waves flatten. Stage III involves T wave inversion, and Stage IV represents normalization of the T waves. In addition to these changes, pericarditis is characterized by PR segment depression, which may be seen in Stages I and II. However, this classical evolution pattern is found in fewer than 50% of patients, and most patients present with some variant of the pattern just described.

The chest radiograph in pericarditis is usually unrevealing. If a significant pericardial effusion is present, cardio-

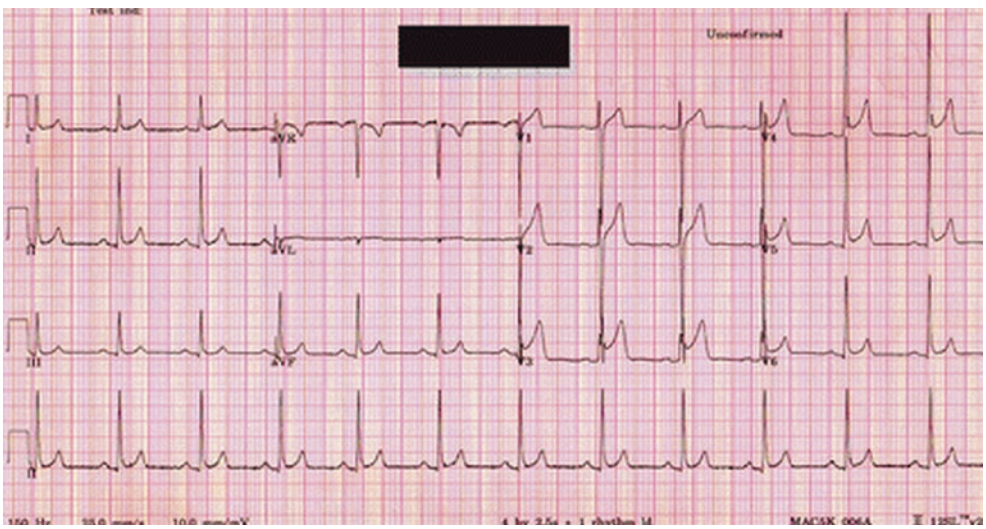

Fig. 1.3 ECG demonstrating widespread saddle shaped ST segment elevation in a young patient with pericarditis. (From Zacharias and Makan [25]; with permission)

megaly and a "water bottle" heart may also be present. An echocardiogram should be obtained to quantify the pericardial effusion, rule out pericardial tamponade, and assess for concomitant myocarditis. The absence of a pericardial effusion does not rule out pericarditis.

Laboratory tests can be useful to confirm the presence and diagnose the cause of pericarditis. The erythrocyte sedimentation rate (ESR) is typically elevated. Cardiac enzyme levels are usually normal, and elevation in troponin levels should suggest myocarditis. Causes of pericarditis and suggested laboratory tests include systemic lupus erythematosus [antinuclear antibodies (ANA), complements, and anti–double-stranded DNA antibodies], uremia [blood urea nitrogen (BUN)], and tuberculosis [purified protein derivative (PPD) and control skin tests].

Gastroesophageal Reflux Disease and Esophageal Spasm

A reasonable initial approach in patients with uncomplicated GERD or esophageal spasm (no dysphagia, weight loss, or hematemesis) is empirical therapy as a diagnostic modality. Empirical therapy should consist of behavioral modification (avoiding alcohol, cigarettes, caffeine, chocolate, heavy meals, or meals within a few hours before sleep) and drug therapy (H_2 blockers or proton pump inhibitors). Patients with complicated, severe, or unresponsive GERD and esophageal spasm should be referred to a gastrointestinal specialist [19].

Musculoskeletal Disorders

Diagnostic testing is generally not useful in this group. If trauma is suspected, then plain films specific to area of injury (e.g., rib fracture) should be considered.

Valvular Heart Disease and Hypertrophic Cardiomyopathy

Patients with significant aortic stenosis or hypertrophic cardiomyopathy probably have evidence of left ventricular hypertrophy on the ECG. The chest radiograph is rarely beneficial. All patients should undergo transthoracic echocardiography with Doppler examination.

In aortic stenosis, the echocardiogram allows for the anatomic assessment of the valve, which may be senile, calcific, congenital, or bicuspid. The peak instantaneous, and mean gradients through the aortic valve can be assessed by Doppler echocardiography. The mean gradient by Doppler has been shown to have an excellent correlation with invasive measurements [20, 21], except for a tendency to underestimate the valve area by Doppler echocardiography in mild aortic stenosis [22]. However, the peak gradients obtained by the two techniques differ because echocardiography measures the peak instantaneous gradient through the aortic valve, whereas cardiac catheterization measures a "peak-to-peak" gradient. Echocardiography is also useful for evaluating concomitant valve disease and left ventricular systolic function and hypertrophy. With the continuity equation, valve area can be calculated. If the aortic valve is poorly visualized by transthoracic imaging, transesophageal echocardiography may be used to obtain the aortic valve area by planimetry and Doppler gradients.

Echocardiography may be useful in diagnosing hypertrophic cardiomyopathy. Findings include systolic anterior motion of the anterior leaflet of the mitral valve into the left ventricular outflow tract, potentially causing a dynamic outflow tract obstruction, asymmetric or concentric left ventricular hypertrophy, and mitral regurgitation. However, the absence of the characteristic echocardiographic findings of hypertrophic cardiomyopathy does not rule out the diagnosis. ECG typically shows left ventricular hypertrophy. Cardiac magnetic resonance imaging is useful in the diagnosis of hypertrophic cardiomyopathy allowing for accurate measurements of wall thickness, myocardial mass as well as myocardial fibrosis which are characterstic of hypertrophic cardiomyopathy.

Initial Management Scheme

Management of chest pain is complicated by the broad range of origins and the need to rule out life-threatening causes. The physician needs to have a comprehensive and efficient plan for evaluating patients with chest pain. A suggested but not exhaustive chest pain evaluation scheme is presented in Fig. 1.1. More detailed management strategies for unstable angina, stable angina, acute myocardial infarction, aortic dissection, pericarditis, and valvular heart disease are discussed in later chapters.

The first step in evaluating patients with chest pain is to take an expeditious history, perform a focused physical examination, and obtain an ECG. If a life-threatening cause (such as PE, aortic dissection, or acute coronary syndrome) is suspected, the patient should be transferred to an emergency room, placed on a cardiac monitor, and have initial laboratory tests, including measurements of cardiac enzymes.

The likelihood of a patient presenting with chest pain having acute coronary syndrome (ACS) can be evaluated from the above steps (Table 1.6).

Algorithms [11] have been developed and published for the evaluation and treatment of the patients with ACS. The algorithms are updated frequently as new information

Table 1.6 Likelihood that signs and symptoms represent an ACS secondary to CAD

Feature	High likelihood Any of the following:	Intermediate likelihood Absence of high-likelihood features and presence of any of the following:	Low likelihood Absence of high- or intermediate-likelihood features but patients may have:
History	– Chest or left arm pain or discomfort as the chief symptom reproducing prior documented angina – Known history of CAD, including MI	– Chest or left arm pain or discomfort as the chief symptom – Age >70 years – Male sex – Diabetes mellitus	– Probable ischemic symptoms in the absence of any of the intermediate likelihood characteristics – Recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (≥1 mm) or T-wave inversion in multiple precordial leads	– Fixed Q waves – ST-segment depression 0.5–1 mm or T-wave inversion >1 mm	– T-wave flattening or inversion <1 mm in leads with dominant R waves – Normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

Table 1.7 TIMI risk score for unstable angina/non-ST-elevation MI

TIMI risk score	All-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization through 14 days after randomization, %
0–1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6–7	40.9
The TIMI risk score is determined by the sum of the presence of 7 variables at admission: 1 point is given for each of the following variables: age 65 y or older: at least 3 risk factors for CAD; prior coronary stenosis of 50% or more: ST segment deviation on ECG presentation: at least 2 anginal events in prior 24 h; use of aspirin in prior 7 days; elevated serum cardiac biomarkers. Prior coronary stenosis of 50% or more remained relatively insensitive to missing information and remained a significant predictor of events	

CAD coronary artery disease, *ECG* electrocardiogram, *MI* myocardial infarction, *y* year

becomes available. The identification of the patient at high risk for death or a non-fatal cardiovascular event can be estimated at the time of initial evaluation in the emergency department [23], (Table 1.7).

If an acute coronary syndrome is suspected, aspirin should be administered unless contraindicated and an initial risk assessment performed, according to the American College of Cardiology/American Heart Association guidelines for the management of unstable angina [11].

Depending on the the likely cause of the chest pain, appropriate testing should be ordered, for example if PE is suspected, would order D-dimer and/or CT PE study. For patients in which aortic dissection is suspected, would hold off on starting anticoagulation while urgently obtaining the necessary diagnostic testing. For patients presenting with possible acute coronary syndrome, further risk stratification into high, intermediate, or low risk categories occurs relatively rapidly and is discussed in further detail in later chapters.

If a clear, non–life-threatening cause of chest pain can be established by history, physical examination, and ECG, appropriate evaluation and treatment can be electively initiated. Patients with noncardiac chest pain can be monitored conservatively, depending on the cause. In those with pericarditis, serial ECGs (over days and weeks) may be obtained to follow the ECG course of the disease, and initial laboratory studies (e.g., erythrocyte sedimentation rate, troponin measurements) conducted. If myocarditis is suspected on the basis of either echocardiography or elevated cardiac enzyme levels, hospitalization should be considered. Patients with significant valvular heart disease, such as aortic stenosis, should undergo echocardiography to assess the anatomy, severity of disease, chamber sizes, and ventricular function. Patients with stable angina and without any recent history of unstable angina can be managed electively as well. If there is a high pretest probability of CAD and no need for risk assessment or prognostication, then empirical CAD therapy can be initiated without a stress test. Otherwise, stress testing should be electively performed to either confirm the diagnosis or provide risk assessment.

A challenging group of patients consists of those in whom a life-threatening cause of chest pain is not suspected and no clear diagnosis is established by history, physical examination, and ECG. This group comprises a large percentage of patients presenting for chest pain evaluation. The physician must balance the consequences of missing the diagnoses of

Table 1.8 Key points and recommendations for exercise testing in chest pain centers

Which patients?	Acceptably safe in chest pain centers when they have been identified as "low risk/low likelihood" (by Goldman criteria) for having an acute coronary syndrome
Clinical protocol	Must include serial clinical assessments, two negative cardiac enzymes drawn at 4-h intervals, resting ECGs
ECG	Exercise ECG testing can be used as first-line noninvasive testing when resting ECG is normal and the patient is not taking digoxin therapy
Facility requirements	Should adhere to the guidelines of the American Heart Association. Exercise testing can safely performed by properly trained nurses, exercise physiologists, physical therapists, or medical technicians working directly under the supervision of a properly trained physician
Supervision	A properly trained physician should be in the immediate vicinity and be available for emergencies. For higher risk patients, exercise testing should be directly supervised by the physician
Exercise protocol	A Bruce treadmill protocol can be used. Elderly or deconditioned patients can be tested with less vigorous protocols such as Cornell, Naughton, ACIP, Balke, and ramp
Adequacy of stress	The patient should attain 85% of the maximum age-predicted heart rate and accomplish at least 6 METS of workload (for patients >75 years of age, 4–5 METS is acceptable)
Prognosis	A negative test result will indicate a low probability of disease and good 30-day outcome in patients who initially have a low pretest probability of disease
Limitations	Even with a negative exercise test result, a small number of low- to intermediate-risk patients will present in the next 30 days with acute myocardial infarction or a need for coronary revascularization

ACIP Advisory Committee on Immunization Practices, *ECG* electroencephalogram, *METS* metabolic equivalents (of oxygen consumption)
Adapted from Fletcher et al. [24]

acute myocardial infarction, PE, or aortic dissection against the need to utilize health care resources appropriately in managing a group of patients with an overall low risk of adverse outcomes. To advise physicians who manage patients in chest pain centers, the American Heart Association has published guidelines for performing exercise ECG testing in chest pain centers [24]. The key points of the guidelines are summarized in Table 1.8. In general, patients without any cardiac risk factors and in whom the cause of the chest pain is not clear from history, physical examination, and ECG are at low risk for adverse cardiovascular outcomes and can be conservatively managed.

In summary, the initial management of chest pain patients involves ruling out life-threatening causes, establishing readily apparent diagnoses, determining prognosis, and determining which patients need evaluation for CAD. A systematic approach is necessary to avoid missing life-threatening causes while still efficiently utilizing vital health care resources. Although numerous clinical guidelines have been developed, ultimately the physician's individual judgment always remains the most important factor in managing chest pain.

Practical Points

- Many patients deny having "chest pain" on initial questioning but admit to "chest discomfort" upon further questioning.
- All patients with acute onset chest pain should be evaluated within 5 to 10 min of presentation and undergo 12-lead ECG.
- The principal life-threatening causes of chest pain are acute coronary syndromes, aortic dissection, PE, and esophageal rupture.
- The principal non–life-threatening causes of chest pain are stable angina, pericarditis, GERD, esophageal spasm, musculoskeletal disorders, valvular heart disease, and hypertrophic cardiomyopathy.
- The initial management of acute chest pain involves obtaining a focused history and physical examination, performing ECG, deciding whether the patient may have a life-threatening cause, and evaluating the patient for high-risk features.
- The chest pain of acute coronary syndromes has a broad overlap with the chest pain of non–life-threatening causes of the pain.
- The most common characteristic of chest pain in aortic dissection is its sudden onset.
- Aortic dissection has an extremely high mortality rate, and its diagnosis requires a high degree of clinical suspicion on the physician's part.
- A positive stress test result in a patient with a low pretest probability of CAD may just as likely be a false positive as a true positive result.

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Dyspnea

2

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Definition

Dyspnea has been variously described as the sensation of breathlessness or of difficult or uncomfortable breathing. The American Thoraci Society defines dyspnea as "… a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience arises from interactions among multiple physiological, psychological, social, and environmental factors and may induce secondary physiological and behavioral responses" [1]. Some degree of dyspnea is normal at high altitude or in the context of vigorous exercise; dyspnea is abnormal when it occurs at levels of activity and in environmental circumstances for which normal individuals would not be breathless. The severity of dyspnea that an individual experiences for a given activity appears to be related to the level of ventilation required for that activity in relation to the ventilatory capacity of the individual.

Breathlessness is an extremely common complaint. In one large study of medical outpatients, it was the third most frequent complaint, following only fatigue and back pain [2]. Dyspnea is the usual presenting symptom for some of the most common chronic conditions afflicting Americans, including chronic obstructive lung disease (14 million people), asthma (ten million individuals), and heart failure (five million Americans). It is a prominent symptom in nearly all other pulmonary disorders and may be the presenting symptom in patients with coronary artery disease.

Usual Causes

Dyspnea can be divided into acute and chronic dyspnea and majority of the conditions presenting with shortness of breath are cardiac or respiratory in origin (Fig. 2.1) Acute dyspnea develops over minutes to days. It usually results from an acute cardiovascular or pulmonary process and, as such, mandates urgent diagnostic evaluation and treatment. Cardiovascular conditions precipitating acute dyspnea include myocardial or valvular abnormalities that cause pulmonary edema (e.g., myocardial ischemia or infarction, acute mitral or aortic regurgitation), hypertensive urgency or emergency, pericardial tamponade, and pulmonary artery thromboembolism. Pulmonary abnormalities include pneumonia, asthma or other reactive airway disease, pneumothorax, upper airway obstruction, or diffuse lung injury as a manifestation of the systemic inflammatory response syndrome. Overdoses of aspirin or ethylene glycol may cause dyspnea by direct stimulation of the respiratory center. Fortunately, the cause of acute dyspnea can usually be determined from a history, a physical examination, basic laboratory studies, a chest radiograph, and an electrocardiogram, with other testing as indicated (e.g., cardiac enzyme levels for myocardial infarction, ventilation/further lung imaging for pulmonary embolism, transesophageal echocardiography for proximal aortic dissection with aortic insufficiency, and peak flow for acute airway disease [3, 4]) (Fig. 2.2a, b). When heart failure is suspected the New York Heart Association Functional class should be documented (Table 2.1).

Increasingly, natriuretic peptides have assumed a central role in the evaluation of acute dyspnea. These peptides are produced and released by cardiac myocytes [5]. B-type natriuretic peptide (BNP) is produced and released almost exclusively by the ventricular myocardium in response to an

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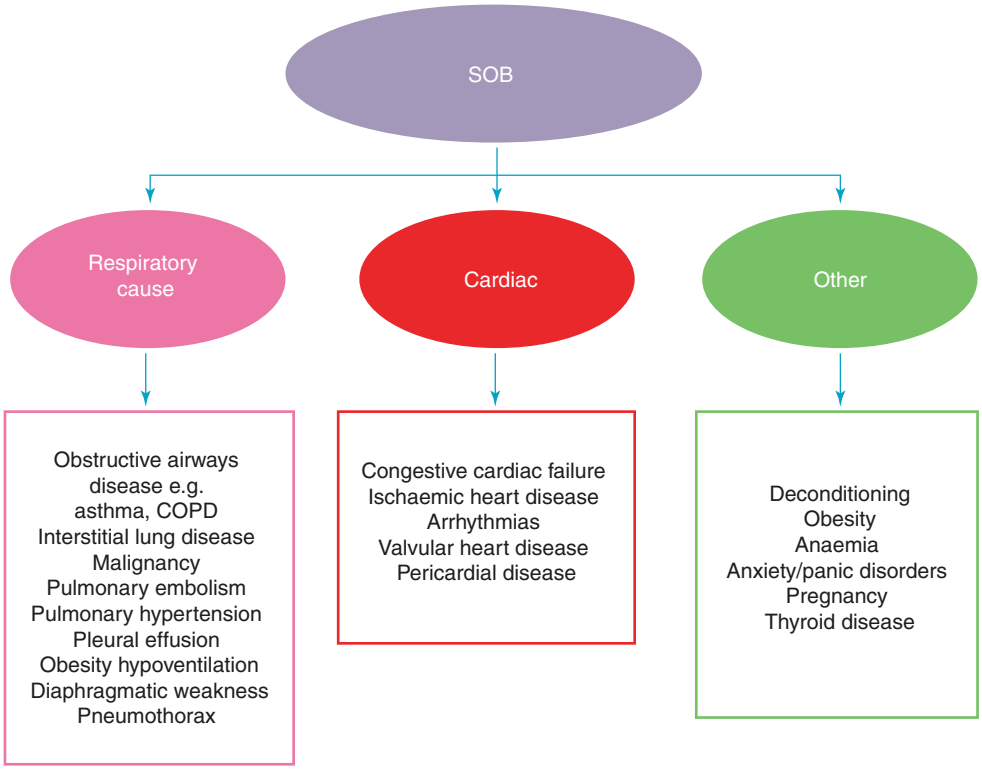

Fig. 2.1 Differential diagnosis of shortness of sreath (SOB). (Adapted from Millar and Sharma [67])

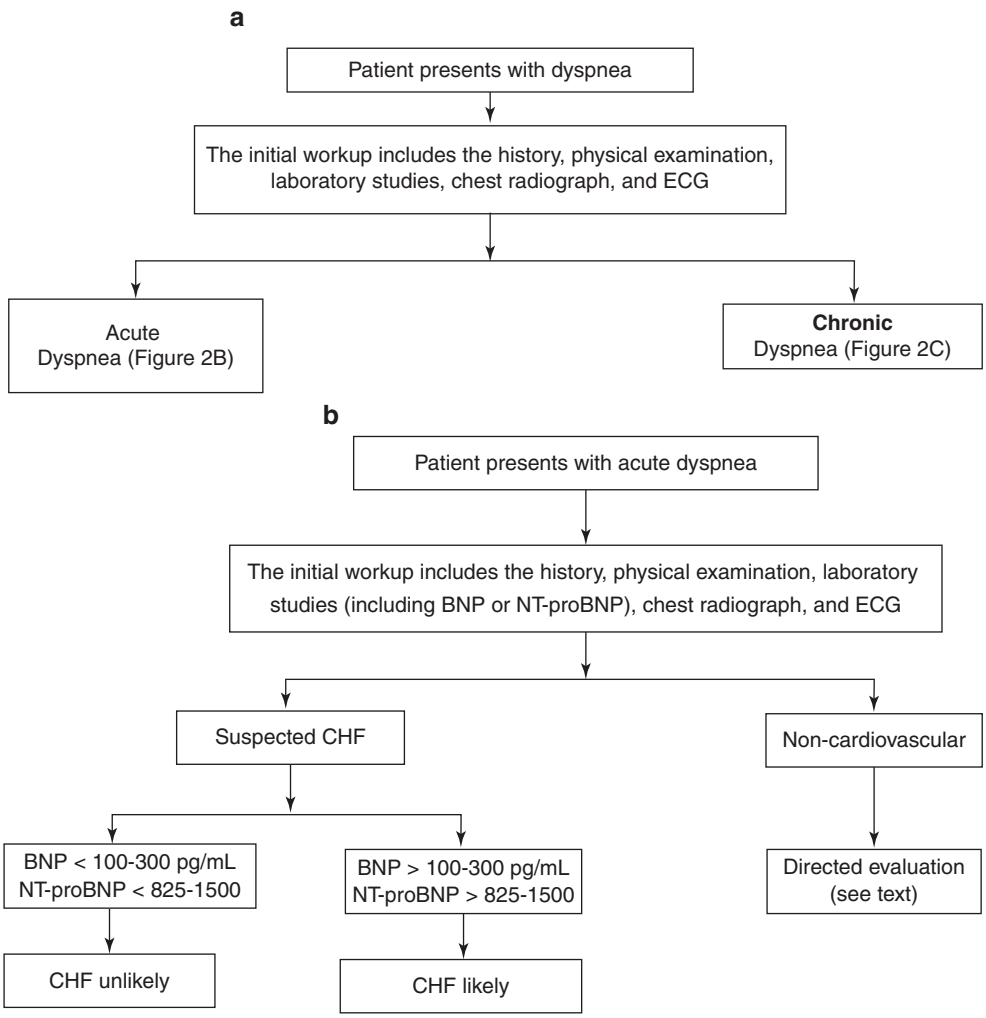

Fig. 2.2 (**a**–**e**) Evaluation for patients presenting with dyspnea. (Adapted from Martinez [68])

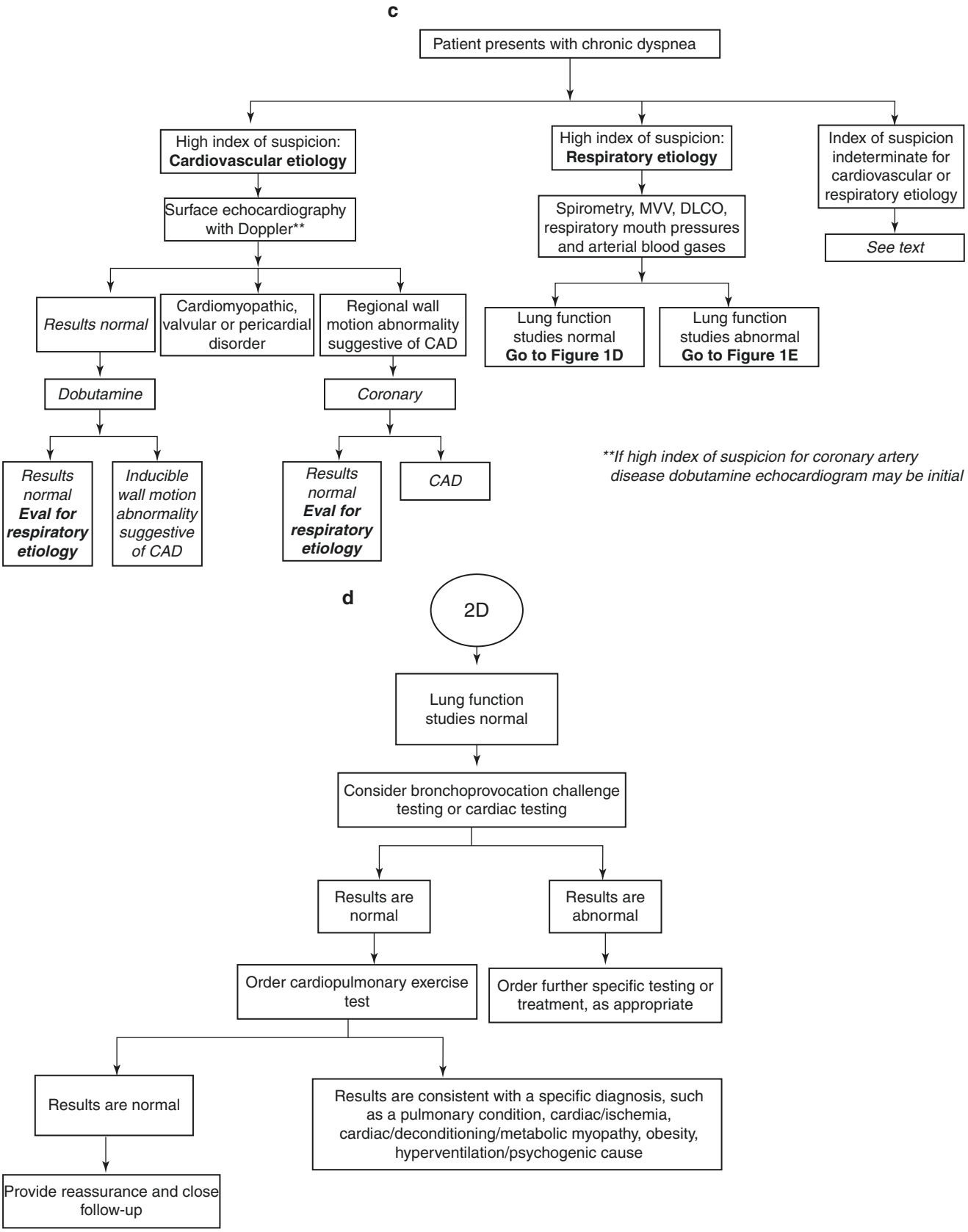

Fig. 2.2 (continued)

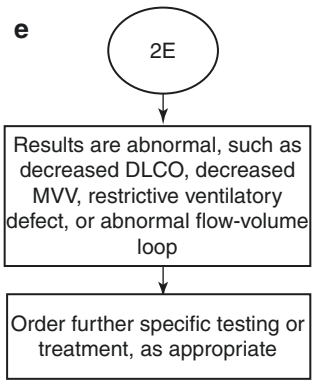

Fig. 2.2 (continued)

Table 2.1 The New York Heart Association functional classification

Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases

Adapted from: The Criteria Committee of the New York Heart Association [70]

elevation in end-diastolic pressure and volume [6]. The propeptide circulates and is cleaved into a biologically active fragment and the N-terminal pro-B-type natriuretic peptide (NT-proBNP) [7]. Assays for BNP and NT-proBNP are available and exhibit different operating characteristics [7, 8], although they correlate closely in dyspneic patients [9]. The NT-proBNP has a longer plasma half-life and considerably higher concentrations [7]. Importantly, in normal subjects and heart failure patients intraindividual coefficients of variation may vary between 24 and 77%, albeit with generally lower levels in stable patients. In addition, plasma BNP and NT-proBNP increase with advancing age and female gender [10, 11], as well as with renal insufficiency and hypertension [12, 13]. Numerous investigators have examined the role of natriuretic peptide concentration in identifying heart failure as the cause of acute dyspnea. A large, multicenter, emergency room-based study confirmed the benefit in 1586 patients evaluated for acute dyspnea [4]. Additional studies have confirmed the value of BNP or NT-proBNP level measurement in acutely dyspneic patients of varying age and gender [14–17]. The threshold value for defining normality in these studies has varied with the assay and study population; generally, for BNP values of 100–300 and for NT-proBNP values of 825–1500 have been utilized. In general, peptide levels provide the greatest diagnostic accuracy in identifying heart failure in acutely dyspneic patients [18]. The most compelling data come from a recent, randomized study of patients evaluated in the emergency department for acute dyspnea; the use of BNP in clinical decision making reduced the need for hospital admission (85% to 75%), the need for intensive care (24% to 15%) and reduced the length of hospitalization (11 days to 8 days) [19]. The mean total cost of treatment was lower in the BNP managed group.

Chronic dyspnea (symptoms present for at least a month) often represents a greater diagnostic challenge and is the focus of the remainder of this chapter. Table 2.2 provides a pathophysiologic framework for the causes of chronic dyspnea, along with specific examples. The causes can be conveniently divided into those characterized by impaired cardiovascular function, by impaired pulmonary function, or by abnormally altered central ventilatory drive or perception. An evaluation is illustrated in Fig. 2.2c–e.

Impaired Cardiovascular Function

Any condition that increases left atrial pressure results in a concomitant rise in pulmonary venous pressure, with vascular congestion and decreased pulmonary compliance. Left atrial pressure rises in patients with elevated left ventricular end-diastolic pressure, whether the latter results from systolic dysfunction (e.g., ischemic or nonischemic cardiomyopathies), diastolic dysfunction (e.g., hypertensive heart disease with left ventricular hypertrophy, hypertrophic cardiomyopathy, or restrictive cardiomyopathy), or an obstruction to left atrial emptying (e.g., mitral stenosis). More profound or acute elevations in pulmonary venous pressure lead to alveolar filling with impaired gas exchange and arterial hypoxemia. Bronchial hyperresponsiveness (i.e., "cardiac asthma") occurs in some individuals in this setting. If the ability to increase cardiac output with exercise is reduced (e.g., left ventricular systolic dysfunction, aortic stenosis), oxygen delivery is compromised and lactic acidosis occurs prematurely. Ventilation must increase to eliminate the excess acid, and this may result in dyspnea, even in the absence of pulmonary congestion.

Coronary artery disease (CAD) is an important and often unrecognized cause of dyspnea in patients with *normal* left ventricular systolic function at rest. Chest pain may be absent in such patients (e.g., many diabetics), for whom dyspnea is the "anginal equivalent." Transient ischemia resulting from increased metabolic demand, heightened coronary vascular tone, or coronary microthrombi may cause papillary muscle dysfunction with acute mitral regurgitation, systolic dysfunction, or diastolic dysfunction.

Table 2.2 Pathophysiologic framework for chronic dyspnea, with specific examples

Category	Example
Impaired cardiovascular function	
Myocardial disease	
Systolic dysfunction	Ischemic cardiomyopathy
Nonischemic cardiomyopathies	
Heart failure with preserved ejection fraction	Hypertensive heart disease
Coronary artery disease	
Hypertrophic cardiomyopathy	
Restrictive cardiomyopathy	
Valvular disease	Aortic or mitral regurgitation
Aortic or mitral stenosis	
Pericardial disease	Constrictive pericarditis
Pulmonary vascular disease	Pulmonary thromboembolism
Primary pulmonary hypertension	
Congenital anomalies	Cyanotic heart diseases (right-to-left shunts)
Impaired pulmonary function	
Airflow obstruction	
Diffuse	Asthma
Focal	Vocal cord dysfunction or paralysis
	Tracheal stenosis
	Endobronchial tumor
Restriction of lung mechanics	
Interstitial lung disease	Idiopathic pulmonary fibrosis
Pneumoconioses	
Lymphangitic carcinomatosis	
Extrapulmonary thoracic restriction	Kyphoscoliosis
Pleural effusion or fibrosis	
Neuromuscular weakness	Phrenic nerve paralysis
	Spinal cord injury
	Amyotrophic lateral sclerosis
Abnormal gas exchange	
Abnormal alveoli/capillary interface	Eosinophilic pneumonia
Right to left shunting	Pulmonary arteriovenous malformations
Altered central ventilatory drive or perception	
Systemic or metabolic disorders	
Increased metabolic requirements	Hyperthyroidism
Obesity	
Decreased oxygen-carrying capacity	Anemias
Metabolic acidosis	Renal failure
Mitochondrial myopathies	
Direct stimulation of respiratory center	Aspirin or ethylene glycol overdose
Physiologic processes causing dyspnea	
Vigorous exercise	
Pregnancy	
Hypoxic breathing at high altitude	
Deconditioning	

COPD chronic obstructive pulmonary disease
Adapted from Sietsema [69]

Dyspnea is a prominent symptom in patients with pericardial and pulmonary vascular disease, even when oxygenation and lung mechanics are normal. The mechanism underlying dyspnea in these settings probably is related to activation of stretch receptors or baroreceptors in the central circulation.

Congenital cardiac anomalies may also manifest with dyspnea. Anatomic abnormalities resulting in right-to-left shunts cause hypoxemia. This stimulates arterial chemoreceptors, which in turn activate respiratory control centers to increase ventilation. Left-to-right shunts, if sufficiently large, will over time result in left ventricular volume overload and progressive systolic dysfunction. In some patients, increased flow though the pulmonary vasculature results in adverse pulmonary vascular remodeling and consequent pulmonary hypertension.

Impaired Pulmonary Function

Conditions that obstruct airflow, whether diffuse [e.g., asthma, chronic obstructive pulmonary disease (COPD)] or focal (e.g., vocal cord paralysis, tracheal stenosis, endobronchial tumor), result in dyspnea. Increased work of breathing is typically noted in these conditions. Heterogenous reduction of airflow, when present, results in regional ventilation/perfusion mismatching, with consequent hypoxemia and increased ventilatory requirements. However, ventilatory muscle fatigue and air trapping reduce ventilatory capacity.

Restriction of lung mechanics may result from abnormalities of the lung parenchyma (e.g., idiopathic pulmonary fibrosis), pleural disease, skeletal abnormalities (e.g., kyphoscoliosis), or neuromuscular disorders. The reduction in ventilatory capacity may be exacerbated by an increase in ventilatory requirements that results from ventilation/perfusion mismatching. Abnormal gas exchange may result from abnormalities of the alveolar/capillary interface or from pulmonary right-to-left shunting.

Altered Central Ventilatory Drive or Perception

Hyperthyroidism and obesity increase respiratory drive because of increased metabolic requirements. Anemic patients have reduced oxygen-carrying capacity, which, when severe, raises the respiratory rate. The lactic acidosis accompanying renal failure and mitochondrial myopathies results in compensatory respiratory alkalosis. Respiratory drive is directly stimulated in aspirin toxicity and is a response to the metabolic acidosis that occurs in this setting, as well.

The prevalence of the aforementioned conditions in patients presenting for evaluation of dyspnea probably depends on the patient sample, physician type, and practice

Table 2.3 Etiology of chronic dyspnea in three series of patients studied in tertiary pulmonary clinics

Study	Number (%) of patients
Pratter et al. [22]	
Asthma	25 (29)
COPD	12 (14)
Interstitial lung disease	12 (14)
Cardiomyopathy	9 (11)
Upper airway disease	7 (8)
Psychogenic disorders	4 (5)
Deconditioning	4 (5)
Gastroesophageal reflux	3 (4)
Extrapulmonary disease	3 (4)
Miscellaneous	5 (6)
DePaso et al. [20]	
Asthma	12 (17)
Interstitial lung disease	2 (3)
Chronic obstructive disease	3 (4)
Pulmonary vascular disease	4 (6)
Neuromuscular disease	3 (4)
Cardiac disease	10 (14)
Hyperventilation syndrome	14 (19)
Thyroid disease	2 (3)
Gastroesophageal reflux	3 (4)
Deconditioning	2 (3)
Upper airway disease	2 (3)
Miscellaneous	1 (1)
Unexplained	14 (19)
Martinez et al. [21]	
Asthma	12 (24)
Interstitial lung disease	4 (8)
Cardiac disease	7 (14)
Deconditioning	14 (28)
Psychogenic disorders	9 (18)
Gastroesophageal reflux	1 (2)
Unexplained	7 (14)
Miscellaneous	1 (2)
Huang et al. [23]	
Heart Failure with Preserved Ejection Fraction	99 (19)
Exercise induced pulmonary hypertension	88 (17)
Dysautonomia	112 (21)
Oxidative myopathy	130 (25)
Hyperventilation	43 (8)
Others	58 (11)

COPD chronic obstructive pulmonary disease

setting. Three studies [20–22] have catalogued the causes of chronic dyspnea and their frequencies in referral samples (Table 2.3). It is evident that airway diseases, such as asthma or COPD, represented the majority of cases, followed by cardiac disease, interstitial lung disease, deconditioning, psychogenic disorders, gastroesophageal reflux, neuromuscular disease, and pulmonary vascular disease. Referral bias may have influenced these studies, inasmuch as they all originated from pulmonary referral clinics. Cardiologists would probably identify a higher proportion of cardiovascular disease in their practices. A report of patients with a chief complaint of "shortness of breath," both acute and chronic, presenting to general practice physicians in Australia identified the most common diagnoses as asthma, COPD, heart failure, acute bronchitis, hypertension, ischemic heart disease, anxiety, and upper respiratory tract infections [24].

Keys to History

An evaluation of the patient should always begin with a detailed history, which in turn begins with the timing of symptoms. An intermittent, acute onset may suggest bronchoconstriction, pulmonary embolism, cardiac ischemia, or airway obstruction caused by foreign body or secretion. In contrast, chronic dyspnea is more likely to reflect slowly progressive disorders such as COPD, congestive heart failure (CHF), or interstitial lung disease.

Precipitating factors, such as the type of activities that causes exertional breathlessness, may provide diagnostic value. Because patients frequently reduce their activity level as disease severity progresses, it is important to inquire about both past and present activity levels. Positional dyspnea may be a useful historical feature. Orthopnea (dyspnea in the supine position) is most common in patients with CHF, severe COPD, ascites, obesity, anterior mediastinal masses, and respiratory muscle weakness. Trepopnea (dyspnea in one lateral position but not in the other) can be seen with patients with unilateral lung disease, unilateral pleural effusion, and unilateral obstruction of the airway. Platypnea (dyspnea in the upright position, which may be relieved by recumbence) can be seen in patients with an intracardiac shunt, parenchymal lung shunts, or hepatopulmonary syndrome.

Associated symptoms, such as cough or wheezing, can provide additional information in the differential diagnosis. The presence of cough may support a diagnosis of airway disease, interstitial lung disease, gastroesophageal reflux disease, or CHF. Similarly, wheezing may suggest airway disease, COPD, or CHF. Inquiries about past medical history, concurrent conditions, previous surgical procedures, social information (including cigarette smoking, previous and current occupations, family or living status), and medication history are essential and equally important. Patients on ticagrelor have reported to have shortness of breath.

The patient should also be questioned about the quality of the respiratory discomfort. Studies have shown that different descriptors of dyspnea exist in patients with various cardiopulmonary diseases, although cultural, racial, and language differences may also alter those descriptions. [25–27]. Table 2.4 demonstrates the clustering of such descriptors with varying cardiopulmonary disorders from one such study [27]. A preliminary report about 11 patients suggested benefit from the use of such a descriptor model in determining the origin of dyspnea [28]. The value of this form of evaluation in the assessment of patients presenting with breathlessness requires further prospective validation.

Table 2.4 Relation between the description of the sensation of dyspnea and the etiology of the breathlessness

Descriptions	Pathologic condition
My breathing requires effort	
My breathing is heavy	
My breathing requires more work	
I feel a hunger for more air	
I feel out of breath	
I cannot get enough air	
I am gasping for breath	COPD
My breathing requires more work	
I feel a hunger for more air	
I feel out of breath	
I cannot get enough air	
I am gasping for breath	
My breathing does not go out all the way	Asthma
My breathing requires effort	
I feel out of breath	
My breathing requires work	
I am gasping for breath	
My breathing is shallow	Interstitial lung disease
My breathing requires effort	
My breathing is heavy	
I feel a hunger for more air	
I feel out of breath. I cannot get enough air	
I feel that I am smothering	
I feel that I am suffocating	
I feel that my breathing is rapid	Congestive heart failure
My breathing does not go in all the way	
My breathing requires effort	
My breathing is heavy. I am gasping for breath	
My breathing require more work	
My breathing is shallow	Neuromuscular disease
My breathing does not go in all the way	
I feel that my breathing is rapid	Pulmonary vascular disease
I feel that I am breathing more	Deconditioning

COPD chronic obstructive pulmonary disease
Data from Simon et al. [27]

Physical Examination

A detailed and directed physical examination, with special attention to the cardiovascular and pulmonary system, is essential. The "view from the door" should take in the extent of respiratory distress (e.g., tachypnea, use of accessory muscles, fatigue). The vital signs may give additional diagnostic clues. A paradoxical pulse is seen with airway obstruction and pericardial tamponade. A weak or alternans pulse suggests severe heart failure. A wide pulse pressure with a bounding, "water-hammer" pulse is associated with aortic insufficiency, whereas a *bisferiens* pulse is seen with the obstructive variant of hypertrophic cardiomyopathy.

The jugular veins should be assessed for elevation (e.g., heart failure, pericardial disease), contours (e.g., V waves of tricuspid regurgitation), and response to the respiratory cycle (e.g., Kussmaul's sign in constrictive pericarditis, pericardial tamponade, or right-sided heart failure). Carotid bruits may be evidence of associated CAD. Respiratory excursions should be examined for symmetry and adequacy. Rapid, shallow breathing may suggest interstitial lung disease or neuromuscular disease. A fixed level of asymmetric dullness with decreased breath sounds in a patient who has undergone recent coronary bypass surgery suggests phrenic nerve injury or a persistent postoperative pleural effusion. Auscultation may reveal wet (e.g., as in CHF) or dry (e.g., as in interstitial lung disease) crackles, wheezing (as in intrathoracic airway obstruction), or stridor (as in extrathoracic airway obstruction).

In an examination of the heart, the physician should seek evidence of left or right ventricular enlargement. Rhythm abnormalities heighten suspicion for cardiac disease, although atrial premature complexes and multifocal atrial tachycardia are common in patients with severe COPD (reflecting the impact of the latter on the right side of the heart). Special attention should be paid to the intensity of the second heart sound: if it is louder than the first heart sound at the left lower sternal border, the pulmonary artery systolic pressure is at least 45 mmHg; if it is louder than the first heart sound over the left ventricular apex, the pressure is at least 60 mmHg. A fourth heart sound may be evidence of diastolic dysfunction from hypertensive heart disease. Patients with severe heart failure often have a palpable and audible third heart sound, but patients with mild or moderate heart failure rarely do. The reader is directed to the appropriate sections of this text for a discussion of dynamic auscultation for murmurs of valvular heart disease. Other organ systems pertinent to the history should also be investigated with equal sensitivity.

Helpful Diagnostic Tests

Blood Testing

Simple blood tests, including a basic metabolic panel, complete blood cell count, and thyroid function tests, are helpful in evaluating basic systemic disorders related to dyspnea. A complete blood cell count is used to identify the presence of anemia. Renal dysfunction should prompt consideration of the connective tissue diseases and vasculitides that affect the lungs and kidneys. Thyroid function testing may uncover hyperthyroidism or hypothyroidism. Hyperthyroid individuals have excessive ventilation with exercise [29], hypothyroid patients may experience reversible diaphragmatic dysfunction [30], and either condition may reduce cardiac contractility. Dyspnea can be seen with either form of thyroid disease. Data supporting BNP level assessment in patients with chronic dyspnea are more limited. One group demonstrated higher BNP levels in patients with chronic diastolic heart failure compared with

those with COPD [31]. In a prospective study of 345 patients referred by general practitioners to a hospital based subspecialty clinic NT-proBNP levels improved the exclusion of heart failure [32]. A separate study which used a randomized design also suggested an improved negative predictive value of adding NT-proBNP to clinical evaluation by general practitioners [33]; the diagnostic accuracy improved 21% in the BNP group compared to control patients.

Chest Radiography

Chest radiography is an important part of the initial workup. It reveals evidence of pneumothorax, hyperinflation, interstitial fibrosis, or pulmonary edema. Cardiac enlargement, enlarged pulmonary arteries (e.g., pulmonary hypertension), and elevated hemidiaphragms (e.g., respiratory muscle weakness or phrenic nerve palsies) may be seen. However, the insensitivity of the technique should be kept in mind. Fibrotic lung disease, for example, may be "invisible" on chest radiographs but clearly manifest on pulmonary function tests and high-resolution computed tomography (CT) [34, 35]. Therefore, the absence of prominent changes on chest radiographs should not be used alone to rule out the presence of a disorder. The American College of Radiology has recently published appropriateness criteria for various imaging modalities in the evaluation of chronic dyspnea [36].

Further Diagnostic Testing

Because of the prevalence of respiratory disease in patients with dyspnea, limited pulmonary function testing [e.g., spirometry with a flow-volume loop and measurement of diffusion capacity (DL_{CO})] has a major role in the evaluation of dyspnea. Most authors suggest that this is an essential test for all dyspneic patients, in view of the predominance of respiratory disorders in the published series. However, we temper this recommendation with the knowledge that all these series originated from pulmonary referral centers and reflect an inherent referral bias. Certainly, patients in whom there is a high index of suspicion for cardiac disorders (e.g., older patients with CAD risk factors or those with exertional chest pain, electrocardiographic evidence of acute or chronic coronary disease, or obvious physical findings of heart failure) can undergo testing and therapeutic trials directed at these processes, with pulmonary function tests reserved for patients with inconclusive test results or inadequate therapeutic responses. In the absence of a high index of suspicion for a cardiac disorder or when pulmonary disease is suspected, pulmonary function testing is the next logical step.

High Suspicion for Cardiovascular Disease

Surface echocardiography with Doppler studies is indicated for evaluation of possible systolic or diastolic heart failure, valvular heart disease, or pericardial disease (Fig. 2.2c). In general, this test is preferable to radionuclide ventriculography (it provides more information about valvular, pericardial, and diastolic abnormalities) and radionuclide single photon emission CT (SPECT) perfusion imaging (see later discussion).

If CAD is suspected, stress testing is warranted. Treadmill testing without imaging certainly confirms an early onset of exertional dyspnea, if present, but many affected patients fail to achieve an adequate double product [i.e., (peak systolic blood pressure × peak heart rate)/100], which renders this test's sensitivity and specificity inadequate for detection of CAD in this setting. Therefore, most patients in whom CAD is suspected as the cause of dyspnea require pharmacologic stress testing with echocardiographic or radionuclide perfusion imaging. Both techniques have excellent sensitivity and specificity in most patients when performed in experienced laboratories, and the choice of modalities is often guided by local expertise. Echocardiography allows concomitant evaluation of left ventricular function, valvular abnormalities, pulmonary hypertension, and pericardial disease and is preferable in patients with left bundle branch block. Radionuclide imaging with sestamibi (but not with thallium) also affords an evaluation of left ventricular function (i.e., gated SPECT) and is preferable in patients in whom echocardiographic images are likely to be of poor quality(e.g., severely obese patients).

Echocardiography can be combined with dobutamine imaging as the initial test to evaluate CAD as the cause of systolic or diastolic dysfunction when the suspicion for CAD is high. Another option would be surface echocardiography, followed by coronary angiography, or coronary angiography combined with contrast-enhanced left ventriculography in patients with obvious coronary disease or cardiac MRI combined with treadmill stress testing.

It is important to be aware of the high prevalence of heart failure in older individuals. In an ambulatory practice and inpatient service of a Department of Family Medicine in a university setting, the frequency of CHF increased with age [36]. In fact, 74% of the patients were older than 65 years. Interestingly, 40% of the patients had preserved systolic function; this was more common in women. Diastolic heart failure is particularly more common in the presence of hypertension, diabetes mellitus, obesity, or valvular disease [37]. Thus, older patients may be best evaluated with specific functional cardiac studies early in the evaluation process.

Further discussion of the relative merits and interpretation of echocardiography and radionuclide imaging studies, with and without exercise or pharmacologic "stress," is available in other chapters of this text.

Other Patients

Pulmonary function testing is the next diagnostic step in most patients with unexplained dyspnea. Spirometric trac-

ings should be examined to make sure that they meet with the "acceptability" and "reproducibility" criteria suggested by the American Thoracic Society [38]. Spirometric testing that does not adhere to these guidelines can lead to significant errors in diagnosis or choices of unnecessary diagnostic tests. Spirometry can be used to determine and define the functional type of respiratory abnormality. The diagnosis of airflow obstruction is confirmed by a decreased ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC). Once a diagnosis of airflow obstruction is made, no further diagnostic evaluation is immediately warranted. During a therapeutic course for obstructive lung disease, further spirometric testing is helpful for assessing response to treatment. If dyspnea persists despite response to therapy, or if there is no objective response to therapy, then further diagnostic evaluation is required. A reduced FVC accompanied by a normal ratio of FEV_1 to FVC is suggestive, but not definitively diagnostic, of restrictive lung disease. Further pursuit of restrictive lung disease requires measurement of lung volumes [39].

Important information can also be obtained by examining the flow-volume curve. For example, in upper airway obstruction, a flattening of either inspiratory or expiratory flow-volume curve or of both may be noted. These flow-volume curves may also be helpful in determining patient effort and intent in the performance of the procedure. Certain changes in the flow-volume loop and in the volume-time curve (such as short expiratory time or staggering of the expiratory loop) may suggest poor effort or potential malingering.

The DL_{CO} is measured to assess the ability of the alveolar-arterial interface to transfer gas without limitation [40]. Decreases in DL_{CO} can reflect destruction of lung parenchyma, changes in the interface secondary to fibrosis or inflammation, loss of pulmonary vascular area, or anemia. Increases can reflect alveolar hemorrhage, polycythemia, or altitude adjustments. It may be useful to identify an isolated reduction in DL_{CO}, which may be suggestive of several possible causes of dyspnea [41].

The measurement of maximal inspiratory and expiratory pressures during pulmonary function testing is a useful tool in the screening of respiratory muscle function. In patients with neuromuscular disease, the earliest physiologic abnormalities are decreases in respiratory pressures measured at the mouth [42, 43]. Syndromes of respiratory muscle weakness may be uncovered with this simple test. Unfortunately, in the setting of dyspnea, the sensitivity and specificity of this test are unknown. The measurement of maximum voluntary ventilation can serve as an additional surrogate measurement of impaired respiratory muscle function [42]. Some investigators have suggested that an isolated decrement in maximal ventilatory volume (MVV), in comparison with that expected for a measured FEV_1, can identify patients with mitochondrial myopathy [44]. Unfortunately, the effort dependence of MVV measurement limits the diagnostic accuracy of this diagnostic study.

Subsequent Diagnostic Testing

Unfortunately, the initial evaluation of dyspnea may not lead to a specific single diagnosis, and the findings will suggest a course for further evaluation. Figure 2.1a demonstrates a potential subsequent approach to the patient with dyspnea. If the initial evaluation suggests a cardiac cause, then further cardiac testing is warranted. Similarly, if initial testing demonstrates pulmonary abnormalities, then further pulmonary function testing can be devised (Fig. 2.1e). For example, the evaluation of a decreased MVV should include assessment of upper airway abnormalities [45] and potential neuromuscular disease [42]. A suspicion of restriction shown on spirometry is best evaluated by the evaluation of lung volume by body plethysmography or by gas dilution techniques [39]. These procedures also give a clear assessment of the severity of the disorder.

An isolated decrease in DL_{CO} can be evaluated with cardiac testing (echocardiography for pulmonary hypertension) [46], diagnostic imaging for parenchymal disease (high-resolution CT for fibrotic or emphysematous lung disease) [47, 48], or imaging for recurrent pulmonary emboli. The most appropriate diagnostic approach in a dyspneic patient with an isolated reduction in DL_{CO} is debatable; in part, modification tailored to the expertise of the evaluating institution is required.

If this initial evaluation does not suggest a clear-cut cardiac or respiratory disorder, further testing is probably required. This can proceed with pulmonary function testing or specific cardiovascular testing, depending on the clinical scenario. For example, in a young individual, particularly in the setting of intermittent breathlessness and normal initial pulmonary testing (Fig. 2.1d), bronchoprovocation challenge (BPC) is probably the best approach, because of the increased likelihood of hyperactive airway disease in this setting [20]. BPC is very sensitive for airway hyperreactivity but is not specific for the diagnosis of asthma [49]; disorders such as sinusitis and recent viral or pulmonary infections can cause a positive result on a methacholine challenge test [50, 51]. However, in the series of Martinez et al. [21], BPC testing was helpful in identifying airway hyperreactivity in patients with a median age of 54 years. Further research is necessary to better define the role of BPC in the evaluation of unexplained dyspnea.

Cardiopulmonary Exercise Testing (CPET)

Cardiopulmonary exercise testing is a diagnostic modality in which the examiner utilizes the measurement of oxygen uptake, carbon dioxide output, and minute ventilation while also monitoring electrocardiography, pulse oximetry, and

symptoms during a maximal symptom-limited exercise tolerance test [52]. Appropriate analysis of the patterns of response can suggest various disorders that can contribute to the sensation of breathlessns. A detailed discussion of the interpretation of these studies is out of the scope of this chapter. Readers are referred to excellent reviews of the topic [53, 54]. A completely normal study finding does not exclude early disease but should serve to reassure the patient that a major disorder is probably not present.

Most patients with psychogenic dyspnea have a normal response to exercise, although an erratic pattern of ventilation may be suggestive [55]. Similarly, a hyperventilation syndrome [56] may be suggested during CPET, although this diagnosis is generally one of exclusion. Abnormal electrocardiographic tracings can suggest the presence of ischemic heart disease, although other findings on CPET are nonspecific. For example, one prospective study has demonstrated the similar responses of patients with deconditioning and those with nonischemic heart disease [21]. In addition, data suggest a similar hyperdynamic and hyperventilatory response in patients with histologically or enzymatically confirmed mitochondrial disease [57, 58].

CPET can be used to identify potential pulmonary disorders in patients with dyspnea. Measurement of arterial blood gases can provide useful information in identifying parenchymal lung disease (changes in Pa_{O_2} and $P(A\text{-}a)_{O_2}$) [59, 60] or pulmonary vascular disease [pulmonary dead space (V_D/V_T) abnormality]. A low DL_{CO} appears to identify a group of patients more likely to demonstrate abnormal gas exchange during CPET [41]. Those patients may be best assessed with collection of arterial blood samples during exercise testing.

Additional data collected during or after CPET may provide valuable diagnostic information. Measurement of pleural and diaphragmatic pressures can identify unexpected respiratory muscle dysfunction [61]. Serial spirometry after exercise may identify patients with exercise-induced bronchospasm, although its sensitivity is clearly less than that of other forms of bronchoprovocation testing [62]. Nevertheless, in view of its simplicity, spirometry should be performed routinely after maximal exercise testing. The addition of tidal flow-volume loop analysis may improve diagnostic accuracy, although specific data are lacking [63]. Examination of vocal cord function during exercise or of flow-volume loops during and after exercise may identify patients with vocal cord dysfunction. One report identified vocal cord dysfunction in 5 of 33 young military personnel evaluated for exertional dyspnea [64]. Because many patients present with multiple disorders that may contribute to their sensation of dyspnea, CPET can been useful in determining which disorders are the predominant source of limitation [21, 65, 66]. The addition of invasive cardiovascular monitoring during CPET has been recently shown to enhance the ability to identify dyspneic patients suffering from heart failure with preserved ejection fraction, exercise induced pulmonary hypertention, dysautonomia, oxidative myopathies, and hyperventilation [23].

When to Refer?

The initial evaluation and diagnostic testing of a patient with dyspnea can be performed by a family physician, internist, pulmonologist, or cardiologist, according to the approach outlined in this chapter. Subsequent diagnostic testing, if needed, often requires specific pulmonary or cardiology expertise. Specialized multidisciplinary clinics for the evaluation of patients with unexplained dyspnea are increasingly available at academic medical centers.

Practical Points

- The severity of dyspnea that an individual experiences for a given activity appears to be related to the level of ventilation required for that activity relative to the ventilatory capacity of the individual.
- CAD is an important and often unrecognized cause of dyspnea in patients with normal LV systolic function at rest.
- A detailed and directed physical examination, with special attention to the cardiovascular and pulmonary system, is essential.
- In the evaluation of dyspnea the insensitivity of chest radiography should be kept in mind. Fibrotic lung disease, for example, may be “invisible” on chest X-ray but clearly manifest on pulmonary function tests and high resolution CT scanning.
- It is important to be aware of the high prevalence of heart failure in older individuals—diastolic heart failure is particularly more likely in the presence of hypertension, diabetes mellitus, obesity or valvular disease
- The initial evaluation of dyspnea may not lead to a specific single diagnosis and the findings will suggest a course for further evaluation
- A completely normal cardiopulmonary stress test does not exclude early disease but should serve to reassure the patient that a major disorder is not likely present.
- Dyspnea may be associated with medications including ticagrelor and amiodarone
- Most patients with psychogenic dyspnea will have a normal response to exercise during cardiopulmonary stress test although an erratic pattern of ventilation may be suggestive.

Conclusion

Dyspnea is a common diagnostic problem, and its evaluation can be challenging. A logical, stepped diagnostic approach can lead to a successful diagnosis in a majority of patients. Further research is necessary to establish the optimal cost-effective diagnostic algorithm in the evaluation of this frequent complaint.

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Palpitations

3

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Definitions

Palpitations refer to an unpleasant awareness of one's heartbeat, often with the perception of irregular, accelerated, or forceful heart beating. Patients use a variety of terms to describe the symptoms including skipped beats, heart fluttering, flip-flopping in the chest, or a pounding sensation in the chest or neck. Palpitations are fairly common and reported in approximately 15% of the general population [1]. They are typically encountered in outpatient settings, reportedly ranking among the top 10 symptom complaints of patients attending a general internal medicine clinic [2]. However, patients may seek emergency room care when their palpitations are especially prolonged, frightening, or associated with other symptoms such as lightheadedness, chest pain, or shortness of breath.

Principal Causes

The differential diagnosis of palpitations is extensive, and a thorough history is important to distinguish cardiac from non-cardiac causes of palpitations to avoid inappropriate and expensive testing. In a study of 190 patients presenting with a chief complaint of palpitations to a university medical center, an etiology was determined in 84% [3]. The cause was cardiac in 43%, psychiatric in 31%, and miscellaneous (eg, medication-induced, thyrotoxicosis, caffeine, cocaine, anemia, amphetamine, mastocytosis) in 10%.

Cardiac causes of palpitations often include atrial or ventricular extrasystoles but may also comprise nonsustained or sustained episodes of supraventricular or, less commonly, ventricular tachycardia. A common mechanism for symptom production in a number of these arrhythmias [e.g., ventricular extrasystoles and atrioventricular (AV) nodal-dependent reentrant paroxysmal supraventricular tachycardias (PSVT)] is an alteration in the normal mechanical systolic AV sequence, such that the atria are contracting simultaneously with or shortly after contraction of the ventricles. Under these circumstances, the AV valves cannot open because of the greater intracavitary pressures prevailing in the ventricles; consequently, regurgitant canon A waves are transmitted from the atria to central and pulmonary venous structures. This phenomenon, especially when occurring in the context of tachycardia, can give rise to dyspnea or a pounding sensation in the neck, or both.

Another mechanism of symptom production involves the pause occurring in the wake of an extrasystole. Independent of whether there is an altered AV sequence associated with the premature beat, the inotropic potentiation associated with a post-extrasystolic ventricular contraction, especially in contrast to the possibly reduced stroke volume accompanying the extrasystolic beat (reflecting reduced filling time), contributes to a perception of intermittent skipped beats or of the heart pounding. A similar mechanism may be operative in the uncommon scenario in which palpitations are experienced in association with second-degree AV block. In high cardiac output states, increased force of ventricular contractions, as well as accompanying sinus tachycardia, may be perceived as palpitations.

Patients may also report symptoms of lightheadedness, weakness, and near-syncope or syncope, depending on the extent of reduced cardiac output that may occur during an arrhythmia. Such compromised cardiac output is expected to be more marked in patients with structural heart disease. AV dyssynchrony may also contribute to symptoms of chest pain and, in the occasional patient, an urge to cough.

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Keys to the History

Characterization of the Palpitations

In addition to documenting the patient's description of his or her symptoms, it is important for the physician to define certain characteristic features of the palpitations.

- *Duration of the Problem*: chronic (weeks, months, years) versus acute or subacute (hours to days)? Whereas the former suggests chronically recurring primary arrhythmias, the latter should raise the possibility of an active causative cardiopulmonary process.
- *Circumstances at Onset*: Onset at rest or during physical activity? The latter suggests a catecholamine-facilitated arrhythmia. Supraventricular tachyarrhythmias, including atrial fibrillation (AF), can be induced during exercise or at the termination of exercise when the withdrawal of catecholamines is coupled with a surge in vagal tone. This type of vagally mediated AF is particularly common in athletic men in the third to sixth decade of life [4]. Do the palpitations cluster in a certain portion of a 24-h period? Patients commonly become aware of ectopic beats at bedtime when they are trying to fall asleep and there is a paucity of distracting external stimuli. Tachyarrhythmias consistently occurring in the middle of the night, interrupting sleep, may also represent episodes of vagally mediated atrial fibrillation [5]. Palpitations that chronically recur with assumption of the upright position are suggestive of sinus tachycardia; most commonly, this phenomenon is secondary to "postural orthostatic tachycardia syndrome," a type of dysautonomic response typically seen in younger (usually female) patients [6]. Less commonly, emotionally startling events precipitating arrhythmias may be seen in patients with the long QT syndrome, especially congenital type 1 or 2, characteristically present with palpitations during periods of vigorous exercise or emotional stress; the mechanism is often a polymorphic VT known as torsades de pointes. Lastly, inappropriate sinus tachycardia is a rare disorder that manifests as palpitations during minimal exertion or with emotional stress. This arrhythmia is characterized by an inappropriate increase in the sinus rate and is most frequently seen in young women; it may result from a hypersensitivity to beta-adrenergic stimulation.
- *Mode of Onset/Offset*: abrupt onset and termination is more consistent with a pathologic tachyarrhythmia, gradual acceleration and deceleration is typical of sinus tachycardia. There may be an overlap between the two types of symptom onset/offset patterns. For example, PSVT may develop suddenly, but the abruptness of tachycardia offset may be partly masked by a sinus tachycardia that reflects an arrhythmia-related catecholamine surge.
- *Rhythm Regularity versus Irregularity*: Asking the patient to tap out the rhythm may clarify not only the irregularity but also rate of arrhythmia. If the patient describes or taps out a fairly irregular rhythm, that might prompt consideration of frequent supraventricular or ventricular beats, or an atrial tachyarrhythmia with an irregular ventricular response.
- *Episode Duration*: Does an episode of palpitations last seconds, minutes, or hours? Fleeting symptoms are much less likely to warrant consideration for treatment, especially in the absence of organic heart disease. Alternatively, supraventricular tachycardia that is persistent for weeks to months and associated with a fast ventricular response may lead to a tachycardia-mediated cardiomyopathy.
- *Symptom Frequency*: It is important to ascertain whether symptoms occur at intervals of hours to days versus weeks to months. Besides its clinical relevance, this information has bearing on the type of diagnostic modality best suited for detecting a culprit arrhythmia.
  - *Accompanying symptoms*: Dizziness, presyncope, or syncope may accompany palpitations and should prompt a search for a hemodynamically significant and potentially serious arrhythmia, most importantly VT. Syncope may also be observed in approximately 15% of patients with SVT, usually just after initiation of rapid SVT or with a prolonged pause after abrupt termination of the tachycardia. Syncope may be associated with AF with rapid conduction over an accessory AV pathway or may suggest concomitant structural abnormalities, such as valvular aortic stenosis, hypertrophic cardiomyopathy, or cerebrovascular disease [7]. On the other hand, palpitations preceded by symptoms of angina or dyspnea might suggest that an arrhythmia or sinus tachycardia may be secondary to ischemia, left-sided heart failure, pulmonary hypertension, or pulmonary embolism.
  - *Medications and social history*: Use of sympathomimetic agents, vasodilators, anticholinergic drugs may worsen symptoms. Medication list should be carefully checked for cardiac or noncardiac QT-prolonging medications. Illicit drug use (eg, cocaine or amphetamines), alcohol abuse, and any temporal relationship between palpitations and excessive caffeine intake should also be sought.

Cardiac History

Critical to the evaluation and management of patients with palpitations is the determination of presence or absence of underlying heart disease. This assessment begins during the history with inquiries regarding any known current or prior cardiac conditions. The presence of ischemic heart disease or congestive heart failure should certainly prompt suspicion of premature ventricular beats or ventricular tachyarrhythmias. Valvular disease including rheumatic heart disease or mitral regurgitation can predispose a patient to atrial arrhythmias.

Arrhythmia History

Knowing that a patient has a history of a specific arrhythmia increases the likelihood that recurrent symptoms represent more of the same. Of course, the physician must always be open to the possibility that a new arrhythmia has developed [e.g., paroxysmal atrial fibrillation in a patient with known left ventricular systolic dysfunction and prior symptomatic premature ventricular complexes (PVCs)]. A history of recent (within a few weeks to months) radiofrequency ablation should prompt consideration of recurrence of the treated tachyarrhythmia, which are not uncommon after even successful procedures [8].

It is also important to determine whether the patient has a pacemaker or implantable cardioverter defibrillator. Interrogation of these devices may aid in diagnosis and even treatment of certain arrhythmias. Ventricular pacing through either of these devices is capable of giving rise to PVC-like symptoms, especially when there is 1:1 retrograde (ventriculoatrial) conduction; the attendant palpitations and other symptoms reflecting a reversed AV sequence are collectively referred to as *pacemaker syndrome*. In patients with dual-chamber pacemakers or defibrillators, palpitations may reflect the occurrence of pacemaker-mediated "endless-loop tachycardias." When these devices employ internal sensors to modulate pacing rate, overly sensitive rate-responsive ventricular pacing during minimal activity may produce a sensation of inappropriately rapid heart beating.

Family History

For patients with a family history of sudden death, the physician should maintain a high index of suspicion that palpitations may be caused by an inherited arrhythmogenic disorder, such as long QT Syndrome (Chap. 16), Brugada syndrome (Chap. 16), or familial catecholamine-mediated polymorphic ventricular tachycardia [9]. With these conditions, palpitations may reflect the occurrence of nonsustained ventricular tachycardia. Clinical concern deepens when there are ancillary symptoms of lightheadedness, near-syncope, or syncope. There is also growing recognition of the existence of certain families that harbor an inherited predisposition to atrial fibrillation [10]; inquiries about such a family history may prove informative.

Possible Endocrine Disorders

A history of symptoms consistent with hyperthyroidism (on an endogenous or iatrogenic basis) may imply that sinus tachycardia or paroxysmal atrial fibrillation is responsible for the palpitations. Patients with pheochromocytoma may come to attention because of palpitations secondary to sinus tachycardia; this diagnosis may be suspected when there are associated symptoms of headache, diaphoresis, and pallor.

Helpful Signs on Physical Examination

In a patient with palpitations, the physical examination should focus primarily on possible evidence of organic heart disease: hypertension; stigmata of congestive heart failure (rales, elevated jugular venous pressures or positive hepatojugular reflux, displaced point of maximum impulse, S3 gallop, and peripheral edema); or murmurs that might suggest valvular or congenital heart disease or hypertrophic obstructive cardiomyopathy. Evidence of chronic obstructive pulmonary disease or obstructive sleep apnea might point to culprit atrial tachyarrhythmias; so too would peripheral stigmata of Graves' disease. Often, however, especially in young adults, the physical examination yields uninformative findings regarding the origin of the patient's palpitations.

Diagnostic Tests

Various diagnostic tests are available for evaluating patients with palpitations. Each has certain advantages and limitations, knowledge of which aids the physician in choosing the tests that are most suitable for a particular patient.

The Resting Electrocardiogram

This test should be performed in all patients. Obviously, a palpitation is not likely to be "caught" during the brief recording period of an electrocardiogram (ECG). However, the resting ECG provides important clues as to the presence or absence of underlying structural heart disease, which can provide a substrate for arrhythmias. A completely normal ECG cannot absolutely exclude coronary artery disease, but it tends to imply preserved left ventricular systolic function [11]. Impaired left ventricular systolic function may be suspected in middle-aged and older patients who exhibit left bundle branch block, nonspecific intraventricular block, or prior myocardial infarction. ECG evidence of left ventricular hypertrophy, whether associated with abnormal left ventricular systolic function or not, raises the possibility of not only PVCs but also atrial tachyarrhythmias, secondary to elevated mean left atrial filling pressure. Marked left ventricular hypertrophy with deep septal Q waves in I, aVL, and V4 through V6 suggests the presence of hypertrophic obstructive cardiomyopathy and a likely substrate for atrial fibrillation. Increased susceptibility to atrial tachyarrhythmias can also be suspected in patients in whom the ECG shows right

and/or left atrial enlargement and signs consistent with chronic obstructive pulmonary disease or mitral stenosis.

In the absence of stigmata of organic heart disease, the ECG should be scrutinized for the possible presence of a delta wave (slurred QRS upstroke with short PR interval). This indicates ventricular preexcitation (Wolff-Parkinson-White syndrome) and suggests the possibility that palpitations are being caused by AV reentrant tachycardias and/or paroxysmal atrial fibrillation with rapid conduction via an accessory pathway [12] (Fig. 3.1). In this regard, it should be noted that the delta wave may be quite subtle (and with PR interval sometimes greater than 0.12 s) in patients with a left lateral accessory pathway, owing to the relatively long intraatrial conduction time from sinus node to the accessory pathway, in comparison with sinus impulse propagation to the ventricles via the normal AV conduction system.

An ECG should also be examined for the possible presence of a prolonged rate-corrected QT interval (longer than 0.45 s in men and longer than 0.46 s in women) and/or "bifid" or "notched" T waves or other ST-T wave morphologic abnormalities, which may suggest long QT syndrome [13] (Fig. 3.2). "Coved"-type ST elevation in the right precordial

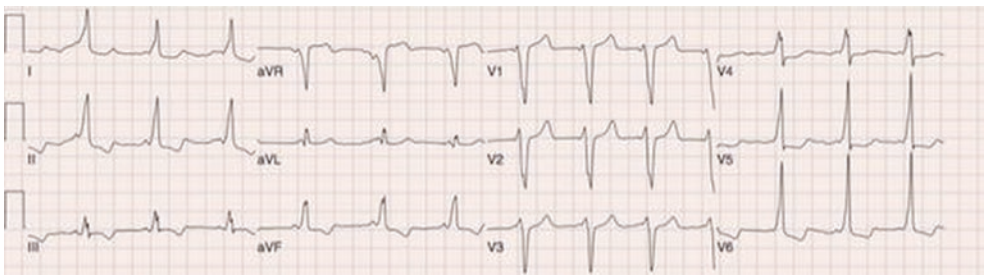

Fig. 3.1 A classic pattern of WPW is demonstrated n ECG with short PR interval and a delta wave preceding the QRS complex. (From Rodriquez [32]; with permission)

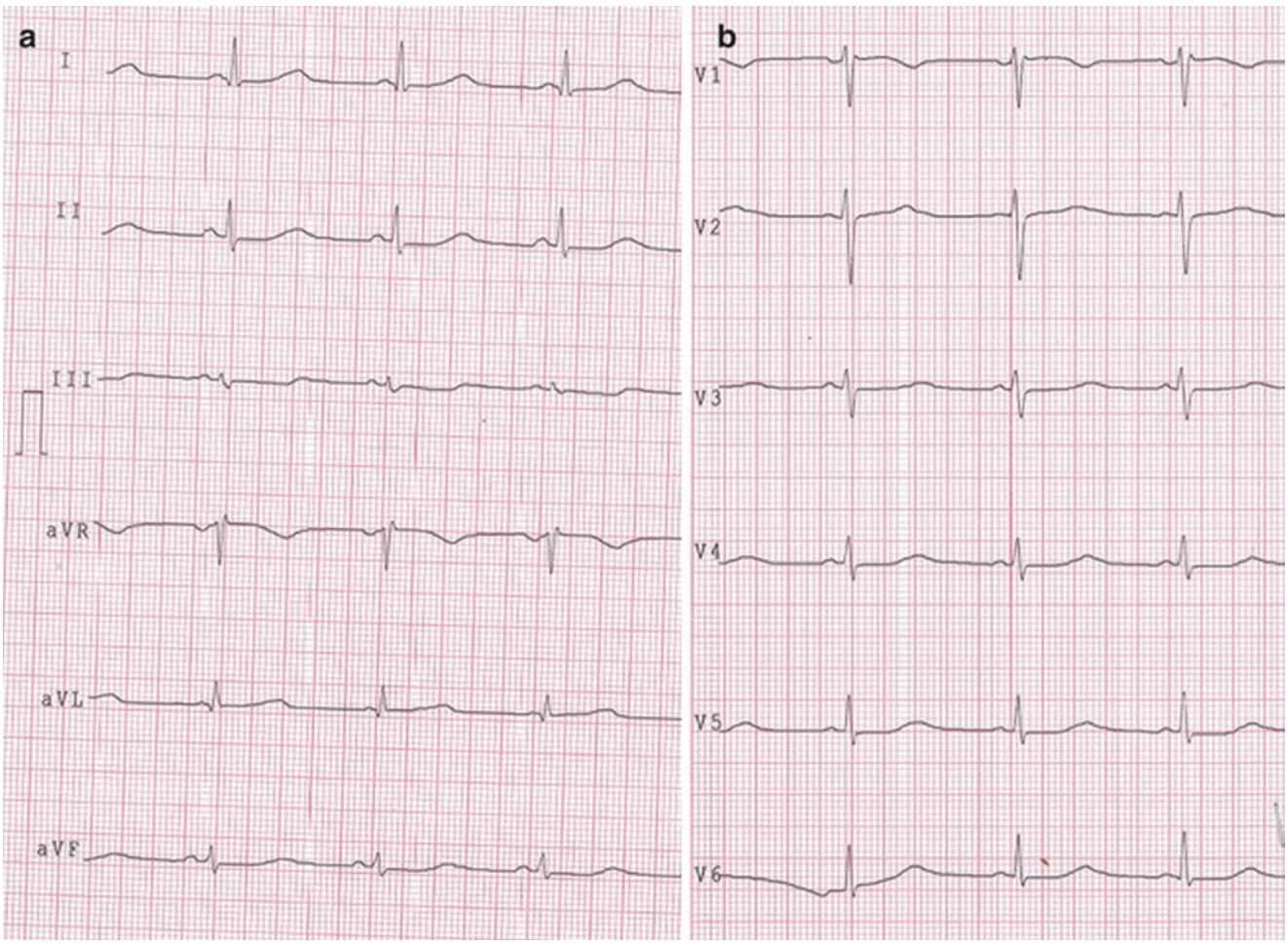

Fig. 3.2 (**a** and **b**), Electrocardiogram of long QT syndrome type 3. Note the marked QT interval prolongation with late peaked T waves. (From Matassini and Maolo [33]; with permission)

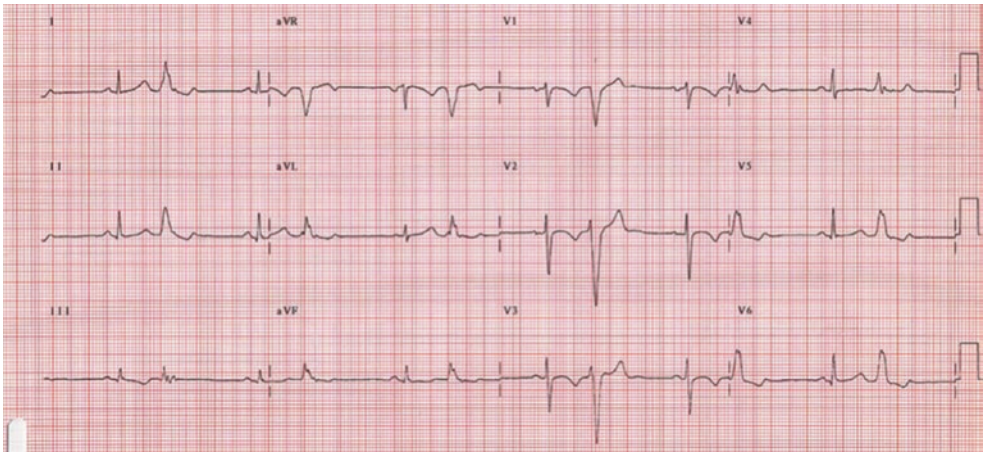

Fig. 3.3 Standard 12-lead ECG in a patient with ARVC/D. There are negative T waves in right precordial leads and premature ventricular beats of left bundle branch block morphology. (From Wojciech et al. [34]; with permission)

leads, with concomitant T wave inversion, and often incomplete or complete bundle branch block pattern in V_1, points to a diagnosis of Brugada syndrome (Chap. 16, Fig. 16.1) [14]. Finally, low-amplitude notching early in the ST segment of the right precordial leads, with associated T wave inversions, suggests a diagnosis of arrhythmogenic right ventricular dysplasia [14] (Fig. 3.3).

Echocardiography

If the history, physical examination, or ECG raises any question about possible cardiac pathology, an echocardiogram can be very useful in ruling in or ruling out overt structural heart disease such as left ventricular systolic dysfunction, atrial enlargement, valvular disease, or less commonly congenital heart disease. For several decades, there has been a widely held belief in some association between mitral valve prolapse and various cardiac symptoms, including palpitations. According to more recent echocardiographic observations, however, the prevalence of this valvular abnormality in a community-based population is low (1 to 2% range), and frequencies of various cardiac symptoms and arrhythmias are no different from those found in individuals without evidence of mitral valve prolapse [15]. Thus, except perhaps in patients with significant attendant mitral regurgitation, mitral valve prolapse, per se, should not be considered a likely explanation for palpitations.

Exercise Testing

Exercise testing is of low yield unless patient's history is suggestive of ischemic heart disease precipitating arrhythmias, or in patients with palpitations that are consistently brought on by exercise. For patients without organic heart disease but with exercise-associated palpitations, exercise testing may aid in inducing and thereby diagnosing frequent PVCs; PSVT; right ventricular outflow tract tachycardia; or polymorphic (in some cases, bidirectional) ventricular tachycardia, in the absence of QT prolongation—a possible marker of a genetically based disorder that confers an increased risk of syncope and sudden cardiac death [9].

24-H Ambulatory Electrocardiographic (Holter) Recording

For patients who experience their palpitations at least once (and, ideally for monitoring, multiple times) per day, a Holter monitor can be helpful in trying to identify a culprit arrhythmia. ECG signals are recorded continuously on two or more channels via chest electrodes, facilitating identification of P waves and potential discrimination of supraventricular from ventricular origin of wide QRS complexes. ECG recordings are scanned by a technician through a computerized interactive program that enables every beat to be classified into a supraventricular or ventricular category; the number of beats in these categories and the characteristics (rate and duration) of tachycardia episodes, if any, are then tabulated in a summary report.

During the 24-h recording period, the patient is also provided with a diary into which he or she is instructed to log various symptoms and times of their occurrence. Because the Holter recorder has a real-time channel, it may be possible to determine a possible correspondence between palpitations (or other symptoms) and specific arrhythmias detected contemporaneously on the Holter recording (Fig. 3.4).

Event Monitor ECG

When palpitations occur less frequently, a 24-h Holter monitor is not likely to be diagnostically helpful. For this common scenario, an event monitor—which allows for on-demand ambulatory ECG recording, synchronous with the patient's

symptoms—is the most appropriate diagnostic modality. The event monitor can be worn for weeks at a time (but is removable periodically, as per patient preference), permitting arrhythmias to be electrocardiographically captured. In general, this approach has a much higher yield than does Holter monitoring for detecting and diagnosing an arrhythmic etiology for palpitations [16, 17]. In addition, continuous loop recorders have proved more cost effective than Holter monitors for the evaluation of palpitations [18].

There are two basic event recorder ECG storage systems utilized in event monitors. The first is called a *memory-loop recorder,* in which there is a buffer memory that is continually updated with single-channel ECG signals recorded from two chest electrodes. Upon experiencing palpitations or other cardiac-related symptoms, the patient can press a "Record" button on the beeper-size, waist-worn device. This serves to freeze the immediately preceding 30–60 s (a programmable duration) of ECG signals stored in the buffer memory, as well as a programmable duration of subsequent ECG signals (typically 30 s). Current devices are capable of storing several such events. A stimulus artifact coincident with the patient's manual activation (triggering) of event storage is indicated directly on the ECG recording channel (Figs. 3.5 and 3.6). A loop recorder is best suited for patients with fleeting symptoms, because the buffer memory affords the patient sufficient time to freeze the corresponding ECG signals.

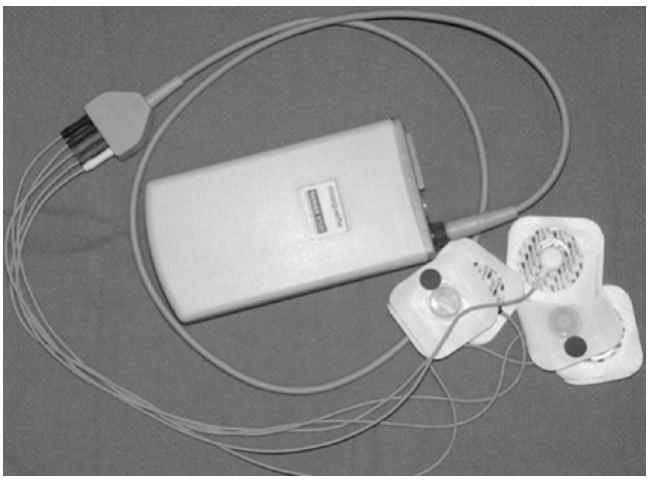

Fig. 3.4 Holter monitor. The recording device is worn by the patient using a shoulder strap or belt loop, attaching to 3–5 skin electrodes for continuous monitoring. An event button located at the top of the device is pressed in the event of symptoms to mark the recording. (From Subbiah et al. [35]; with permission)

In patients with more prolonged palpitations (lasting at least 1 to 2 min), a non–memory-loop event recorder may suffice. This type of device records only forward in time from the point of activation by the patient. The inconvenience of continually worn chest electrodes can be avoided because electrode introduction is needed only with the onset of symptoms. One way of accomplishing this is by applying directly to the chest a small hand-held recorder that has exposed electrode contacts. A more popular version of the non–memory-loop type of event recorder is one that is worn on the wrist. This so-called *wrist recorder* has an electrode on its undersurface that is in contact with the skin. When the patient experiences palpitations or related symptoms, he or she can begin to record the cardiac rhythm by pressing the thumb and forefinger of the opposite hand against two opposing electrodes on the recording device. With electrode contact now spanning the two upper extremities, the wrist device essentially records limb lead I ECG signals.

Regardless of the type of event recorder utilized, all the devices have in common the ability to transmit to a central

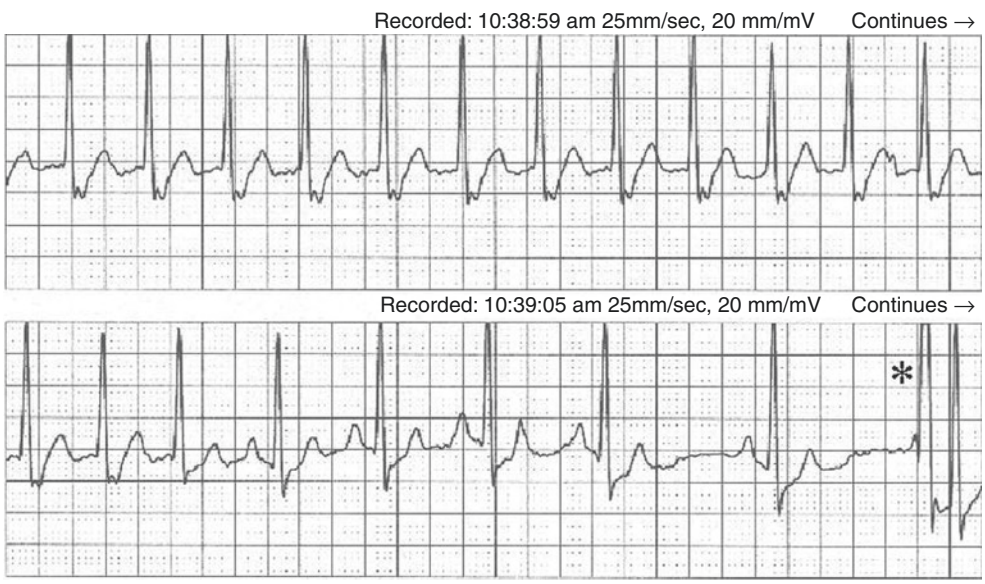

Fig. 3.5 Segment of supraventricular tachycardia captured on an event monitor of the memory-loop type. *Asterisk* denotes stimulus artifact, indicating manual activation of the "Record" function in response to symptoms of "heart pounding." Note that the tachycardia terminates after the third QRS complex on the bottom strip. Although this abnormal rhythm starts and stops before the patient's activation of the "Record" function, these signals are retrievable from the event monitor's buffer memory

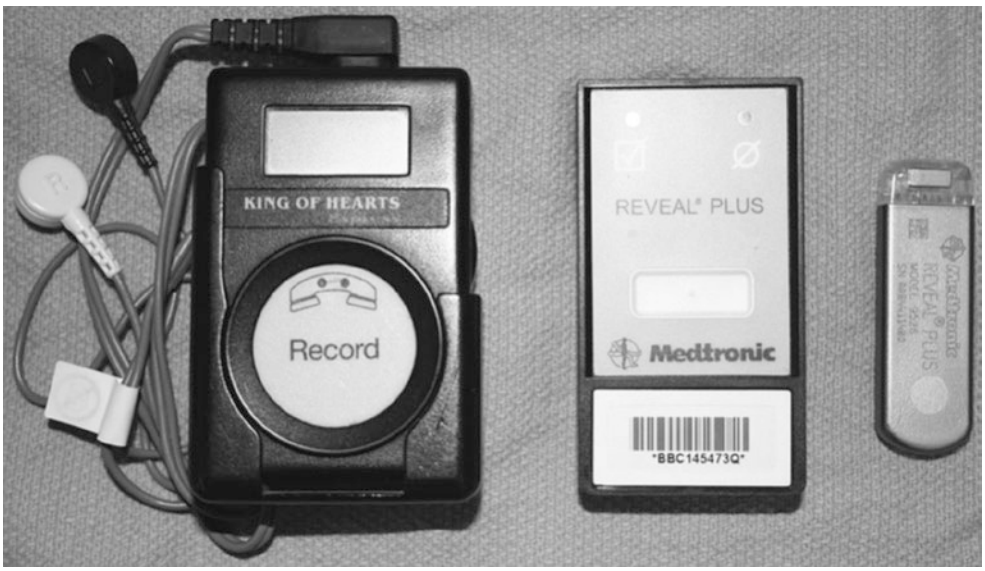

Fig. 3.6 Loop recorders. An external loop recorder *(left)* with cables that attach to the patient. An implantable loop recorder (*center)* and patient activator (*right*). (From Subbiah et al. [35]; with permission)

monitoring station via transtelephonic module the most recent stream or streams of stored ECG signals. The central monitoring station is staffed 24 h a day, 7 days a week, by technicians or nurses who render an initial interpretation of the transmitted rhythm and notify the referring physician in the event that potentially clinically significant tachyarrhythmias or bradyarrhythmias (defined by prespecified criteria) are observed. Final overreading and official interpretation of the transmitted ECG recordings can subsequently be performed by either the referring physician or a cardiologist employed by the monitoring company.

Electrophysiologic Testing

With an intracardiac electrophysiologic (EP) study, electrical pacing techniques make it possible to provoke tachyarrhythmias, thereby facilitating diagnosis. In patients with palpitations, this invasive procedure is usually not undertaken until a tachyarrhythmia has first been documented by one of the noninvasive tests (Table 3.1) [19]. Exceptions to this rule may be made for individuals in high-risk occupations, such as competitive athletes, airplane pilots, or bus drivers, or when there is a high probability of a serious arrhythmia, particularly in patients with underlying heart disease.

Implantable Loop Recorder

For palpitations that are too infrequent even for an event recorder, a small continuous recording device can be implanted subcutaneously in the infraclavicular area. The device is capable of storing ECG signals typically for 10 min at a time (8 min before and 2 min after activation); storage of signals can be initiated by the patient (through application of a magnet) or can be accomplished automatically through the use of preprogrammed rate limit parameters (see also Chap. 5). This diagnostic modality, however, is usually reserved for patients with syncope (Fig. 3.6).

Table 3.1 ACC/AHA Recommendations for electrophysiologic (EP) study in patients with unexplained palpitations

Class I: There is evidence and/or general agreement that EP testing is useful and effective
1. Patients with palpitations who have a pulse rate documented by medical personnel as inappropriately rapid and in whom ECG recordings fail to document the cause of the palpitations
2. Patients with palpitations preceding a syncopal episode
Class II: There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of EP testing
Patients with clinically significant palpitations, suspected to be of cardiac origin, in whom symptoms are sporadic and cannot be documented. Studies are performed to determine the mechanisms of arrhythmias, direct or provide therapy, or assess prognosis
Class III: There is evidence and/or general agreement that EP testing is not useful and in some cases may be harmful
Patients with palpitations documented to be due to extracardiac causes (e.g., hyperthyroidism)

ACC/AHA American College of Cardiology/American Heart Association, *ECG* electrocardiographic
Adapted from Zipes et al. [19]

Holter/Event Monitor Data: Interpretational Issues

Arrhythmia-Symptom Correlation

It is extremely important to confirm reproduction of palpitation symptoms coincident with the detected arrhythmia, as a prerequisite for labeling the arrhythmia as etiologic. Such a diagnostic requirement is necessitated by the high prevalence

of atrial or ventricular extrasystoles and occasional occurrence of "complex" PVCs (e.g., multifocal, couplets, or longer runs) in the general population (see later discussion). On the other hand, documenting a consistent lack of correlation between the symptoms and arrhythmias—especially when no arrhythmias are ever recorded in association with documented palpitations—helps exclude an arrhythmic origin for the patient's symptoms.

Premature Ventricular Complexes

Ventricular arrhythmias detected on Holter and event monitor recordings, even when asymptomatic, continue to be a source of anxiety for physicians. Patients commonly become more symptomatic with their PVCs once they sense their physician's heightened concern, which possibly prompts fear that these arrhythmias may lead to a "heart attack." Such anxieties can be minimized if physicians are aware of the spectrum of PVC frequency and complexity in the general population.

Table 3.2 summarizes PVC-related observations from nine Holter studies involving 962 healthy young and middle-aged adults [20–26] and 156 predominantly healthy elderly individuals (75 years of age or older) [27, 28]. Over a given 24-h period, on average, at least one PVC is recorded in 57% of such a broad population sample; PVC prevalence increases with age but does not differ significantly by sex. In the approximate ninety-fifth percentile for PVC frequency, the average is 65 PVCs per 24 h in young adults and 300 PVCs per 24 h in middle-aged adults; thus, some 5% of healthy nonelderly subjects may exhibit even more frequent PVCs (as high as 1000 or more per 24 h). Complex PVCs are not so rare: multiform PVCs can be found in 9.7%, ventricular couplets in 2.4%, and runs of ventricular tachycardia in 1.3% of healthy nonelderly adults, on average. When observed, ventricular tachycardia episodes typically occur no more than once during a given 24-h period and are *not* sustained, consisting of only three to eight consecutive PVCs at rates usually of less than 200 (rarely up to 300) beats per minute. Elderly individuals tend to have more frequent and complex PVCs.

There is more recent conflicting data regarding prognostic significance of frequent and complex ventricular ectopy in patients with apparently normal hearts. At present it is believed that in the absence of organic heart disease or genetic arrhythmogenic disorders, frequent or complex PVCs may not carry an increased risk of life-threatening sustained ventricular tachyarrhythmias or sudden death [29].

Sinus Tachycardia

Not uncommonly, the only arrhythmia documented in association with symptoms is sinus tachycardia. Of course, the examiner must clarify that this is occurring at rest, in the absence of external sources of physical or emotional stress. The sinus tachycardia that may be observed on Holter or event monitor recordings in such a scenario has a rate typically in the range of 100 to 120 beats per minute, although rates up to 140 to 150 beats per minute are sometimes observed. When the physician fails to uncover more serious arrhythmias, there is a natural tendency to consider the monitor test "negative," with attribution of symptoms to "anxiety," especially in young or middle-aged patients (often women) with no underlying organic heart disease. An anxiety disor-

Table 3.2 Prevalence of PVCs in the general adult population[a] on 24-h ambulatory electrocardiograms

Study	No. subjects	Males	Age [range (mean)]	At least one PVC	PVC frequency for ≈ 95% of population (no./24 h)	"Complex" PVCs		
						Multifocal	Couplets	VT
Young								
Brodsky et al. [20]	50	100%	23–27 (NA)	50%	≤30	12%	2%	2%
Sobotka et al. [21]	50	0%	22–28 (NA)	54%	≤100	10%	0%	2%
Middle-aged								
Kostis et al. [22]	101	50%	16–68 (49)	39%	≤500	4%	0%	0%
Bjerregaard et al. [23]	260	65%	40–79 (54)	69%	≤200	23%	8%	2%
Bethge et al. [24]	170	69%	18–70 (42)	41%	≤240[b]	10%	3%	2%
Rasmussen et al. [25]	111	51%	20–79 (50)	61%	≤500	NA	2%	1%
Takada et al. [26]	220	69%	20–79 (47)	44%	≤50[c]	9%	2%	0%
Elderly								
Camm et al. [27]	106	NA	75–95 (NA)	69%	≤2,400[d]	22%	4%	4%
Kantelip et al. [28]	50	12%	81–100 (NA)	96%	≤2400	18%	8%	2%

NA information not available, *PVC* premature ventricular complex, *VT* ventricular tachycardia (≥3 consecutive PVCs at rate >100 beats/min)
[a]All deemed to be "healthy" (by history, physical examination, and 12-lead electrocardiogram) except for a subset of the active elderly subjects studied by Camm et al. [27]
[b]Applied to 90% of population
[c]Applied to 93% of population
[d]Applied to 88% of population

der may well be present in a subset of these cases. However, the physician should also be mindful of the possibility that patients whose palpitations are associated with sinus tachycardia may be suffering from some type of dysautonomia or intrinsic disturbance of sinus nodal function. Assuming that the physician is not dealing with situations of acute or subacute blood loss, he or she may suspect *postural orthostatic tachycardia syndrome* if the heart rate increases by 30 or more beats per minute (in the absence of significant hypotension) within 5 min of changing from a supine to a standing position [4]. *Inappropriate sinus tachycardia* should be considered in patients with an average heart rate of over 90 beats per minute throughout a 24-h Holter ECG recording, once an endocrine disorder has been excluded. The underlying pathological basis for inappropriate sinus tachycardia is likely to be multifactorial, but two main mechanisms have been proposed: enhanced automaticity of the sinus node and abnormal autonomic regulation of the sinus node with excess sympathetic and reduced parasympathetic tone [30]. A high proportion of patients with inappropriate sinus tachycardia are healthcare professionals, and approximately 90% are female. The mean age of presentation is 38 plus or minus 12 years [31].

Management Considerations

The overall diagnostic approach to a patient with palpitations is summarized. At any point along this evaluation process, various findings may warrant referral of the patient to the emergency room (Table 3.3) or to a cardiologist (Table 3.4).

It is important to ascertain whether the patient has organic heart disease, because this factor has a significant impact on prognosis and therapeutic decision making. Besides information gleaned from the history and physical examination, noninvasive tests, particularly echocardiography, can be very helpful in more definitively establishing the presence or absence of underlying structural heart disease. The advisability of cardiac catheterization should be based on conventional indications for this invasive procedure, ordinarily not warranted by a complaint of palpitations alone. The therapeutic options depicted must be tailored to the arrhythmia and to the patient's cardiovascular diagnoses.

For the majority of patients, whose palpitations are occurring in the absence of organic heart disease and without associated syncope or near-syncope, PVCs, even short runs of nonsustained ventricular tachycardia, are generally thought to carry a benign prognosis [27], and the patient can be reassured accordingly; this is also the case for patients who are found to have premature atrial complexes, including short runs. Precipitating factors, such as excessive caffeine, alcohol, nicotine intake, recreational drugs, or hyperthyroidism, should be reviewed and eliminated. Use of medical therapy in these cases should be discouraged, unless the patient remains considerably symptomatic even after he or she verbalizes understanding of the benign nature of the condition. For such individuals, empirical therapy is typically limited to beta-adrenergic blockers or calcium channel blockers, in

Table 3.3 Palpitations: when to refer to the emergency room

Palpitations with
New-onset syncope
New-onset or worsening chest pain or dyspnea
Recent onset palpitations (especially with any suggestion of lightheadedness) in patients with
Possible drug-induced long QT syndrome
Known or family history of long QT syndrome, Brugada syndrome, catecholamine-induced polymorphic VT, or arrhythmogenic right ventricular dysplasia
Sustained regular SVT, especially with associated hypotension, lightheadedness, chest pain, or dyspnea
Atrial fibrillation or flutter with
Hypotension, lightheadedness, chest pain, or dyspnea
Average ventricular response >120 beats/min
Onset clearly within 48 h, regardless of rate, potentially amenable to acute cardioversion
Onset of uncertain duration but known history of TIA, stroke, or other thromboembolic event in a patient not currently receiving anticoagulation therapy
Sustained VT
Nonsustained VT in association with unexplained syncope, new-onset or worsening chest pain, or dyspnea, especially in patients with known organic heart disease
Asymptomatic polymorphic VT with
Underlying organic heart disease
Prolonged QT interval
Brugada syndrome
Induction by exercise
Rate ≥120 beats/min

SVT supraventricular tachycardia, *TIA* transient ischemic attack, *VT* ventricular tachycardia

Table 3.4 Palpitations: when to refer to a cardiologist

Patients with Wolff-Parkinson-White syndrome, particularly if atrial fibrillation or flutter or other SVT has previously been documented
Atrial fibrillation, atrial flutter or regular SVT in patients with
Syncope
Impaired left ventricular systolic function
Hypertrophic cardiomyopathy
Suboptimal response or intolerance to AV nodal blocking medication
Severe valvular disease
Nonsustained VT in patients with organic heart disease
Frequent, symptomatic PACs or PVCs not responsive to beta or calcium channel blockers
Chronic palpitations in patients with family history of long QT syndrome, Brugada syndrome, catecholamine-induced polymorphic VT, or arrhythmogenic right ventricular dysplasia

AV atrioventricular, *PAC* premature atrial complex, *PVC* premature ventricular complex, *SVT* supraventricular tachycardia, *VT* ventricular tachycardia

view of concerns about serious adverse effects (especially proarrhythmia) with other antiarrhythmic agents.

For patients with persistent or inappropriate sinus tachycardia etiologies such as anemia, pulmonary disease, physical deconditioning or endocrine abnormalities should be ruled out. Conservative therapy including increasing fluid and salt intake (in the absence of heart failure), exercise endurance may be recommended. If patient report persistent symptoms, beta blockers or nondihydropyridine calcium-channel blockers may be useful. For patients with inappropriate sinus tachycardia and depressed cardiac function in the absence of traditional risk factors for left ventricular dysfunction, an electrophysiology evaluation may be considered.

When palpitations are accompanied by syncope, near-syncope, or other manifestations of compromised cardiac function, or when detected arrhythmias are occurring in the setting of organic heart disease, more aggressive therapeutic interventions are warranted. These include AV nodal blocking medication with oral anticoagulation for patients with atrial fibrillation or atrial flutter; consideration of radiofrequency ablation procedures for various symptomatic sustained supraventricular tachyarrhythmias (Chaps. 14 and 15); ablation for certain sustained ventricular tachycardias; and, less commonly, automatic defibrillator implantation for sustained ventricular tachyarrhythmias (spontaneous or induced) in patients with various cardiomyopathic disorders or in symptomatic high-risk patients with primary ventricular tachyarrhythmias (e.g., long QT syndrome and Brugada's syndrome).

Practical Points

- In the history, characterize duration of palpitations, circumstances surrounding occurrence, rapidity of onset/offset, whether regular or irregular, episode duration, and frequency.
- Paroxysmal supraventricular tachycardia may masquerade as "panic attack," leading to misdiagnosis.
- Search for evidence of structural heart disease by history, physical examination, ECG, and, if indicated, noninvasive tests.
- In the absence of significant mitral regurgitation, mitral valve prolapse is *not* a plausible explanation for palpitations.
- The ECG may point to an arrhythmic etiology (e.g., Wolff-Parkinson-White syndrome).
- A 24-h recording by Holter monitor is useful only if symptoms are occurring at least daily.
- An event monitor (with memory loop), worn for days to weeks, is the higher yield ambulatory ECG test for detecting arrhythmias associated with palpitations.
- For either Holter or event monitor recordings, a given arrhythmia must be strongly correlated with palpitations to be considered etiologic.
- Premature ventricular complexes are fairly common in the general population and should be of prognostic concern only if associated with organic heart disease and/or syncope.
- Sinus tachycardia recorded during palpitations—in the absence of exertion—should not be presumed a "negative" finding (or automatically attributed to "anxiety"); the patient could be suffering from postural orthostatic tachycardia syndrome or inappropriate sinus tachycardia.
- Management of palpitations is guided by the nature of the detected arrhythmia, the severity of associated symptoms (e.g., syncope), and the presence and extent of underlying heart disease.

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Edema

4

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Definitions

Edema is an abnormal increase in the interstitial fluid volume and is typically first noted in the lower extremities. It is a nonspecific finding to a spectrum of clinical diseases and correlating it to the underlying etiology could be challenging to the treating clinician without the clear understanding of the pathogenesis of edema formation. It may be localized or diffuse depending on the underlying etiology and extent of the collected interstitial fluid. *Dependent edema*, the most common edema seen in clinical practice is the collection of fluid at specific sites in response to the hydrostatic effects of gravity. It is usually first noted in the feet and ankles but can often be missed in bed bound patients where it first appears on sacrum. *Anasarca,* or *dropsy* is defined as large and generalized accumulation of interstitial fluid. Depending on the underlying mechanisms, both anasarca and smaller amounts of lower extremity edema may be associated with collection of fluid in the serous cavities. This can manifest as ascites—accumulation of fluid in the peritoneal cavity or pleural effusion—accumulation of fluid in the pleural cavity. On clinical exam edema is demonstrated by applying pressures on the skin against a bony surface—for example, over the tibia, fibula, or sacrum. After release of pressure if the indentation persists, it is called *Pitting edema. Non pitting edema* is often seen in chronic lymphedema. *Brawny edema* is a nonpitting fibrotic thickening of the subcutaneous tissues, which results from chronic tissue swelling [1].

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Principles of Edema Formation (Starling Forces)

In an average adult male 60% of total body weight is comprised of water. About 2/3rd of this is distributed in the intracellular compartment and 1/3rd in the extra-celluar compartment (Fig. 4.1). The plasma volume comprises 25% of extracellular volume and the remaining 75% is made up of the interstitial fluid volume. As edema results due to expansion in interstitial volume, it often takes more than 4 kg of excess total body fluid before the development of edema. In the microcirculation starling forces operate to keep the fluid balance in check at the tissue level. Edema develops as a result of imbalance between these forces [2, 3]. The *hydrostatic pressure* within the vascular system and the *colloid oncotic pressure* within the interstitial fluid facilitate the movement of fluid out of the vascular compartment and into extravascular space. The *tissue tension* (plasma colloid oncotic pressure and interstitial hydrostatic pressure) promotes the movement of fluid from the extravascular space into the vascular compartment. Larger molecules and proteins which can't return through the venous end of microcirculation are returned through the lymphatic system back into the plasma. In addition degree of vascular permeability is another important factor in pathogenesis of edema.

An increase in the capillary pressure may result from an elevation of venous pressure. The increased venous pressure may be generalized, as with congestive heart failure (CHF), or localized, as with extrinsic mechanical compression from a mass (tumor) or a deep venous thrombosis (DVT) [4]. The plasma colloid oncotic pressure may be altered by hypoalbuminemia from malnutrition, liver disease, urinary protein loss, or a severe catabolic state. The reduction in oncotic pressure lessens the movement of interstitial fluid into the vascular compartment.

A fall cardiac output, as in congestive heart, reduces the effective arterial blood volume and systolic blood pressure (hypotension) and decreases renal blood flow. Compensatory activation of the sympathetic nervous system and

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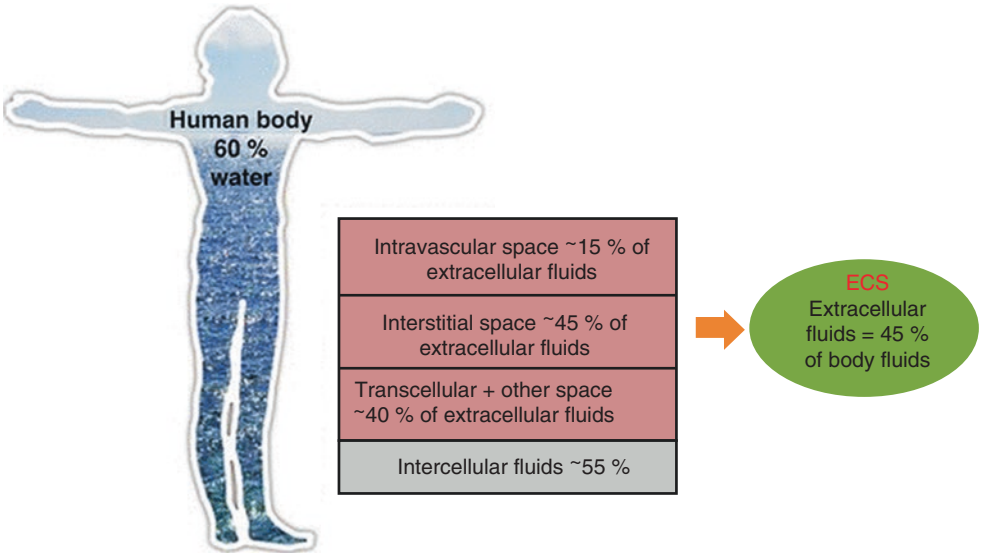

Fig. 4.1 Body water distribution. (From Agrò and Vennari [27]; with permission)

renin-angiotensin system promotes renal vasoconstriction, a reduction in renal salt and water excretion, and an expansion of the extracellular volume with edema formation. In addition, the mechanisms responsible for maintaining a normal serum osmolality are activated promoting thirst and secretion of antidiuretic hormone. If the increase in total body salt and water is insufficient to restore and maintain an appropriate effective arterial volume, then the stimuli promoting renal salt retention are not turned off and the severity of the edema is progressive.

The nephrotic syndrome and hepatic cirrhosis are associated with a severe reduction in serum albumin by either an increase in the loss of protein or a reduction in protein synthesis. The reduction in the plasma colloid oncotic pressure reduces plasma volume and the effective arterial blood volume, further promoting renal salt and water reabsorption [5].

Damage to the capillary endothelium increases vascular permeability and the movement of fluid and protein into the interstitial space. The vascular injury is often the result of infection, drugs, hypersensitivity reactions, or thermal or mechanical damage. This manner of vascular damage usually results in a nonpitting edema with associated inflammation. In addition, an occlusion of the lymphatic drainage of a specific site results in edema.

Keys to the Clinical Evaluation

Distribution

Unilateral edema (Table 4.1) is a common clinical complaint, particularly of the lower extremities. Most patients with unilateral lower extremity edema should be evaluated for a DVT. Establishing pretest probability using a Well's criteria has been very well validated. Subsequent testing with either a D-dimer if the probability is low to intermediate or venous Doppler if the pretest probability is high should be considered regardless of whether it is associated with pain or not (Chap. 30) [6–10].

Besides a DVT, mechanisms for a painful unilateral swelling may include the following. The postphlebitic syndrome commonly follows a DVT [11]. A ruptured popliteal (Baker's) cyst produces posterior knee tenderness and occasionally petechiae and may clinically resemble a DVT [12]. A tear or rupture of the gastrocnemius muscle is often acute and can be confused with a DVT [13]. Soft tissue infections (cellulitis and fasciitis) can initially present with swelling and pain, before the development of erythema or warmth. A psoas muscle hematoma or abscess can also produce unilateral swelling and may be associated with flank or hip pain as well as a painful leg lift test result (psoas sign).

Bilateral lower extremity or *generalized edema* (Table 4.2) is the primary result of three mechanisms: an increase in central venous pressure, such as in pulmonary hypertension; renal sodium and water retention, as with a primary renal disease; or a reduction in cardiac output with activation of the sympathetic nervous system and the renin-angiotensin system, as seen with CHF. The distribution of the edema is influenced by the hydrostatic effects of gravity (dependent edema) and by the limitation in venous and lymphatic return, and the edema often accumulates in dependent structures such as the scrotum or the abdominal pannus in obese patients. Generalized edema limited primarily to above the diaphragm can result from infection, dermal irritants, or compression or obstruction of the superior vena cava and mediastinal vasculature, as is seen with chest neoplasms [14].

Table 4.1 Unilateral edema

Deep venous thrombosis
Postphlebitic syndrome
Baker's cyst rupture
Gastrocnemius rupture
Cellulitis
Trauma
Insect stings
Venous insufficiency
Varicosities
Lymphatic obstruction
Post procedure groin hematoma
Post procedure arterial venous fistula
Use of compression devices can cause a proximal DVT

Table 4.2 Generalized edema

Deep venous thrombosis
Left ventricular systolic and diastolic dysfunction
Valvular heart disease
Right ventricular volume and pressure overload.
Chronic lung disease
Sleep apnea
Pulmonary embolism
Primary pulmonary hypertension
Hepatic dysfunction
Renal disease
Venous insufficiency/varicosities
Constrictive pericardial disease
Drug induced
Loss of venous tone secondary to lack of exercise
High-output cardiac failure
Thyrotoxicosis, Beriberi, AV malformations
Hypothyroidism
Idiopathic cyclic edema
Exercise edema
High-altitude edema
Tropical edema
Lymphedema
Malnutrition
Milroy's Disease – Hereditary Lymphedema
Meige's Disease – Hereditary Lymphedema Type II
Kippel-Trenaunay Syndrome --abnormalities of capillaries, veins, and lymphatic

AV arteriovenous

Chronic right ventricular failure may be the result of left ventricular dysfunction, pulmonary hypertension, sleep apnea or chronic lung disease. It produces marked bilateral edema, often with ascites, as a result of an increase in central venous pressure. Acute right-sided heart failure secondary to a large pulmonary embolism or a myocardial infarction also produces elevated central venous pressures, however edema may be absent at the time of acute presentation. A careful review of the history to seek evidence of chest pains consistent with angina or a prior cardiac history (myocardial infarction or angina) should be completed early in the evaluation of generalized edema. CHF resulting from left ventricular systolic or diastolic dysfunction, or both, is one of the most common mechanisms for bilateral edema and is often associated with pleural effusion or ascites. Hepatic cirrhosis is the end point of chronic liver disease (e.g., viral hepatitis, alcoholic liver disease). Edema of hepatic origin is primarily in the lower extremities and abdominal cavity and is proportional to the elevation in portal venous pressure. A history of a change in urinary frequency, hematuria, or foamy urine supports a renal process for the edema. The edema associated with the nephrotic syndrome (urinary protein loss of more than 3.0 g per day) is the result of a marked reduction in serum albumin and occasionally by venous thrombosis that results from the associated hypercoagulable state. Minimal change disease, membranous glomerulopathies, diabetic renal disease, human immunodeficiency virus infection, glomerulosclerosis, and myeloma kidney are common causes of the nephrotic syndrome [15].

Table 4.3 Causes of lymphatic obstruction

Metastatic carcinoma or lymphoma
Radiotherapy or chemotherapy
Retroperitoneal fibrosis
Sarcoidosis
Filariasis
Milroy's disease
Meige's syndrome
Klippel-Trenaunay syndrome

Idiopathic cyclic edema is an episodic swelling, often with abdominal distention, noted primarily in women, and is unrelated to the menstrual cycle. Many of these patients may have used diuretics extensively in the past. *Exercise edema* is occasionally noted as facial and ankle edema in healthy subjects performing strenuous exercise. *High-altitude edema* is a lower limb and facial edema typically noted in persons hiking at altitudes above 2400 meters. It is augmented by a high-salt diet and resolves with the return to lower altitudes. *Tropical edema* is a pitting edema of the ankles that often occurs abruptly in normal adults within 48 h after traveling from a temperate climate to the heat of the tropics. It spontaneously resolves within a few days of acclimatization. *Carcinoma,* most significantly cervical, colorectal, prostate, or *lymphomas,* can result in edema by local extension and obstruction of venous and lymphatic drainage.

Lymphedema (Table 4.3) can have several causes [16]. Primary or congenital lymphedema manifesting at or soon after birth is rare. Most forms of primary lymphedema manifest after puberty with lower extremity swelling and more often affect women. Secondary lymphedema manifesting with the onset of swelling in a single limb suggests proximal lymphatic obstruction. Pelvic causes of venous or lymphatic obstruction such as tumors or thrombosis should be sought in evaluation of lower extremity swelling. Prior treatments for

cancer, such as a lymph node dissection for breast cancer or radiotherapy, are common causes. Relapsing tumors should always be considered when limb swelling develops after a cancer treatment. Worldwide, filariasis is a secondary cause of lymphedema and should be considered in a patient who has traveled or lived in an endemic area. Characteristic skin changes are swelling in the subcutaneous layers, thinning, hyperkeratosis, and occasionally elephantiasis.

Drugs Associated with Edema

Reviewing medication history can provide important insights in evaluation of edema. And discontinuing the culprit medication can be the single most important step in the management. Nonsteroidal antiinflammatory drugs (NSAIDs) are an extremely common mechanism for drug-related lower extremity swelling [17] (Table 4.4). As a class, they promote salt and water retention via renal microvascular constriction and a diminished glomerular filtration rate. These drugs may adversely limit the therapeutic effects of antihypertensive medications and diuretics. They are often found to frustrate the management of excessive volume in conditions such as CHF. As a class, cyclooxygenase-2 (COX-2) inhibitors are also associated with edema formation. Antihypertensive medications that are direct arterial or arteriolar dilators have a high rate of producing edema. Alpha-adrenergic antagonists have become popular medications because of their role in reducing symptoms of prostatic obstruction, but they have also been implicated in causing lower extremity edema. Calcium channel blockers is another class of commonly used antihypertensive drugs with similar side effects. Adrenal corticosteroids and estrogens are implicated in edema formation caused by salt and water retention, primarily by their effects on the aldosterone-sensitive sodium channel in the cortical collecting ducts of the nephron. Corticosteroids are occasionally associated with a metabolic alkalosis and mild degrees of hypokalemia.

Table 4.4 Drugs associated with edema

NSAIDs and COX 2 inhibitors
Antihypertensives
Minoxidil
Hydralazine
Clonidine
Methlydopa
Guanethidine
Calcium channel blockers
Alpha-adrenergic antagonists
Steroids
Corticosteroids
Anabolic steroids
Estrogens
Progestins
Cyclosporine
Growth hormone
Immunotherapies
IL-2
OKT3

COX-2 cyclooxygenase 2, *IL-2* interleukin-2, *NSAID* nonsteroidal anti-inflammatory drug, *OKT3* anti-CD3 monoclonal antibody

Helpful Signs on Physical Examination

The physical characteristics of the edema should be assessed carefully to provide insight in to the process responsible for it. Skin changes, such an erythema and blanching associated with an infection, or rubor (hemosiderin staining of the skin) in venous insufficiency, are helpful in defining its mechanism and chronicity. Concerns for a unilateral swelling in the lower extremities are still initially best assessed by the measurement of the calf's circumference with a tape measure around the bilateral calves at the same level below the patella. Clinical signs supportive of a DVT are inconsistent but should be reviewed—for example, Homans' sign (calf pain with dorsiflexion of the foot). Regional lymph nodes should be palpated. Muscle rupture is typically associated with local tenderness and pain with movement. The clinical signs of thyroid disease, both hyperthyroidism and hypothyroidism, should also be reviewed.

In evaluating cardiac mechanisms for edema, the physical examination should focus on the following. Elevation of jugular venous pressure, which is a direct measure of central venous pressure, is best assessed in supine position with the head elevated to approximately 30–45°. The detection of a right ventricular heave is indicative of pressure or volume overload. Dilation of the left ventricle with displacement of the maximal impulse is best assessed with careful palpation of the anterior chest. Auscultation of the heart should be performed with attention to murmurs suggestive of significant valvular disease, gallops (S3) suggestive of left ventricular congestion, and pericardial rubs or a knock. The chest examination should also be focused to evaluate the presence of inspiratory rales, which suggest CHF, or the finding of chronic lung disease, such as increased anteroposterior diameter, flattened diaphragms, poor air movement, prolonged expiration, wheezing, coarse rales, or rhonchi.

Hepatic causes of edema often have the following physical findings. The presence of ascites is demonstrated by an increase in the abdominal girth, shifting dullness, a puddle sign, or a fluid wave. In primary hepatic disease, the jugular venous pressure is normal or low, although gross volume expansion (anasarca) can exist. If there is associated cardiac dysfunction, then the jugular venous pressure is likely to be elevated. Signs of chronic liver disease may include jaundice, palmar erythema, spider angiomata, male gynecomastia, testicular atrophy, caput

medusa, asterixis, an enlarged liver, a small nodular liver, and central nervous system changes suggestive of an encephalopathy.

Renal disease is typically associated with systemic hypertension, diabetic end-organ disease (retinopathy or neuropathy), and clinical signs of uremia (fetor of the breath, periorbital edema, a pericardial rub).

Diagnostic Tests

Clinical probability of DVT commonly assessed by Well's score is the best guide for further evaluation. D-dimer is useful if the probability is low to intermediate due to its high negative predictive value. If the pretest probability is high, it is best assessed by venous Doppler. If the clinical suspicion is still high despite a negative venous Doppler, magnetic resonance venogram should be considered to evaluate pelvic veins (Chap. 30). The postphlebitic syndrome should be differentiated from an acute DVT by appropriate testing. A popliteal cyst rupture is best evaluated with ultrasonography, magnetic resonance imaging (MRI), or arthrogram of the knee. Gastrocnemius muscle rupture is best assessed with MRI. A cellulitis is evaluated with measurements of the white blood cell counts, cultures, and other markers of inflammation.

Measurements of serum sodium, potassium, blood urea nitrogen (BUN), creatinine, BUN/ creatinine ratio, uric acid, liver enzymes, serum albumin, and cholesterol are helpful in assessing specific organ function. The selection of appropriate tests should be directed by findings in the history and physical examination. Hyponatremia may occur with CHF, cirrhosis, or hypothyroidism. Hepatic disease is best assessed by the measurement of liver enzymes and bilirubin. When significant liver injury is present, abnormal laboratory test results may include hypokalemia, hypoalbuminemia, respiratory alkalosis, low magnesium and phosphorus levels, the presence of ethanol, macrocytosis, and a low serum folate level. Markers of renal disease include elevated creatinine and BUN levels, hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, an anemia that is typically normocytic, an active urinary sedimentation rate, a low serum albumin level (less than 2.0 g per deciliter with a nephrotic syndrome), and proteinuria that is typically more than 3+ on dipstick testing or greater than 500 mg per deciliter in a 24-h urine collection. Thyroid-stimulating hormone and thyroid hormone levels should be reviewed when indicated.

Noninvasive testing is often needed. The use of a two-dimensional cardiac echocardiogram is very useful for assessing left ventricular function, valvular disease, Doppler assessment of right and left sided filling pressures, pulmonary artery pressures or any significant pericardial disease. Right ventricular function (ejection fraction) is often best assessed by means of a nuclear ventriculogram. Liver ultrasonography rapidly evaluates the presence of regenerative nodules or frank cirrhosis. Renal ultrasonography is helpful in measuring the size of the kidneys and in screening for obstruction (hydronephrosis).

Investigation of the causes of lymphedema may include lymphoscintigraphy. After the injection of a radiolabeled colloid into the dorsum of the foot, tracer uptake within the lymph nodes is assessed after a defined interval and distinguishes lymphedema from edema of nonlymphatic origin. The appearance of tracer outside the main lymph routes, particularly the skin, indicates lymph reflux and suggests proximal obstruction. Poor transit of the isotope from the injection site suggests hypoplasia. Lymphangiography injection of tracer directly into a peripheral lymphatic vessel, usually in the dorsum of the foot, is a means for diagnosing obstruction. Computed tomography or MRI can be used to detect a characteristic honeycomb pattern in the subcutaneous compartment that is not seen with other causes of edema. The muscle compartment deep to the fascia is enlarged in DVT but is unchanged with lymphedema.

Treatment

Treatment of edema with lifestyle modifications and diuresis is incomplete without addressing the underlying etiology (Fig. 4.2). Dietary intervention, specifically the restriction of sodium intake, regardless of the cause of the edema, is essential for the successful management of excessive interstitial fluid. Typically, a diet restricting sodium intake to less than 3 g per day is the first goal and is readily achieved by avoiding the addition of salt to prepared foods. Elimination of added salt during food preparation and avoidance of canned and processed food can further reduce sodium intake to approximately 1.5 g per day. A restriction in water intake is typically limited to patients with severe diseases that have led to the edema, particularly CHF and cirrhosis. Limiting water intake to 2 L per day is moderately restrictive and can be achieved with appropriate patient education. More stringent restrictions, to approximately 1 L per day, are difficult to achieve in ambulatory patients.

Diuretic therapy is the primary means of reducing excessive volume via the kidney. These compounds belong to three principal groups (Table 4.5). Thiazides are well absorbed, have a late onset and peak in action, and are conveniently taken once a day. Thiazides' primary site of action is the distal renal tubule. As a group, they are less effective in patients with renal insufficiency and are associated with hyponatremia. Loop diuretics inhibit sodium reabsorption by the ascending limb of the loop of Henle. They can be given orally or intravenously and typically have a potent and rapid onset of action. The duration of action, however, is short, and twice-a-day dosing may be required. When renal impairment

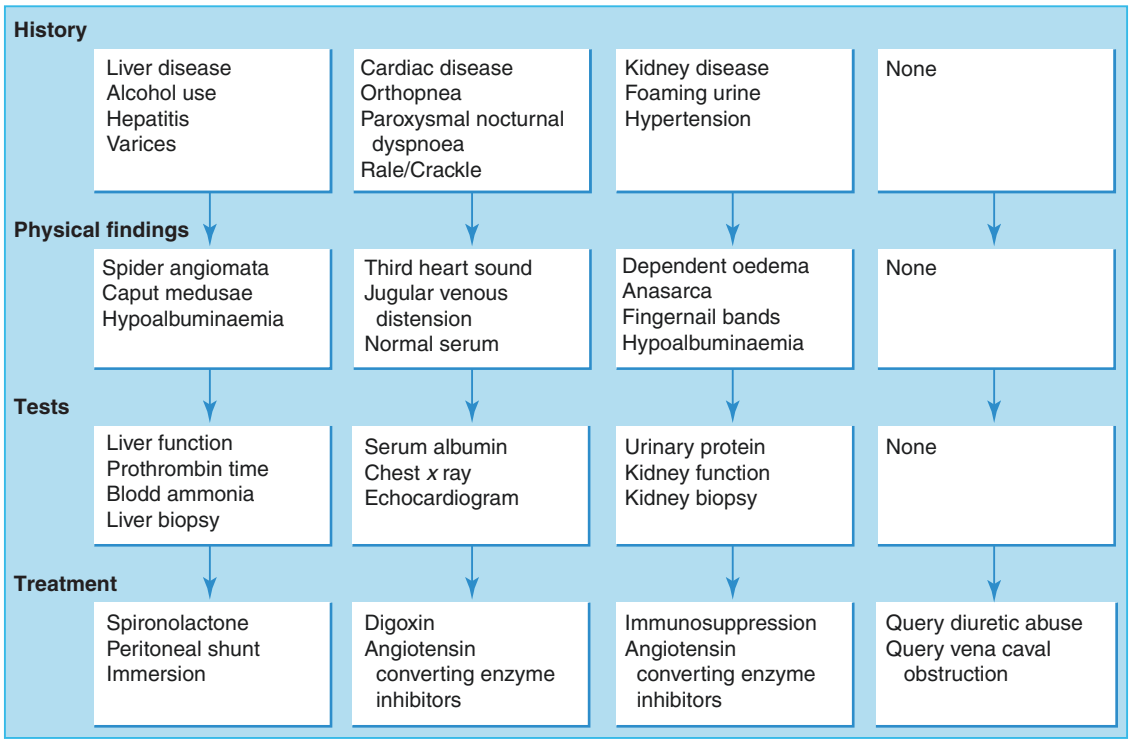

Fig. 4.2 Algorithm for diagnosing and treatment of edema. (From Diskin et al. [14]; with permission)

Table 4.5 Diuretic therapy

Diuretic class	Name	Dose range (mg)	Half-life	Potency	Class effects and adverse reactions
Thiazide	Chlorthalidone	50–100	~3 days	++	Hypokalemia, hypomagnesemia, hypercalcemia, hyponatremia, hyperuricemia, increased blood glucose and lipid levels
	Hydrochlorothiazide	25–200	10–12 h	++	
	Metolazone	2.5–20	8–14 h	+++	
Loop	Bumetanide	0.5–2	1–1.5 h	+++	Hypokalemia, hypomagnesemia, hypochloremia, metabolic alkalosis, hypocalcemia, hyperuricemia, increased blood glucose and lipid levels
	Ethacrynic acid	25–100	1.4 h	+++	
	Furosemide	20–100	1 h	+++	
	Torasemide	5–100	>3 h	+++	
Potassium sparing	Amiloride	25–20	6–9 h	+	Hyperkalemia, metabolic acidosis; spironolactone: Antiandrogen/gynecomastia
	Spironolactone	12.5–100	1–1.5 h	+	
	Triamterene	50–100	1–6 h	+	

is present, they are more effective than thiazides. When a patient's condition becomes refractory to their action, the addition of a distal tubule agent can be synergistic in promoting a more aggressive diuresis.

Potassium-sparing diuretics also act at the distal renal tubule and, as a class, are weak agents. Their ability to mitigate potassium loss during chronic diuretic therapy makes them useful in treatment of chronic conditions such as CHF. Spironolactone, an inhibitor of aldosterone-sensitive sodium transport, has been demonstrated to have marked mortality benefits for patients with significantly symptomatic CHF [18]. When first prescribed, they should be given in lower doses with a gradual increase in dose to mitigate the potential for significant hyperkalemia.

A poor response to diuretic therapy is often noted in specific individuals. Mechanisms for diuretic resistance include excessive dietary sodium intake, chronic use of loop diuretics, and the development of hypertrophy of the distal nephron, which facilitates renal sodium retention, severe renal hypoperfusion secondary to a loss of effective arterial blood volume (CHF, cirrhosis) or to progressive arterial occlusions, and diminished gastrointestinal tract absorption because of progressive bowel wall edema [19]. These patients often improve after a course of intravenous diuretics to decrease wall edema and demonstrate improved responses to oral agents. When admitted continuous infusion with loop diuretics showed no significant clinical benefit compared to intravenous bolus therapy in acute

decompensated heart failure [20]. Heart failure patients who fail to respond to the diuretic strategy or develop worsening renal function despite clinical signs of congestion may need intravenous inotropic support to improve renal perfusion and cause more effective diuresis [21].

The presence of hypoalbuminemia and the use of NSAIDs, including newer COX-2 inhibitors, and steroids, such as prednisone, contribute to diuretic resistance. The addition of amiloride, spironolactone, hydrochlorothiazide, chlorthalidone, or metolazone to a loop agent may facilitate improved volume reductions but confer a higher risk of hypokalemia [22].

Electrolytes and acid-base status should be monitored regularly. With the increasing use of spironolactone for CHF, the incidence of symptomatic hyperkalemia is increasing. Continuous ambulatory intravenous infusions of loop diuretics or inotropes have been limited to patients with refractory CHF and advanced renal failure, and, if carefully managed, it can be an effective means of decreasing volume. In patients with the nephrotic syndrome or cirrhosis who demonstrate a severe reduction in albumin and plasma colloid oncotic pressure, the administration of 25% albumin that was previously thought to lead to improved diuresis has demonstrated no significant clinical benefit in recent studies [23].

Management of lymphedema includes the following. Promoting exercise and its dynamic muscle contraction encourages both passive and active increase in lymphatic drainage. Compression stockings, which act as a force to counter muscle contraction, and generate greater interstitial pressure. Manual lymphatic drainage by a form of massage that stimulates lymph flow is potentially effective in more proximal, normally draining lymphatic areas. Multilayer bandaging, pneumatic compression, elevation of the limbs, and the prevention of infection with good skin care, good hygiene, and antiseptic dressing for minor wounds are paramount in lymphedema. Diuretics are of limited benefit. Surgery is occasionally needed if the weight of the limb inhibits it use, and the aim is either to remove excessive tissue or to bypass local lymphatic defects [24].

When to Refer

The majority of patients with edema can be managed in an outpatient primary care setting with little difficulty or risk. Referrals should be made when the underlying diseases promoting the collection of fluid are severe or are unclear. Individuals with CHF require a systematic evaluation of the mechanisms of its onset and severity and a determined effort to find a potential cause that may be addressed by medications or surgery. Such a comprehensive approach may involve decisions about invasive hemodynamic monitoring, intravenous inotropic support, devise based therapies and mechanical circulatory support which can beneficially affect the morbidity and mortality associated with heart failure and is often best directed by a cardiologist. The development of renal failure or the nephrotic syndrome should also be considered appropriate indications for consultation. In addition, the treatment of significant hepatic dysfunction, which causes a generalized edema, is often benefited by consultation with a specialist.

Individuals with a DVT generally do not require a referral unless it is associated with a prothrombic state (protein C or S deficiency, antithrombin III deficiency, lupus anticoagulant, or factor V Leiden mutation). In this scenario a review by a hematologist is appropriate. Finally, when a malignancy or a recurrence is thought to play a role, the advice of an oncologist is essential.

When to Admit

Venous thromboembolism has been traditionally treated in inpatient setting with intravenous heparin overlapping with Vitamin K antagonist. Recently safety of the use of low molecular heparin and some of the newer oral anticoagulants in the outpatient management of a DVT has been established and recommended by guidelines [25, 26]. But as a group, these patients should be considered candidates for hospitalization particularly if they are at high risk (Chap. 30).

Factors that indicate the benefits of hospitalization are related more to the severity and symptoms of the underlying disease that precipitated the edema. The need to administer intravenous medications is the most common reason to admit—for example, cellulitis, diuretic resistance, or the acute need for cardiac medications.

Symptomatic heart failure, unstable angina, a potential myocardial infarction, syncope, the need to remove a large volume of fluid, a poor response to maximal oral diuretic, the associated metabolic complications of CHF (hyponatremia, hypokalemia, progressive renal insufficiency), need for inotropic support and the need to remove fluid from the pleural or abdominal cavity are common reasons to hospitalize patients with cardiac edema.

Uremic symptoms, the need for dialysis, hyperkalemia, severe hypertension, volume overload, a marked metabolic acidosis, and the need of invasive testing to diagnose or treat the mechanisms of a primary cause of renal failure are common reasons to hospitalize patients with edema related to renal failure.

Hepatic encephalopathy, a coagulopathy, anasarca, marked ascites, suspected subacute bacterial peritonitis, gastrointestinal bleeding, and severe anemia are examples of the adverse complications of hepatic disease that often precipitate admissions.

Practical Points

- Most patients with unilateral lower extremity edema should be evaluated for a DVT and appropriately evaluated with D-dimer or venous Doppler assessment based on their risk.
- Bilateral lower extremity or generalized edema is the primary result of three mechanisms: an increase in central venous pressure, such as in pulmonary hypertension; renal sodium and water retention, as with a primary renal disease; or a reduction in cardiac output.
- NSAIDs are an extremely common mechanism for drug-related lower extremity swelling.
- Clinical signs supportive of a DVT are inconsistent.
- Dietary intervention, specifically the restriction of sodium intake, regardless of the cause of the edema, is essential for the successful management of excessive interstitial fluid. Fluid intake (~2 L/day is recommended in heart failure patients who need diuretic therapy)
- The majority of patients with edema can be managed in an outpatient primary care setting with little difficulty or risk. Referrals should be made when the underlying diseases promoting the collection of fluid are severe or are unclear.

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Syncope

5

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Definition

Syncope (from the Greek *Syn* with *koptein,* meaning to cut off) is the sudden, transient loss of consciousness and postural tone with subsequent spontaneous recovery. Before syncope, the patient may experience a variety of prodromal symptoms, typically including the awareness of an impending faint. The latter "near-syncopal" or "presyncopal" state may not always progress to frank loss of consciousness, if the underlying pathophysiologic disturbances that would otherwise culminate in syncope are aborted (either spontaneously or via countermaneuvers, such as assuming the recumbent position). Hypotension with cerebral hypoperfusion distinguishes true syncope from other syndromes, such as hypoglycemia, with which it may be confused. Syncope should also not be confused with sudden cardiac arrest. A person with sudden cardiac arrest loses consciousness suddenly but will die unless they recieve immediate medical attention. However, a person with syncope recovers quickly, almost always without treatment. Although, injuries can occur during a syncopal episode and recurrent episodes can be worrisome.

Most individuals with the "common faint" (vasovagal syncope, described later) do not consult a doctor, and hence the prevalence of syncope is difficult to determine. About one third of adults experience at least one episode of syncope in their lifetime, and syncope accounts for about 3% of emergency room visits and up to 6% of general hospital admissions in the United States [1]. The recurrence rate is as high as 34% on 3-year follow-up [2].

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The range of prognoses in syncope is wide and the main task of the clinician, therefore, is to determine whether the patient has a benign or a life-threatening cause for syncope [3, 4]. One must be concerned about the possibility that the syncopal event actually represents a self-aborted cardiac arrest, with a potentially catastrophic outcome the next time around. Yet even when syncope is not a harbinger of sudden death, it may incur serious secondary morbidity consequent to trauma.

An important caveat to bear in mind for a patient with syncope is recognition that that the actual event has come and gone, leaving the physician to, in effect, "reconstruct" what transpired. Even when abnormalities are uncovered in the course of various diagnostic procedures, it is not immediately evident that the physician has determined the true cause. The physician must integrate all available information, with focused use of diagnostic tests, and then apply sound clinical judgment to arrive at the most reasonable working diagnosis, which will guide therapy selection. Often, only with the passage of time is the accuracy of the hypothesized cause borne out (suppression of further events) or refuted (syncope recurrence)—in which case diagnostic reevaluation is required.

Principal Causes (Table 5.1)

Neurally Mediated Syncope

Patients with these conditions have in common the paroxysmal occurrence of peripheral vasodilatation, bradycardia. or both, which reflects sympathetic withdrawal and hypervagotonia [5].

Vasovagal, vasodepressor, or *neurocardiogenic* syncope—also called the "common faint"—is often caused by a precipitating event such as prolonged standing, hypovolemia (commonly dehydration), fear, severe pain, heat exposure, the sight of blood, strong emotion, or instrumentation; however, it can also occur without obvious cause. In a typical

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Table 5.1 Principal causes of syncope

Neurally mediated syncope
Vasovagal
Situational
Carotid sinus
Orthostatic syncope (drugs, autonomic insufficiency, volume depletion)
Cardiac syncope
Arrhythmic
Structural
Metabolic disturbances
Neurologic, psychiatric disorders
Unexplained etiology

episode of the common faint, there is a prodrome in which the patient may feel unsteady, "feel bad," be confused, yawn, or experience ringing in the ears or visual disturbances (dimming, blurring, or seeing spots). Often there is associated warmth and nausea, sometimes with vomiting; facial pallor and diaphoresis are common. These presyncopal features (typically lasting from 30 to 60 s) are not seen in all patients; the faint may occur suddenly without warning, not allowing time for protection against injury. At the onset of syncope, there is hypotension, often (but not necessarily) accompanied by bradycardia. With protracted hypotension, there may be attendant seizurelike activity (involuntary muscle jerking). On recovery, along with return of consciousness, color returns to the face, blood pressure increases, and bradycardia resolves. Characteristically, consciousness is regained rapidly after the individual is in the supine position, although there is commonly a feeling of postevent fatigue. In patients who have minimal presyncopal warning, telltale symptoms and signs of vasovagal syncope—nausea, warmth, diaphoresis, and pallor—sometimes become apparent only during the recovery phase. The long-term prognosis in neurocardiogenic syncope is generally excellent; however, in some patients, recurrences are frequent and are a major cause for seeking medical attention.

Situational or *reflex* syncope is loss of consciousness during or immediately after coughing, micturition, swallowing, or defecation. Alcohol has been implicated in micturition-related syncope.

Carotid sinus syncope is induced by carotid sinus stimulation, resulting in hypotension, bradycardia, or both. Sensitive individuals, typically elderly men, may develop carotid sinus syncope with tight shirt collars or while shaving the neck.

Orthostatic Syncope

This type of syncope results from orthostatic hypotension, diagnosed by documentation of a 20 mmHg or more fall in systolic blood pressure during the initial 5 min after the patient is in upright position; the associated heart rate either remains unchanged or increases (in contrast to vasovagal syncope). Orthostatic hypotension is a common cause of syncope in the elderly and is exacerbated by medications (as discussed later). Detection of orthostatic hypotension should trigger an investigation for fluid depletion and blood loss, particularly with syncope of new onset. A major intraabdominal hemorrhage (e.g., gastrointestinal or from ectopic pregnancy) can precipitate syncope before overt signs of bleeding are apparent. Autonomic insufficiency is a cause of orthostatic hypotension in diabetic patients, patients with Parkinson's disease, and the elderly.

Cardiac Syncope

A cardiac cause of syncope is seen in about one fifth of patients. Syncope associated with cardiovascular disease portends a much higher risk of mortality than is the case in the absence of underlying structural heart disease. Patients with cardiac syncope are at highest risk of dying within 1–6 months [6]. The 1-year mortality rate is 18–33%, in comparison with that of syncope with noncardiac causes (0–12%) or syncope in patients with no etiology (6%) [7]. The incidence of sudden death in patients with a cardiac cause is substantially higher than in the other two groups. Cardiac causes of syncope include the following:

Arrhythmic syncope results from tachyarrhythmias (ventricular or supraventricular) and bradyarrhythmias. Specific examples include sinus arrest; atrial fibrillation with very rapid conduction over an accessory pathway in patients with Wolff-Parkinson-White syndrome; and sustained monomorphic ventricular tachycardia (VT). Patients with complete heart block may develop self-limiting syncopal episodes in which there is no effective cardiac output as a result of transient asystole or ventricular tachyarrhythmias (Stokes-Adams attacks).

Torsade de pointes is a polymorphic VT that occurs in patients with prolonged ventricular repolarization [long QT syndrome (LQTS)]. LQTS may occur either on a congenital or acquired basis (e.g., hypokalemia or exposure to certain drugs, as described below). Torsade de pointes can readily progress to ventricular fibrillation. Thus, individuals with LQTS are at risk not only for syncope but also for "seizures" (from transient cerebral hypoxia) and sudden death. Other congenital, potentially lethal arrhythmic disorders include Brugada syndrome (ST segment elevation in precordial leads V_1, V_2, and V_3, often with incomplete or complete right bundle branch block) [8], familial catecholaminergic polymorphic VT [9], and arrhythmogenic right ventricular dysplasia with associated ventricular arrhythmias [10]. In some variants of hypertrophic cardiomyopathy, patients may exhibit minimal, if any, cardiac hypertrophy, and yet affected individuals

may be predisposed to sudden death, presumably from sustained ventricular tachyarrhythmias. Another explanation for syncope in hypertrophic cardiomyopathy is the obstructive type in which there is an intraventricular gradient.

Pacemaker and implantable cardiac defibrillator (ICD) malfunction may be a cause of syncope in patients with these devices. With ICDs, however, it should be appreciated that even when a rapid ventricular tachyarrhythmia is successfully treated by the device, syncope may nonetheless occur, depending on the duration of hypotension preceding the termination of tachyarrhythmia. ICD interrogation can provide information about possible tachyarrhythmia occurrence and therapy delivery/outcome coincident with the syncopal event in question.

Structural syncope is caused by valvular stenosis (aortic, mitral, pulmonic), prosthetic valve dysfunction or thrombosis, hypertrophic cardiomyopathy, pulmonary embolism, pulmonary hypertension, cardiac tamponade, and anomalous origin of the coronary arteries. Syncope in aortic stenosis occurs during exertion when the fixed valvular obstruction prevents an increase in cardiac output into the dilated vascular bed of the exercising skeletal muscles. The syncope can occur during exertion or immediately afterward. Syncope can also occur at rest in aortic stenosis when paroxysmal tachyarrhythmias or bradyarrhythmias accompany this valvular abnormality. Aortic dissection, subclavian steal, severe left ventricular dysfunction, and myocardial infarction are other important causes of cardiac syncope. In elderly patients, syncope may be the presenting feature in acute myocardial infarction [11]. Left atrial myxomas or ball-valve thrombi that fall into the mitral valve during diastole can result in the obstruction of ventricular filling and in syncope.

Lastly, cardiac involvement should be excluded in patients with neuromuscular diseases, eg, Duchenne dystrophy. As a result of cardiac involvement, these patients may develop cardiomyopathy, complete AV block, ventricular tachycardia, or ventricular fibrillation leading to syncope.

Metabolic Disturbance

Syncope due to hypoglycemia is the loss of consciousness that accompanies a blood glucose level of less than 40 mg per deciliter and is preceded by tremors, confusion, salivation, hyperadrenergic state, and hunger. Hypoglycemic syncope should be suspected in diabetic patients who take insulin or oral hypoglycemic agents. In contrast to true syncope, the loss of consciousness caused by hypoglycemia is not associated with hypotension, persists even when the patient is in the supine position, and usually does not resolve until the blood glucose level is restored to normal. Hypoadrenalism, which can cause postural hypotension as a result of inadequate cortisol secretion, is an important and treatable, albeit uncommon, cause for syncope and should be suspected when long-term steroid therapy is suddenly discontinued or when there are other stigmata of adrenal insufficiency.

Neurologic Disease

Neurologic conditions can mimic syncope by causing impairment or loss of consciousness; these conditions include transient cerebral ischemia (usually in the vertebrobasilar territory), migraines (basilar artery territory), temporal lobe epilepsy, atonic seizures, and unwitnessed grand mal seizures. Disorders resembling syncope, but without loss of consciousness, include drop attacks (sudden loss of postural tone), cataplexy, and transient ischemic attacks of carotid origin. In neurologic conditions associated with severe pain, such as trigeminal or glossopharyngeal neuralgia, the loss of consciousness is usually caused by vasovagal syncope.

Psychiatric Disorder

Syncope or syncopelike syndromes associated with psychiatric conditions are not associated with increased rates of mortality but have high 1-year recurrence rates (up to 50%) [12]. The association between syncope and psychiatric disorders may be complicated. First, psychiatric disorders may represent comorbidity in a patient with syncope and have no role in syncope occurrence. Second, psychiatric disorders may cause syncope-like states, often involving a conversion reaction. Psychiatric conditions associated with syncope include generalized anxiety and panic disorders (in which hyperventilation leads to cerebral vasoconstriction and possible loss of consciousness), major depression, alcohol and substance abuse, and somatization disorders. Finally, it is possible that recurrent syncope itself may secondarily give rise to psychiatric conditions such anxiety and panic attacks. A diagnosis of syncope resulting from psychiatric disorders is usually made after organic causes have been excluded. Diagnosis may be difficult when patients have both organic and psychogenic seizures.

Unexplained Etiology

Earlier studies reported that, in about half of the patients with syncope, no cause could be determined. However, with the wider use of tilt testing, event monitoring, electrophysiologic studies, and more aggressive investigation of elderly patients and those with suspected psychiatric causes, the proportion of syncope cases in which the cause can be determined has increased.

Keys to the History

A meticulously documented history is critical in the assessment of syncope. For new-onset syncope, the examiner focuses primarily on ruling out underlying structural heart disease and other life-threatening conditions as such as acute myocardial infarction and stroke, which necessitates evaluation in the emergency department. In contrast, the diagnostic assessment of recurrent syncope (Figs. 5.1 and 5.2) involves a broader consideration of causes and is often undertaken in an ambulatory setting. The history and physical examination should identify a cause of syncope in about 45% of patients [13]. These basic elements of a medical evaluation can lead to recognition of ischemic heart disease, heart failure, aortic stenosis, hypertrophic cardiomyopathy, and pulmonary embolism; neurologic causes such as seizure disorder and subclavian steal syndrome; and familial conditions such as long QT syndrome. Emphasis should be placed on the circumstances surrounding the syncopal event, the nature of prodromal and associated symptoms, characterization of the recovery period, medications and drugs, the presence of known cardiac disease, family history (e.g., cardiomyopathy or LQTS), and psychiatric history. Observations from witnesses or a family member may be helpful. In documenting the history, the examiner should focus on the relation of syncopal events to posture, exertion, and palpitations. The examiner should determine the number and chronicity of prior syncopal and near-syncopal episodes; the latter may be more frequent (albeit of shorter duration) than full-blown syncopal events and may provide an opportunity for diagnostic electrocardiographic monitoring to capture a clinically relevant event. Inquiry also should be made into whether the patient has sustained any trauma in association with the symptoms; serious secondary injury warrants a more aggressive diagnostic and treatment strategy aimed at preventing subsequent morbidity.

Circumstances Surrounding Onset

Painstaking attention should be paid to the chronology of symptoms: sudden onset without a prodrome may suggest arrhythmias, whereas protracted autonomic symptoms

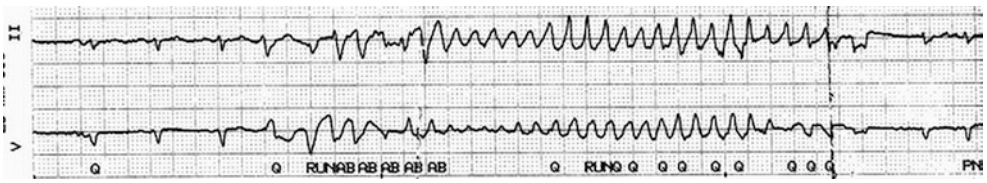

Fig. 5.1 ECG monitor strip revealing nonsustained polymorphous VT in a patient who presented with recurrent syncope. Although the tachycardia resembles torsades, the patient did not have evident LQTS and the onset was not of the "long-short" form. Correction of electrolyte disturbance (marked hypokalemia) appeared to resolve the problem, but an ICD was placed as well. (From Puppala et al. [44]; with permission)

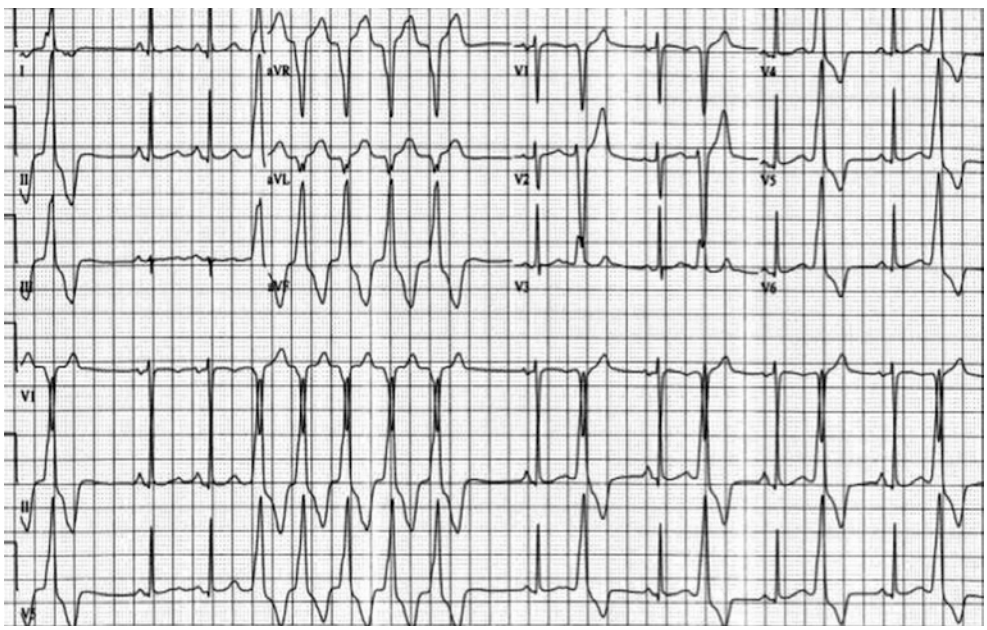

Fig. 5.2 Recordings obtained in a 36-year-old male with a clinically normal heart who presented for evaluation of recurrent syncope. A Holter monitor recording showed frequent ventricular ectopic beats and nonsustained ventricular tachycardia, which correlated well with his symptoms. The morphology of these ventricular ectopic beats on 12-lead ECG was consistent with RVOT origin. He underwent electrophysiological study, and his ventricular arrhythmias were successfully ablated. (From Puppala et al. [44]; with permission)

(pallor, diaphoresis, nausea) in association with a precipitating factor suggest vasovagal syncope. Loss of consciousness after prolonged standing at attention suggests vasovagal syncope, whereas that which occurs immediately on standing is caused by orthostatic hypotension. Situational syncope occurs during or immediately after swallowing, coughing, defecation, and micturition. Alcohol ingestion may be the most important predisposing factor in micturition syncope. Alcohol ingestion has also been implicated in about 10% of syncope cases in young adults, and the syncope in those cases has been attributed to orthostatic stress because of impaired vasoconstriction [14]. Carotid syncope occurs with head rotation while the person is wearing tight collars. Exertional syncope suggests possible structural heart disease such as aortic stenosis, hypertrophic cardiomyopathy, or exercise-induced tachycardias. In highly competitive athletes, vasovagal syncope documented by history and head-up tilt testing has been shown to occur during as well as after exertion [15]. Syncope associated with arm exercise is a feature of subclavian steal syndrome. A history of exertional chest pain, as well as exertional syncope, in an adolescent or young adult raises the possibility of anomalous origin of a coronary artery [16]. Syncope in patients with LQTS may occur in association with physical exertion (particularly swimming), during emotional stress, or in response to sudden, unexpected acoustic stimuli (e.g., sound of an alarm clock or telephone) [17]. Palpitations preceding syncope, especially an awareness of rapid heart beating, suggests an arrhythmic origin – although tachyarrhythmic syncope need not be accompanied by such prodromal symptoms. Features of neurologic syncope include brainstem findings (vertigo, dysarthria, ataxia, visual disturbances), whereas postevent confusion is more likely to be caused by seizures. Loss of consciousness associated with headache indicates migraine or seizures, whereas that associated with throat or facial pain suggests glossopharyngeal or trigeminal neuralgia.

Posture at the Onset of Attack

Vasodepressor syncope typically occurs in the upright position; once the patient is horizontal, the autonomic derangements begin to reverse. In some instances, if the patient returns to the upright position too soon, there can be a recurrent faint. Syncope resulting from arrhythmias and other causes of loss of consciousness that resembles syncope, such as hypoglycemia and hyperventilation, can occur independently of posture. Moreover, syncope caused by pain or emotion-related vasovagal syncope (e.g., after a needlestick or on the sight of blood or injury) need not occur while the patient is upright.

Differentiating Syncope from Seizures

This distinction can be clinically challenging (Table 5.2), and eyewitness accounts are often helpful in discriminating between the two conditions. Both phenomena involve loss of consciousness. As a further confounding factor, myoclonic jerking may occur during the course of true syncope secondary to transient cerebral hypoxia [18]. The best discriminatory features between syncope and seizures are sensorium of the patient after the episode and the patient's age. When a patient older than 45 years is disorientated after an episode, seizures are five times more likely than syncope to have occurred [19]. Older individuals with prolonged disorientation after an episode of loss of consciousness are therefore more likely to have had a seizure. An exception would be arrhythmic syncope with a prolonged hypotensive episode, which may secondarily cause transient cerebral hypoxic injury and postevent disorientation. Other clinical features suggestive of a seizure include cyanotic facial appearance, as opposed to pallor, during the episode; frothing at the mouth; unconsciousness lasting more than 5 min; feeling sleepy after the episode; aching muscles; and tongue biting along the lateral aspect of the tongue. Seizures are also suggested by an aura before the event, horizontal eye movement during the event, and a headache after the episode. Fecal and urinary incontinence can occur in both syncope and seizures but are far more common with seizures. Temporal lobe seizures can easily be mistaken for syncope because they usually lack tonic-clonic movements and are associated with autonomic changes such as flushing and fluctuating changes in the level of consciousness.

Age at Onset

In younger individuals (younger than 30 years), common causes (Table 5.3) include neurally mediated syncope, undiagnosed seizures, Wolff-Parkinson-White syndrome and other supraventricular tachycardias, hypertrophic cardiomyopathy,

Table 5.2 Characteristics of syncope versus seizures

Clinical features	Syncope	Seizures
Loss of consciousness precipitated by pain, micturition, exercise, pain, defecation, or stressful events	+	–
Sweating and nausea before or during the event	+	–
Aura	–	+
Tongue biting	–	+
Clonic or myoclonic jerks or rhythmic movements	+/–	++
Disorientation after the event	–	+
Slowness in returning to consciousness	–	+
Unconscious >5 min	–	+

Table 5.3 Causes of syncope by age

Age	Causes
Youth (<30 years)	Neurally mediated syncope
	Situational
	Alcohol
	Undiagnosed seizures
	Cardiac syncope:
	Hypertrophic cardiomyopathy
	Coronary artery anomalies
	WPW syndrome, other SVT
	Long QT syndrome and other inherited arrhythmic disorders
Middle-aged (30–65 years)	Neurally mediated syncope
	Cardiac (arrhythmic, mechanical/obstructive)
Elderly (>65 years)	Neurally mediated syncope
	Cardiac (arrhythmic, mechanical/obstructive)
	Drugs: Antihyperhypertensive medications, antidepressants, etc. (see text for list)
	Orthostatic hypotension

SVT supraventricular tachycardia, *WPW* Wolff-Parkinson-White

LQTS and other inherited arrhythmic disorders, and congenital coronary anomalies [16].

In middle-aged individuals, typical causes of syncope are neurally mediated and cardiac (arrhythmic, mechanical/obstructive) in origin.

Syncope in the elderly (older than 65 years) may be overlooked when the episode is described by the patient simply as a "fall," owing to postsyncope retrograde amnesia [4]. In the elderly, the cause of syncope is often multifactorial, and older patients tend to have serious arrhythmias (sustained VT in the setting of cardiomyopathy), orthostatic hypotension, or neurologic disorders that are contributory [3]. Elderly patients are also prone to neurally mediated syncope related to known triggers, such as micturition, defecation, coughing, laughing, swallowing, and eating. Postprandial hypotension (secondary to splanchnic vascular volume shifts) can result in syncope during or after a meal. Another confounding factor in this age group is polypharmacy: Many medications at therapeutic doses cause postural hypotension. Aortic stenosis, myocardial infarction, and carotid sinus hypersensitivity are other conditions that predispose to syncope in the elderly. Carotid sinus hypersensitivity has been suggested to be responsible for syncope or "falls" in the elderly [4]. The multifactorial nature of syncope in older patientsoften necessitates a management approach aimed at correcting many of these factors simultaneously.

Other Historical Clues

Cardiac syncope must be kept in mind in patients with structural heart disease, particularly ischemic heart disease with left ventricular dysfunction. A family history of sudden death (including accidental drownings) or seizures is a feature of hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, LQTS, Brugada syndrome and catecholaminergic polymorphic VT. A history of LQTS is particularly important in syncope precipitated by medications (to be described).

Features of the history that suggest syncope caused by VT or atrioventricular (AV) block (odds ratio greater than 5) are male gender, age older than 54 years, three or fewer episodes of syncope, and a 6-s or shorter duration of warning before syncope [20].

Drugs

Drugs can frequently cause syncope, particularly in the elderly. Antihypertensive and antidepressant medications are the most commonly implicated agents. Culprit antihypertensive agents include doxazosin, clonidine, hydralazine, prazosin, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Other drugs associated with syncope are morphine, nitroglycerin, phenothiazines, perioperative amiodarone, calcium channel blockers (e.g., nifedipine), citrated blood, aggressive diuretic therapy, interleukin-2, protamine, and quinidine. Documentation of drug-induced syncope may require ambulatory monitoring of blood pressure.

Drug history is also important in patients with syncope who are suspected of having LQTS. After exposure to drugs that prolong ventricular repolarization, even previously asymptomatic gene carriers may suddenly develop syncope or cardiac arrest caused by torsade de pointes. A detailed list of QT-prolonging drugs can be found at *www.qtdrugs.org*. A partial list of such drugs known to precipitate syncope caused by torsade de pointes include (a) *cardiac drugs,* such as quinidine, procainamide, sotalol, disopyramide, amiodarone, and dofetilide, and (b) *noncardiac drugs,* such as macrolide antibiotics, tricyclic antidepressants, phenothiazines, methadone, some antihistamines, and cisapride. Of note, QT-prolonging drugs are prone to induce torsade de pointes more frequently in women than in men [21, 22].

Pregnancy

Syncope is relatively common in pregnancy [3], but its exact mechanism and prognosis remain unclear. In the third trimester, syncope can occur even in the supine position as a result of compression of the aorta and inferior vena cava in the abdomen by the enlarged uterus. Pregnant women with known cardiac disease, palpitations or arrhythmias, exertional syncope, or pathologic murmur merit further evaluation.

Helpful Signs on Physical Examination

Clinical signs are not readily apparent, and findings depend on the underlying cause of syncope. Clinical examination should be targeted to identify underlying causes suspected from the history. Physical examination is most useful in diagnosing syncope caused by postural hypotension, cardiovascular conditions, and neurologic diseases. Preliminary assessment includes the following:

- Recording of the heart rate: Severe bradycardia may suggest second- or third-degree heart block, whereas tachycardia should trigger an investigation of ventricular or supraventricular tachyarrhythmia. "Postural orthostatic tachycardia syndrome," with associated symptoms of near syncope, may overlap with the clinical picture of vasovagal syncope [23]. Postural orthostatic tachycardia should be suspected when there is an increase of 30 beats per minute within 5 min of standing, accompanied by symptoms of orthostatic intolerance (lightheadedness, dizziness, near syncope).
- Recording of supine and erect blood pressure for orthostatic hypotension: Erect blood pressure should be recorded at least 3 min after the patient stands upright. Orthostatic hypotension should be suspected when there is a 20-mmHg fall in systolic blood pressure or a 10-mmHg fall in diastolic blood pressure within 5 min after the patient stands upright. Patients with autonomic insufficiency typically lack a compensatory sinus tachycardia.
- Assessment of pulse deficit and blood pressures in the arms when aortic dissection is suspected.
- Auscultation of the heart for ejection systolic murmur of aortic stenosis and hypertrophic cardiomyopathy and for gallops.
- Pulmonary examination includes assessment of respiratory rate and other findings to help exclude tension pneumothorax, congestive heart failure, and chronic obstructive pulmonary disease.
- Carotid sinus massage is useful in elderly patients with suspected carotid sinus syncope. It is best performed with a cardiac monitor but should be deferred in a patient with carotid bruits; in the setting of a recent myocardial infarction, stroke, or transient ischemic attacks; or in patients with a history of VT. Before massaging the carotid sinus, the physician should ensure that there are no carotid bruits and then massage one side at a time, 5 s per attempt. The massage should be performed with the patient both supine and erect. An abnormal test result is associated with a pause of greater than 3 s with or without prolonged hypotension. The test result is more meaningful if the patient's symptoms of presyncope are reproduced. The reproducibility of the test is enhanced when the symptoms are elicited with the patient in both the supine and erect positions, usually with a tilt table.
- Neurologic examination and auscultation for carotid bruit should be performed when a stroke or focal neurologic deficits are suspected.

Diagnostic Tests

The investigation of syncope is limited by fact that there are no diagnostic gold standards against which the diagnostic tests can be assessed. For example, the detection of coronary artery disease in a patient who has fainted does not necessarily imply that such a pathologic process is the cause of syncope.

- **Baseline Laboratory Tests:** Routine laboratory testing is not warranted, and these tests should be performed only if suggested by the history or clinical examination findings. Useful measurements include blood glucose to exclude hypoglycemia and hematocrit to exclude blood loss. Hypokalemia and hypomagnesemia should be ruled out if QT prolongation is observed. Pregnancy testing should be considered in women of childbearing age, particularly before head-up tilt testing or electrophysiologic testing.
- **Twelve-Lead ECG** should be recorded in all patients with syncope, and rhythm strips recorded by paramedics should be reviewed. Although yield of the ECG is low, there is no risk, and the test is relatively inexpensive. Moreover, abnormalities such as previous myocardial infarction, nonsustained VT, or bundle branch block may guide further evaluation. These findings, however, do not necessarily point to a unique cause. For example, a patient with bifascicular block and prior myocardial infarction may turn out to have VT rather than AV block as the cause of syncope [4]. Left ventricular hypertrophy may suggest underlying cardiomyopathy. A completely normal ECG implies a more favorable prognosis and tends to reduce (but does not absolutely exclude) the likelihood of a ventricular tachyarrhythmic origin. The ECG is particularly useful in identifying acute ischemia; sinoatrial conduction disturbances; bundle branch/bifascicular blocks; second- or third-degree heart block; supraventricular tachycardia; nonsustained VT; accessory pathways with ventricular preexcitation [e.g, Wolff-Parkinson-White syndrome, with short PR interval and slurred QRS upstroke ("delta wave")]; prolonged QT interval; ST segment elevation in the right precordial leads (V_1, V_2, and V_3), possibly with incomplete/ complete right bundle branch block (Brugada syndrome; Chap. 16); and, on occasion, the "epsilon waves" of arrhythmogenic right ventricular dysplasia, with associated T wave inversions, in the right precordial leads.

- For diagnosing LQTS, a rate-corrected QT (QTc) of more than 0.44 s (in the absence of bundle branch block) has traditionally been considered prolonged. However, it should be recognized that in normal persons, the upper 95% confidence limit for QTc is 0.46 s in women and 0.45 s in men [24]. Thus, although longer intervals are probably truly abnormal, QTc values of 0.42 to 0.46 s are diagnostically equivocal, because both LQTS gene carriers and noncarriers may exhibit QTc intervals in that normal/borderline range [25]. The QTc is calculated as $QT / \sqrt{RR}$, where the QT (traditionally measured in lead II) and RR intervals are measured in seconds. Because computerized ECG measurements are not always reliable, manual assessment of QTc in patients with syncope is advisable. Care should be taken to avoid inclusion of the U wave in the measurement of QT interval [26]. Certain T wave morphologic features, particularly "notches"/"humps", may also be present in LQTS patients even with borderline or normal QTc intervals [26, 27].
- **Exercise Stress Testing** is useful for diagnosing underlying myocardial ischemia when an ischemic substrate is suspected to be the cause of arrhythmogenic syncope. In addition, it may be useful in the detection of rate-dependent AV block, exercise-induced tachyarrhythmias (such as familial catecholaminergicpolymorphic VT [9]), or exercise-associated syncope [15]. Before exercise testing, all patients with exertional syncope must have an echocardiogram to rule out aortic stenosis or hypertrophic cardiomyopathy. In young patients and athletes, congenital anomalous coronary arteries should also be considered prior to exercise testing.
- **Echocardiogram:** Echocardiogram is particularly useful when structural heart disease, such as aortic stenosis, hypertrophic cardiomyopathy, left ventricular dysfunction, right ventricular dysplasia, or pulmonary hypertension, is suspected [28] (Table 5.4). Right ventricular wall motion and function should be explicitly assessed when the examiner tries to exclude right ventricular dysplasia by echocardiography; if any question about this diagnosis remains, computed tomographic scan and/or cardiac magnetic resonance imaging should be considered.
- **Head-up tilt table testing** (Table 5.5) is useful in patients suspected of having neurally mediated syncope and low suspicion of cardiac syncope. Patients are tilted passively to an angle of 60 to 70° for 20 to 45 min, depending on the protocol utilized, with frequent or continuous monitoring of vital signs. The procedure may involve the use of a provocative agent, such as isoproterenol or nitroglycerine, to augment the sensitivity of the test, when initial results are negative. It is generally accepted that occurrence of hypotension (*vasodepressor* response)—often, but not necessarily, accompanied by bradycardia (*cardio-*

Table 5.4 ACC/AHA recommendations for echocardiography

Class I: There is evidence and/or general agreement that echocardiography is useful and effective
Syncope in a patient with clinically suspected heart disease
Periexertional syncope
Class IIa: The weight of evidence/opinion is in favor of usefulness/efficacy
Syncope in a patient in a high-risk occupation (e.g., a pilot)
Class IIb: Usefulness/efficacy is less well established by evidence/opinion
Syncope of occult etiology with no findings of heart disease on history or physical examination
Class III: There is evidence and/or general agreement that echocardiography is not useful and in some cases may be harmful
Recurrent syncope in a patient in whom previous echocardiographic or other testing was demonstrated as a cause of syncope
Syncope in a patient for whom there is no clinical suspicion of heart disease
Classic neurogenic syncope

ACC/AHA American College of Cardiology/American Heart Association
Adapted from Cheitlin et al. [28]

Table 5.5 ACC recommendations for tilt-table testing

Class I: Tilt-table testing is warranted
Recurrent syncope or single syncopal episode in a high-risk patient whether the medical history is suggestive of neurally mediated (vasovagal) origin or not and
No evidence of structural or cardiovascular disease or
Structural cardiovascular disease is present but other causes of syncope have been excluded by appropriate testing
Further evaluation of patients in whom an apparent cause has been established (e.g., asystole, atrioventricular block) but in whom demonstration of susceptibility to neurally mediated syncope would affect treatment plans
Part of the evaluation of exercise-induced or exercise-associated syncope
Class II: Conditions in which reasonable differences of opinion exist regarding tilt table testing
Differentiating convulsive syncope from seizures
Evaluating pateints (especially the elderly) with recurrent unexplained falls
Assessing recurrent dizziness or presyncope
Evaluating unexplained syncope in the setting of peripheral neuropathies or dysautonomias
Follow-up evaluation to assess therapy of neurally mediated syncope
Class III: Conditions in which tilt-table testing is not warranted
Single syncopal episode, without injury and not in a high-risk setting, with clear-cut vasovagal clinical features
Syncope in which an alternative specific cause has been established and in which additional demonstration of a neurally mediated susceptibility would not alter treatment plans
Relative contraindications to tilt-table testing
Syncope with clinically severe left ventricular outflow obstruction
Syncope in the presence of critical mitral stenosis
Syncope in the setting of known critical proximal coronary artery stenoses
Syncope in conjunction with known critical cerebrovascular stenoses

ACC American College of Cardiology
Adapted from Benditt et al. [1]

inhibitory response)—during head-up tilt is akin to spontaneous vasovagal syncope.

About half of the patients with unexplained syncope have a positive test result with passive tilt; after the administration of isoproterenol, the overall response rate increases to 64% [29]. The exact mechanism of enhanced response with isoproterenol remains to be determined but probably involves vasodilatation as well as stimulation of afferent myocardial mechanoreceptors. The sensitivity of the tilt test is 32% to 85%, whereas the overall specificity is about 90% [1]. Note that a "negative" tilt test can occur even in the presence of an obvious case of neurally mediated syncope, and a "positive" test can occur when syncope is clearly due to other causes [1].

The procedure is not advisable for pregnant women, patients with hypertrophic cardiomyopathy, aortic stenosis and the elderly because hypotension is especially detrimental to these patients. The test is not indicated for individuals who have had a single episode of syncope that is characteristic of vasovagal syncope and during which no injury was sustained. Head-up tilt testing is recommended for patients with recurrent syncope in the absence of cardiac cause.

- **Ambulatory Electrocardiographic (Holter) Monitoring for 24 to 48 H:** This type of monitoring (Table 5.6) is used to detect arrhythmogenic causes of syncope [30]. The yield of this investigation is enhanced when a record is obtained during an episode of syncope (a rare, fortuitous occurrence). The optimal duration for monitoring is not known; however, several studies have suggested that it is not cost effective to monitor for periods longer than 48 h [30]. In general, culprit tachyarrhythmias or bradycardias are sporadic and transient, and continuous ambulatory recordings are thus often unrewarding. Nonetheless, Holter monitoring is recommended for patients with a high pretest probability of arrhythmias, such as patients with structural heart disease, an abnormal ECG, brief sudden loss of consciousness without a prodrome, or palpitations associated with syncope. Holter monitoring is most likely to be informative in patients with frequent (virtually daily) episodes of presyncopal symptoms. Nondiagnostic arrhythmias found during Holter monitoring (i.e., those not correlated with symptoms of presyncope or syncope) usually do not require treatment; this issue frequently arises with regard to premature ventricular complexes, which are commonly seen in the normal population (see Chap. 3).
- **Event Monitors** (see Chap. 3) are useful when patients have presyncopal symptoms every few days to weeks. The devices commonly utilize a "memory loop" to store ongoing ECG signals, which can be "frozen" into memory by patient activation (in response to symptoms) and subsequently retrieved for transtelephonic transmission and analysis. Event monitors are typically used for 2- to 4-week periods at a time and are therefore more likely than the Holter monitors to capture an arrhythmia. Loop-type monitors are especially valuable for detecting fleeting arrhythmias. In about 8–20% of patients, event monitors detect arrhythmias with symptoms; in an additional 27%, symptoms are present without arrhythmias [31]. Patients who use event monitors usually must be capable of activating the device and performing the transtelephonic transmissions; the former capability is not necessary when an "auto-triggered" device with prespecified rate criteria is utilized. Patient-activated event monitoring is a particularly useful diagnostic modality when syncope is associated with prodromal palpitations or dizziness, or when there are also episodes of near-syncope. For syncope that occurs suddenly, however, the patient is not likely to have time to signal a symptom; in these cases, an "auto-triggered" device is the preferred type of event monitor.
- **Implantable Loop Recorders** are helpful in recurrent syncope that is undiagnosed after initial investigations including Holter monitoring and electrophysiologic testing [32]. These subcutaneous implantable recorders allow electrocardiographic monitoring for periods up to 18 months. The devices are single-lead ECG systems and, when activated by patients, can store rhythms recorded for several minutes before and after the device is activated. Newer generation devices can be programmed to record rhythms automatically, on the basis of prespecified upper and lower rate thresholds. As with pacemakers and ICDs, the stored recordings can be retrieved by radiotelemetry-based interrogation of the device. More important, implantable loop recordings can lead to a correct diagnosis, thereby avoiding misdirected therapy

Table 5.6 ACC/AHA recommendations for ambulatory electrocardiography

Class I: There is evidence and/or general agreement that ambulatory electrocardiography is useful and effective
Patients with unexplained syncope, near syncope or episodic dizziness in whom the cause is not obvious
Class IIb: Usefulness/efficacy is less well established by evidence/opinion
Patients with symptoms such as syncope, near syncope, episodic dizziness or palpitation in whom a probable cause other than an arrhythmia has been identified but in whom symptoms persist despite treatment of this other cause
Class III: There is evidence and/or general agreement that the ambulatory electrocardiography is not useful and in some cases may be harmful
Patients with symptoms such as syncope, near syncope, episodic dizziness, or palpitation in whom other causes have been identified by history, physical examination or laboratory tests

ACC/AHA American College of Cardiology/American Heart Association
Adapted from Crawford et al. [30]

that is based on a presumed, but erroneous, cause of syncope.

The 2009 European Society of Cardiology syncope guidelines include the following recommendations for use of ILRs: ILR is indicated for early phase evaluation in patients with recurrent syncope of uncertain origin, absence of high-risk criteria, and a high likelihood of recurrence within the battery life of the device; an ILR is recommended in patients who have high-risk features in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment; an ILR should be considered to assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain reflex syncope with frequent or traumatic syncopal episodes [33].

- **Signal-Averaged Electrocardiogram**: The routine use of signal-averaged ECG is not recommended until further studies are available regarding the utility of this diagnostic modality.
- **Electrophysiologic Testing:** Electrophysiologic (EP) testing (Table 5.7) can aid in uncovering as yet undocumented arrhythmic propensities that may give rise to syncope [34]. EP testing involves intracardiac electrical stimulation and monitoring of electrophysiologic parameters to detect bradyarrhythmias and tachyarrhythmias. Most protocols, for induction of tachyarrhythmias, consist of delivery of up to three extrastimuli at one or two sites in the ventricle. Isoproterenol is used to increase the sensitivity for detecting tachyarrhythmias, but it reduces specificity. Parameters that are usually evaluated include sinus node function, AV conduction, and the inducibility of supraventricular and ventricular arrhythmias. Sustained VT is an important abnormality identified in patients with syncope and structural heart disease [35]. Other abnormalities that can be detected include His-Purkinje block and sinus node dysfunction. By comparison, the induction of nonsustained ventricular tachycardia, polymorphic ventricular tachycardia, and ventricular fibrillation is less helpful, as these findings may be nonspecific and may represent "nonclinical" responses. In patients with structural heart disease, such as coronary artery disease, cardiomyopathy, and valvular or congenital heart disease, the diagnostic yield of this procedure is as high as 50%, whereas in the absence of structural heart conditions, the yield is about 10% [36].

Limitations of EP testing include the possibility of not identifying an arrhythmic cause; lack of informativeness for all patient populations, with poor negative predictive value in patients with reduced left ventricular function [37]; and possible detection of multiple abnormalities, with difficulty in proving which is etiologic for syncope. A negative EP test result (with no demonstrable induction of sustained VT or ventricular fibrillation) is generally predictive of a low risk of sudden death [38]. However, unexplained syncope in nonischemic dilated cardiomyopathy may still reflect an occult propensity to ventricular tachyarrhythmias despite a negative EP study result; indeed, prophylactic implantable defibrillators have been shown to reduce mortality rates in this setting [39, 40].

Patients whose hearts appear normal clinically, with normal ECG and normal echocardiogram, should rarely undergo EP testing, whereas patients with structural heart disease, such as myocardial infarction or congestive heart failure, or those with other anatomic abnormalities that might predispose to arrhythmic syncope (e.g., Wolff-Parkinson-White syndrome) should be considered for the procedure early in the diagnostic cascade. Although EP tests are relatively safe in the assessment of syncope, fewer than 3% of the patients may develop significant morbid conditions, including cardiac perforation, arteriovenous fistula, pulmonary embolism, and myocardial infarction [36].

- **Pacemakers and Implantable Cardiac Defibrillators:** These devices must be tested when device malfunction is suspected.
- **Routine Nonselective Neurologic Testing:** These types of tests, such as head-computed tomography, electroencephalogram, and carotid Doppler studies, are all too often performed routinely. These laboratory evaluations rarely provide diagnostic information unless clinical features suggest a neurologic condition; therefore, they should be selectively performed as directed by clinical data.
- **Psychiatric assessment** is usually made only after other investigations have excluded structural heart disease. In such cases, the hyperventilation maneuver (open-mouthed deep respiration for 2–3 min for possible precipitation of syncope) and other screening instruments for mental disorders may be useful [41].

Table 5.7 ACC/AHA recommendations for electrophysiologic testing

Class I: There is evidence and/or general agreement that electrophysiologic testing is useful and effective
Patients with suspected structural heart disease and syncope that remains unexplained after appropriate evaluation
Class II: There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of electrophysiologic testing
Patients with recurrent unexplained syncope without structural heart disease and a negative head-up tilt test
Class III: There is evidence and/or general agreement that the electrophysiologic testing is not useful and in some cases may be harmful
Patients with a known cause of syncope for whom treatment will not be guided by electrophysiologic testing

ACC/AHA American College of Cardiology/American Heart Association
Adapted from Zipes et al. [34]

When to Admit, When to Refer, and to Whom

The threshold for admitting a patient with syncope is relatively low (Table 5.8). All patients with a first episode of syncope—excluding a classic case of vasovagal syncope in a young patient with history and physical examination findings negative for any acquired or familial cardiac disorder and with a normal ECG—should be referred to the exclude life-threatening conditions as discussed earlier. Patients with recurrent syncope may also require hospitalization for a variety of reasons—for example, if their syncope has not previously been evaluated or treated, especially if cardiopulmonary disease is suspected or there is an untreated known or suspected arrhythmic cause; if there is a family history of sudden death; if there is a history of or concern regarding possible secondary injury; if the recent clinical events represent failure of treatment for syncope (especially of cardiac origin); or if pacemaker or ICD malfunction is suspected [4]. Patients with recurrent syncope that remains unexplained after initial medical evaluation or with syncope of known or suspected cardiac origin, should be referred to a cardiologist or electrophysiologist to aid in the in the diagnosis and management of the patient.

Table 5.8 ACP indications for hospital admission in patients with syncope

Indicated (associated with such adverse outcomes as myocardial infarction, stroke, or arrhythmias)
History of coronary artery disease, congestive heart failure, or ventricular arrhythmia
Accompanying symptoms of chest pain
Physical signs of significant valve disease, congestive heart failure, stroke, or focal neurologic disorder
Electrocardiographic findings: Ischemia, arrhythmia (serious bradycardia or tachycardia), increased QT interval or bundle branch block
Often indicated
Sudden loss of consciousness with injury, rapid heart action, or exertional syncope
Frequent spells, suspicion of coronary disease or arrhythmia (for example, use of medications associated with torsade de pointes)
Moderate to severe hypotension
Older than 70 years of age

ACP American College of Physicians
Adapted from Linzer et al. [36]

Syncope and Driving

Although the incidence of syncope-related motor vehicle accidents is low [4, 41], syncope can have devastating consequences on the patient and others involved in such an accident. Therefore, when a patient is undergoing evaluation for syncope, the physician must carefully consider the implications regarding driving restrictions, taking into account pertinent laws of the relevant state or country, the chances of recurrent syncope, whether syncope occurs when the patient is standing up or on sitting down, and the presence of a prodrome (which might give the patient time to avoid injury). Guidelines for determining length of driving restrictions, if any, are available [42].

Conclusions

The approach to syncope requires that both the science and art of medicine come together. A major challenge in the evaluation of syncope is that it is a transient symptom, not a disease, with causes ranging from benign to life-threatening. There is rarely an opportunity to capture a spontaneous episode during diagnostic evaluation, and there is no gold standard test for establishing the diagnosis. Syncope in the elderly is especially problematic, in view of its multifactorial causation. However, with the appropriate use of history, physical signs, and diagnostic tests (Fig. 5.3), patients with life-threatening syncope can be identified with a high degree of accuracy, and a diagnosis can be established, overall, in about 75% of patients with syncope [43]. This allows appropriate treatment to be initiated in these patients. For those in whom syncope recurs without clear explanation, especially after institution of what initially appears to be appropriate therapy based on thorough evaluation, further observation and investigation over time (e.g., through use of an implantable loop recorder) may reveal the underlying cause.

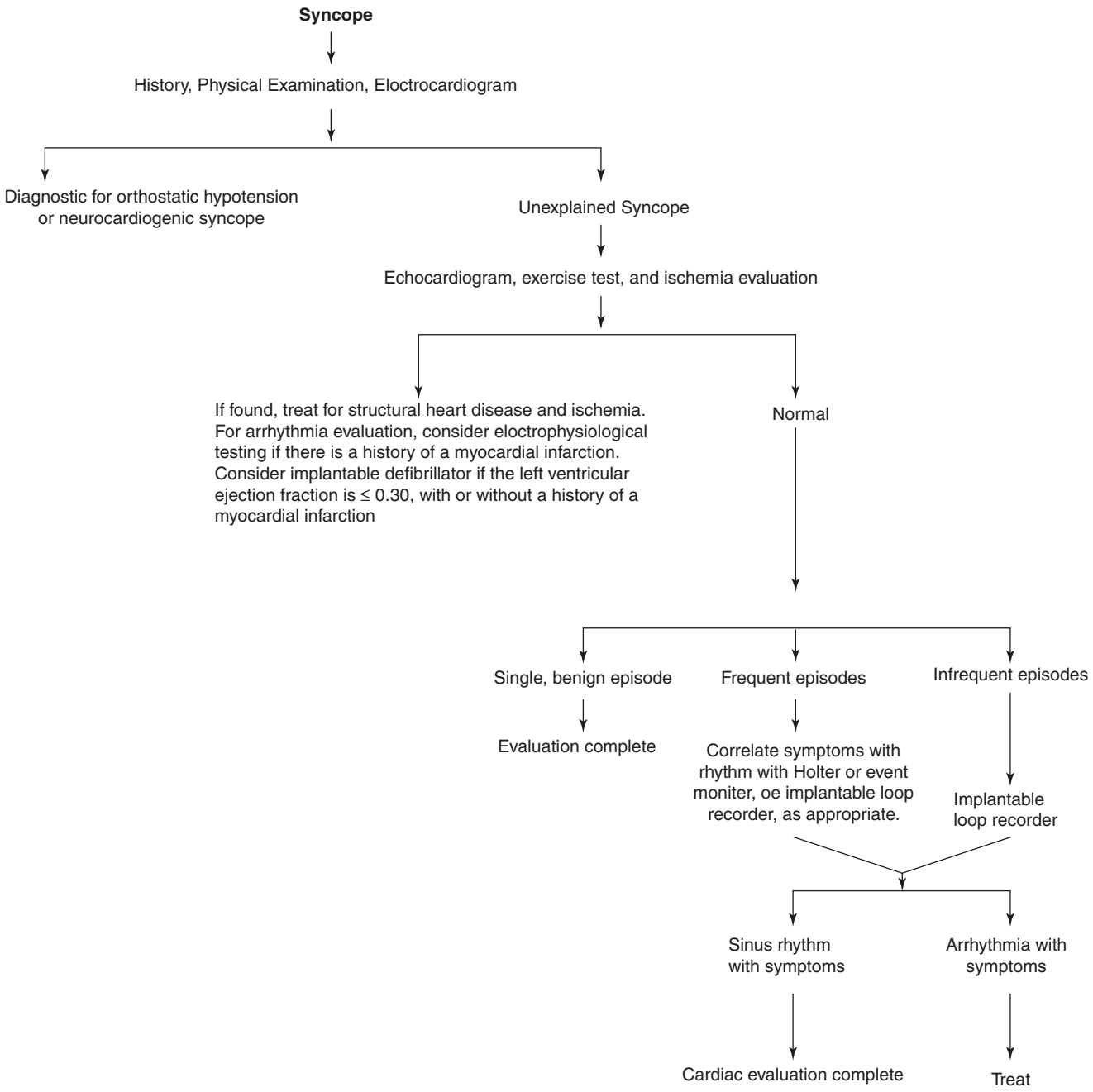

Fig. 5.3 Flow chart for the diagnostic approach to the patient with syncope. (From Strickberger et al. [45]; with permission)

Practical Points

- Patients with a first episode of syncope should evaluated for life-threatening conditions.
- The multifactorial origin of syncope in the elderly often necessitates management approaches aimed at correcting many of these factors simultaneously.
- Key questions during initial evaluation include the following: (a) Is the loss of consciousness attributable to syncope or another cause? (b) Is cardiac disease absent or present? (c) Are there clues in the history suggesting the diagnosis? (Brignole et al. 2004 [4]).
- After return of consciousness, rapid restoration of normal sensorium is the rule in syncope, whereas persistent confusion (more than 5 min) suggests a seizure.
- Ventricular arrhythmias should be suspected in patients with underlying structural heart disease, particularly ventricular involvement.
- ECG findings suggestive of an arrhythmic cause of syncope include sinoatrial dysfunction; second- or third-degree AV block; bifascicular block; Q waves (prior myocardial infarction); delta wave; prolonged QTc; Brugada sign; and right precordial T wave inversion with epsilon wave (ARVD).
- Evaluation for LQTS should include manual measurement of QTc and a search for T wave morphologic abnormalities (e.g., "notches" in left precordial or limb leads or both).
- Event monitors have a higher yield than do Holter monitors for identifying possible arrhythmic causes of near syncope.
- Electroencephalogram, head computed tomographic scan, and carotid ultrasonography should be reserved for cases of syncope in which clinical features suggest a neurologic etiology.
- Patients with clinically normal hearts and with normal ECG and echocardiogram should rarely undergo EP testing, whereas patients with structural heart disease, such as myocardial infarction, congestive heart failure, or ventricular preexcitation, should be considered for the procedure early in the diagnostic cascade.
- Implantable loop recorders are helpful in documenting recurrent but infrequent syncope that is undiagnosed after initial investigations, including Holter monitoring and electrophysiologic testing.

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Primary Prevention of Coronary Artery Disease

6

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The advances in the detection and management of cardiovascular diseases (CVDs) have resulted in a 31% decline in the death rates attributable to CVD in the United States from 2001 to 2011 [1]. Coronary, or ischemic heart disease (CHD), is the largest contributor to CVD mortality. Deaths from CHD have declined in both men and women [2], however CVD and CHD still account for 31.3% of all deaths in the United States [1]. Eighty-six million Americans have CVD [1]. Nearly 800,000 people died of CVD in 2011 [1]. Each year, approximately 600,000 men and women will experience a first myocardial infarction (MI) and about 800,000 will have a stroke [1]. In addition, CVD is the leading cause of death worldwide, accounting for 17.5 million deaths/year in 2012 and is expected to rise to 22.2 million deaths/year by 2030 [3].

Observational studies and randomized trials provide evidence that lifestyle changes and drug therapies can reduce coronary events, strokes, and mortality rates in asymptomatic men and women [4]. Clearly, if CHD can be detected in the preclinical stage and a high percentage of those destined for an acute event can be identified by risk stratification, a considerable amount of the related disability and death is preventable. Effective coronary disease prevention requires five major steps: (a) a society willing to pay for prevention, (b) accurate knowledge of the pathobiology of atherosclerosis, (c) an understanding of the contributing risk factors and risk markers, (d) a method of reliable risk stratification or early detection, and (e) safe and effective therapy for risk factors and preclinical disease.

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Pathobiology of Atherosclerosis

Atherosclerosis is a systemic vascular disease involving the aorta and the coronary, carotid, and peripheral arteries. It is the result of inflammation in response to endothelial injury by one or more risk factors, such as hypertension, oxidized low-density lipoprotein (LDL),smoking, and infection [5]. The earliest lesions, fatty streaks, are found in some children and in all men and women between the ages of 15 and 34 years who die of noncardiac causes. Diffuse nonocclusive coronary plaque has been found in 25–50% of young people at postmortem examination and by intravascular ultrasonography [6, 7], and the amount of fatty streaks and plaque correlates with the prevalence of classic coronary risk factors [6].

At least six major processes occur in the development of atherosclerotic plaque (atheroma), and each is a potential therapeutic target: (a) injury of the endothelial lining, which facilitates entry of monocytes and adherence of platelets and microthrombi that release growth factors; (b) active and passive transport of LDL and very low density lipoprotein (VLDL) remnant particles into the subendothelial space, followed by lipid peroxidation; (c) conversion of monocytes to macrophages that ingest oxidized LDL and transform to lipid-engorged foam cells that coalesce into fatty streaks; (d) inflammatory T lymphocyte response and release of cytokines and chemotactic proteins that stimulate smooth muscle cells to migrate to the intimal layer and convert from contractile to secretory function; (e) smooth muscle cells and fibroblasts, which provide a matrix skeleton of collagen, fibrin, and calcification; and (f) spontaneous death or digestion of foam cells with release of cholesterol and other lipids to form a lipid pool [5, 8].

Histological evidence suggests that plaque growth may be gradual over years with bursts of growth from periodic intraplaque hemorrhage and repair. The predominant type of plaque in individuals is a major determinant of risk of acute coronary events [8, 9] demonstrates the two extremes of plaque morphology. Angina pectoris and stress-induced ischemia are usually caused by flow-limiting, partially occlusive,

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stable coronary stenosis composed of fibrocalcific plaque abundant in smooth muscle and fibrous tissue with or without a lipid pool. There is both clinical and pathologic evidence that most acute coronary events are the result of an occluding or partially occluding thrombus at the site of a vulnerable plaque in nonocclusive coronary segments [9]. The vulnerable plaque has a large lipid pool and a thin fibrous cap that can rupture, often at the junction of the plaque and normal wall, which results in unstable angina, MI, and sudden death [9].

Calcification is uniformly present in early and mature plaque and begins in the second and third decades [10]. The calcium is present as a hydroxyapatite identical to that found in bone. There is a highly significant relationship between calcium plaque area and atherosclerotic plaque area as measured histologically, and calcium accumulation is more prevalent in complex plaques that may have undergone rupture and healing [11]. As with other factors associated with atherosclerosis and the response to injury hypothesis, it is highly likely that the amount of calcification of plaque is regulated or influenced by several related and unrelated genes.

The arterial *endothelium* provides a protective vascular barrier and produces a wide variety of peptides involved in regulating vascular tone, thrombosis, and cellular adhesion, migration, and growth. Nitric oxide (NO·) and prostacyclin are released in response to wall shear stress and autonomic tone. Prostacyclin, acting through the cyclic adenosine monophosphate (AMP) pathway, and NO·, acting through the cyclic guanidine monophosphate pathway, are vasodilators with antithrombotic, antiplatelet, antiproliferative, and antioxidant functions. The formation and release of prostacyclin and NO· by the endothelium is impaired in all stages of coronary atherosclerosis in conduit vessels with or without plaque and in the intramyocardial resistance vessels.

Risk Factors and Risk Markers

Coronary risk factors (CRF) are defined as factors whose presence are associated with or are correlated with an increased likelihood that disease will be present at a later time [12]. The test of whether a given factor is independent of others and causative generally requires a graded response [e.g., level of LDL cholesterol (LDL), tobacco], time exposure (decades), and a response to treatment in placebo-controlled trials (hypertension, cholesterol). However, controlled trials are not always possible or necessary. Observational studies provide adequate evidence of the benefits of smoking cessation, exercise, and weight control. A very large international study (nearly 30,000 cases and controls) known as INTERHEART found that the potentially modifiable risk factors associated with a myocardial infarction did not differ by ethnicity or country of origin and that 90% of the population attributable risk for incident acute myocardial infarction is attributable to nine easily measured (and potentially reversible) risk factors: smoking, lipids, hypertension, diabetes, obesity, diet, physical activity, alcohol consumption, and psychosocial factors [13].

Family history of premature CHD is a major risk factor, but the mechanism is usually illusive or multifactorial. Seventy-five percent of the CHD risk attributed to family history may relate to lifestyle factors, including smoking, diet, obesity, and physical inactivity. There is also evidence for a strong interaction between genetic polymorphisms and the risk attributable to lifestyle.

Risk factors can be divided into three major categories: (a) causal, (b) conditional, and (c) predisposing.

Causal risk factors include smoking, hypertension, diabetes mellitus, and elevated LDL. Each factor can be considered to have a continuum of risk from an optimal value (e.g., blood pressure lower than 140/90 mmHg with risk increasing for every unit, quartile, or decile), can be considered a categorical risk (e.g., smoking or not), or can be defined by a cut point (blood pressure higher than 140/90 mmHg). The presence of risk factors substantially increases one's risk for CVD. Data from the Cardiovascular Lifetime Risk Pooling Project, which involved 18 cohort studies and combined data on 257,384 black men and women and white men and women, found that those with optimal risk factor profiles had a substanstantial lower lifetime risk of CVD compared with those with 1 major risk factor (1.4% versus 39.6% among men; 4.1% versus 20.2% in women) [14]. Having ≥2 major risk factors further increased lifetime risk to 49.5% in men and 30.7% in women. Diabetes is a particularly strong risk factor, possibly because of its association with other risk factors such as hypertension, low HDL, small LDL particle size, and increasing triglyceride levels. The absolute risk of CVD in diabetics is two-fold greater than in non-diabetics [15].

Conditional risk factors [e.g., psychosocial (depression, stress, low locus of control) homocysteine, C-reactive protein, and lipoprotein (a)] are associated with an increased risk for CHD, but the causal link to CHD is uncertain. The uncertainty may be due to their having less influence than the major risk factors, their low frequency, or a required interaction with other factors that is yet unknown.

Predisposing risk factors generally intensify causal risk factors or conditional risk factors and may be independent and causal but in unidentified ways (e.g., family history, marital status, ethnicity, education and other socioeconomic factors).

Risk Stratification

Intensity of preventive efforts is determined by an individual's risk for CVD. This has been the foundation of guidelines in the prevention of CVD for many years. In 2013, the

American College of Cardiology/American Heart Association (ACC/AHA) published the ACC/AHA Guideline on the Assessment of Cardiovascular Risk, which described Pooled Cohort Equations [16] to be used in conjunction with the jointly released ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [17]. The Pooled Cohort Equations were a novel method designed to assess atherosclerotic cardiovascular disease (ASCVD) risk in the primary prevention population. The Work Group in the publication of the ASCVD risk score acknowledged that the risk score had not been formally evaluated in randomized control trials of screening strategies with CVD events as outcomes. However, they felt this method provided a framework to balance an individual's likelihood of benefit from therapy versus harm.

The prior method of risk assessment, recommended in the Third Report of the National Cholesterol Education Program Expert Pane on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III), relied on the modified Framingham 10-year risk score. The 2013 ACC/AHA Cardiovascular Risk Assessment Guideline authors chose to not retain this method of assessment given its derivation from an exclusively Caucasian population and limited scope in outcome (CHD alone). Rather, the Work Group for the 2013 ACC/AHA Cardiovascular Risk Assessment Guideline authors chose to derive new equations from community-based cohorts that are broadly representative of the U.S. population of Caucasians and African Americans and focused on estimation of first hard ASCVD events (defined as first occurrence of nonfatal myocardial infarction or CHD death or fatal or nonfatal stroke). The final pooled cohort included participants from several large, racially and geographically diverse, modern NHLBI-sponsored cohort studies, including ARIC (Atherosclerosis Risk in Communities) study, Cardiovascular Health Study and CARDIA (Coronary Artery Risk Development tin Young Adults) study, combined with applicable data from the Framingham Original and Offspring Study cohorts. Statistical methods were used to derive and internally validate the Pooled Cohort Equations which provided sex-and race-specific estimates of the 10-year risk for ASCVD for African-American and Caucasian men and women 40 to 79 years of age. The variables that were statistically relevant to the equations were age, total and HDL-cholesterol, systolic blood pressure, diabetes and current smoking status. A downloadable spreadsheet, web-based calculator and "app" for smart phones were made available to ease of the risk equations. The 2013 ACC/AHA Cardiovascular Risk Assessment Guideline authors recognized that extrapolation of these equations to non-Hispanic whites and Asian-Americans had not been validated and further work was needed to create risk prediction equations in these populations. The 2013 ACC/AHA Cardiovascular Risk Assessment Guidelines are to be used in conjunction with the 2013 ACC/AHA Blood Cholesterol Guidelines to determine lipid management of an individual.

The National Lipid Association (NLA) Recommendations for Patient-Centered Management of Dyslipidemia advocate a different approach to risk assessment [18]. In these guidelines, the number of individual's risk factors is ascertained, with increasing risk factors corresponding to increased risk. In addition, the ATP III Framingham risk score and the 2013 Pooled ASCVD Risk Equations are recommended for risk assessment.

Risk Markers

The 2013 ACC/AHA Cardiovascular Risk Guideline examined new risk markers [16]. These included several blood and urine biomarkers (high sensitivity C-reactive protein [hsCRP], apolipoprotein B [ApoB], creatinine [or estimated GFR] and microalbuinuria), several measures of subclinical cardiovascular disease (calcium score, carotid intima media thickness [CIMT] and ankle brachial index), family history and cardiorespiratory fitness. It was the opinion of the 2013 ACC/AHA Cardiovascular Risk Guideline authors that assessments of family history of premature CVD, measurement of hsCRP, calcium score (CAC) and ankle brachial index (ABI) show some promise for clinical utility among novel risk markers, based on limited data. It was noted that measuring ApoB, albuminuria, GFR or cardiorespiratory fitness is of uncertain value. The use of CIMT in routine clinical practice was not recommended by the 2013 ACC/AHA Cardiovascular Risk Guideline authors.

C-Reactive Protein

There is a correlation between high-sensitivity C-reactive protein (hsCRP) and coronary risk [19, 20]. HsCRP is an acute-phase reactant produced in the liver in response to inflammatory cytokines (interleukins [IL]1 and IL-6 and tumor necrosis factor α) and is a marker or barometer of systemic inflammation at a given point in time. It can be influenced by acute or chronic infections, but the level in healthy persons is relatively stable over years [20]. The standard CRP measurement is not capable of distinguishing coronary risk. The high-sensitivity method (hsCRP), for which laboratory standards have been developed, has a range of normal (0.1 to 8 mg/L; median, 1.6 mg/L; fiftieth percentile, 2.1 mg/L; seventy-fifth percentile, 3.75 mg/L), and the measurement is similar in ethnic groups throughout the world [19, 21]. It is increased by obesity, female gender, estrogens, smoking, any infection or inflammation (including dental),

and diabetes. The JUPITER trial, which randomly assigned patient with an LDL <130 mg/dL and hsCRP ≥2 mg/L to treatment with rosuvastion 20 mg or placebo and demonstrated better outcomes in the treated group [22]. The 2013 ACC/AHA Cardiovascular Risk Guideline consider a individual's hsCRP value ≥2 mg/L to support revising risk assessment upward.

ABI

The *ankle/brachial index* (ABI) is a simple tool that can be used effectively to diagnose vascular claudication as well as detect atherosclerotic disease in asymptomatic men and women older than 55 to 60 years [23]. The ABI is the ratio of the average posterior tibial or dorsalis pedis artery systolic pressure by pulse Doppler on both feet to the Doppler pressure average of both arms. The normal value is 1 to 1.3, and peripheral vascular disease (PVD) is defined by an ABI of less than 0.9. The test is usually performed in vascular diagnostic laboratories, but can be performed after minimal training by medical assistants. Considering that peripheral vascular disease correlates highly with CHD and mortality, it is not surprising an abnormal ABI in men and women older than 60 years is highly correlated with coronary events [23]. The 2013 ACC/AHA Cardiovascular Risk Assessment Guideline recommends that an ABI < 0.9 supports revising an individual's risk assessment of ASCVD upward [16].

Coronary Artery Calcium Score (CAC)

Electron beam computed tomography (EBT) and *multidetector computed tomography* (MDCT) of the chest can detect small amounts of coronary artery calcification present in the very early stage of atherosclerosis. The presence of coronary artery calcium (CAC) is highly sensitive but only moderately specific for the presence of >50% angiographic stenosis [24]. Diagnostic accuracy is improved by using age-and gender-specific thresholds [25]. The absence of CAC, particularly in an asymptomatic patient, is highly predictive of the absence of significant coronary artery stenosis and implies a favorable prognosis [25]. CAC screening, especially for intermediate risk patients, can enhance the prediction of risk in asymptomatic individuals and increase the predictive value of the Framingham risk score [26, 27]. The 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults give a Class IIa recommendation for the measurement of CAC for CVD risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10 year risk) [28]. The 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults also states that measurement of CAC may be reasonable for CVD risk assessment in persons at low to intermediate risk (6% to 10% 10 year risk), as a Class IIb recommendation. The 2013 ACC/AHA Cardiovascular Risk Guideline states that a CAC score > 300 Agatston units or > 75 percentile for age, sex and ethnicity supports revising the risk assessment upwards [16].

Risk Factor Modification

Risk factor modification by lifestyle changes and drug therapies can reduce the risk of CHD and stroke by more than 50% in men and women, regardless of age. An estimated 75% of coronary risk is modifiable by lifestyle changes. Each of the major modifiable causal and conditional coronary risk factors is influenced by lifestyle and behavior.

The 2013 ACC/AHA Blood Cholesterol Guidelines strongly recommend attention to identifying adverse lifestyle patterns and institution of lifestyle change that addresses diet, exercise, and weight management [17].

Smoking

Cigarette smoking increases the risk of MI threefold in men and six fold in women and has an attributable risk more than double that of other risk factors. Smoking is the most important modifiable coronary risk factor and the most preventable cause of mortality from cardiovascular and other diseases. Annually from 2005 to 2009, smoking was responsible for >480,000 premature deaths in the United States among those ≥35 years of age [1]. Almost one third of deaths of CHD were attributable to smoking and second hand smoke exposure. Smoking tobacco can increase the risk of atherosclerosis, coronary events, and stroke by one or more of several mechanisms, including (a) impairment of endothelial function; (b) decrease in HDL and increase in triglyceride levels; (c) increase in catecholamine release with increase in heart rate and vasoconstriction; (d) hypertension; (e) increase in hsCRP, (f) chronic oral or respiratory infection and inflammation; (g) increase in fibrinogen, platelet aggregation, plasminogen activator inhibitor–1 (PAI-1), and thrombosis; and (h) increase in oxidation of lipoproteins. Both active and passive cigarette smoking leads to increased plaque, rate of plaque progression, plague rupture, and acute events [29]. Smoking cessation results in immediate benefit in people of all ages. Commonly used pharmacologic approaches are nicotine substitutes (gum and topical), the anti-depressant bupropion and varenicline, a partial α4β2 nicotinic acetylcholine receptor partial agonist.

Lipids and Lipid Management Guidelines

The effectiveness of lipid lowering treatment (particular with statins) in men and women with and without evidence for vascular disease is among the most convincing and highly proven therapies in medicine. Management of cholesterol is detailed in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (Fig. 6.1) [17]. This guideline represents a major paradigm shift from the prior NCEP ATP III guideline, in which risk assessment was made by assessment of risk factors, use of the Framingham risk score to determine an individual's risk category and the use of LDL and non-HDL targets. Rather, the 2013 ACC/AHA Blood Cholesterol Guideline advocates a new method of risk assessment, using Pooled ASCVD Risk Equations, and the elimination of LDL and non-HDL targets. Instead, in the 2013 ACC/AHA Blood Cholesterol guidelines, four categories of "statin-benefit" groups are identified: (1) those with known clinical ASCVD, (2) those with LDL ≥190 mg/dL, (3) diabetics aged 40–75 years of age, and (4) those with an elevated ASCVD risk score of 7.5% (Table 6.1). These guidelines were stringent in that only data from randomized control trials was included. In addition, they regarded less favorably the use of non-statin medications and multi-drug therapy. They eliminated the concept of "treating to target" as the guideline authors did not feel that clinical trial data is clear on what the target should be and what the magnitude of additional ASCVD reduction that would be achieved with one target lower than another. It also eliminated the concept that "lowest is best," however, acknowledged that future clinical trials may address this question.

The 2013 ACC/AHA Blood Cholesterol Guidelines also made no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II-IV ischemic heart failure or in patients on maintenance hemodialysis.

The 2013 ACC/AHA Blood Cholesterol Guidelines did recommend additional risk factors that may be considered in determining if an individual should begin a statin: primary LDL-C ≥ 160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years in a first degree male relative or < 65 years in a first degree female relative, hsCRP ≥2 mg/L, CAC score, ≥ 300 Agatson units or ≥ 75th percentile for age, sex and ethnicity, ABI < 0.9, lifetime risk of ASCVD or a predicted ASCVD risk score of 5–7.5%.

The 2013 Blood Cholesterol Guidelines state the high-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant may consider the addition of a nonstatinn cholesterol-lowering therapy. The guideline recommended that physicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk reduction benefits that outweigh the potential for adverse effects.

The National Lipid Association's Recommendations for Patient-Centered Management of Dyslipidemia retained the use of LDL and non-HDL targets, based on the level of risk of an individual (similar to NCEP ATP III) [18]. Another major difference between the 2013 ACC/AHA Blood Cholesterol Guidelines and the NLA Recommendations is that the NLA recommendations included evidence from both randomized control trials and observational evidence from epidemiologic studies. The NLA recommendations strongly support the concept of the "LDL and non-HDL hypothesis", in which an elevated level of cholesterol carried by circulating ApoB containing lipoproteins is the root cause of atherosclerosis. In addition, the NLA strongly supports the use of treatment goals as a systematic means to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event and to facilitate communication between physicians and patients. The NLA Recommendations also note additional risk factors that may be considered for risk refinement: (1) a severe disturbance in a major ASCVD risk factor, such as multipack per day smoking or a strong family history of premature CHD, (2) indidcators of subclinical disease, including coronary artery calcium (≥300 Agatston unites is high risk), (3) LDL ≥160 and/or non-HDL ≥190, (4) hsCRP ≥2.0 mg/L, (5) Lipoprotein (a) ≥50 mg/dL, (6) urine albumin-to-creatinine ratio ≥30 mg/g.

Lipid lowering agents encompass several classes of medications—including hydoxymethylglutaryl CoA reductase (HMG CoA reductase) inhibitors or statins, fibrates, bile acid resins, cholesterol absorption inhibitors, and nicotinic acid (Table 6.2). Statins are first-line therapy to lower cholesterol. A number of trials have demonstrated the benefit of statin therapy in both primary and secondary prevention in the prevention of cardiovascular events and in mortality [30, 31]. Several statins are currently available, and include lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin. The mechanism of action of statins is to inhibit HMG CoA reductase, the rate-limiting step in the synthesis of cholesterol. A reduction of intrahepatic cholesterol leads to an increase in LDL receptor turnover, thereby lowering bloodstream levels of LDL. Statins also reduce VLDL production. LDL falls by 30–63% depending on the statin and dosage. HDL modestly rise (about 5%) with statin use. Triglycerides fall by 20–40%. The largest effect on LDL is seen with the initiation of the statin; subsequently doubling of the statin dosage leads to an additional LDL lowering of 6–7%. The 2013 ACC/AHA Blood Cholesterol guidelines classified statins into moderate and high intensity statins based on ability to reduce LDL (Tables 6.2 and 6.3).

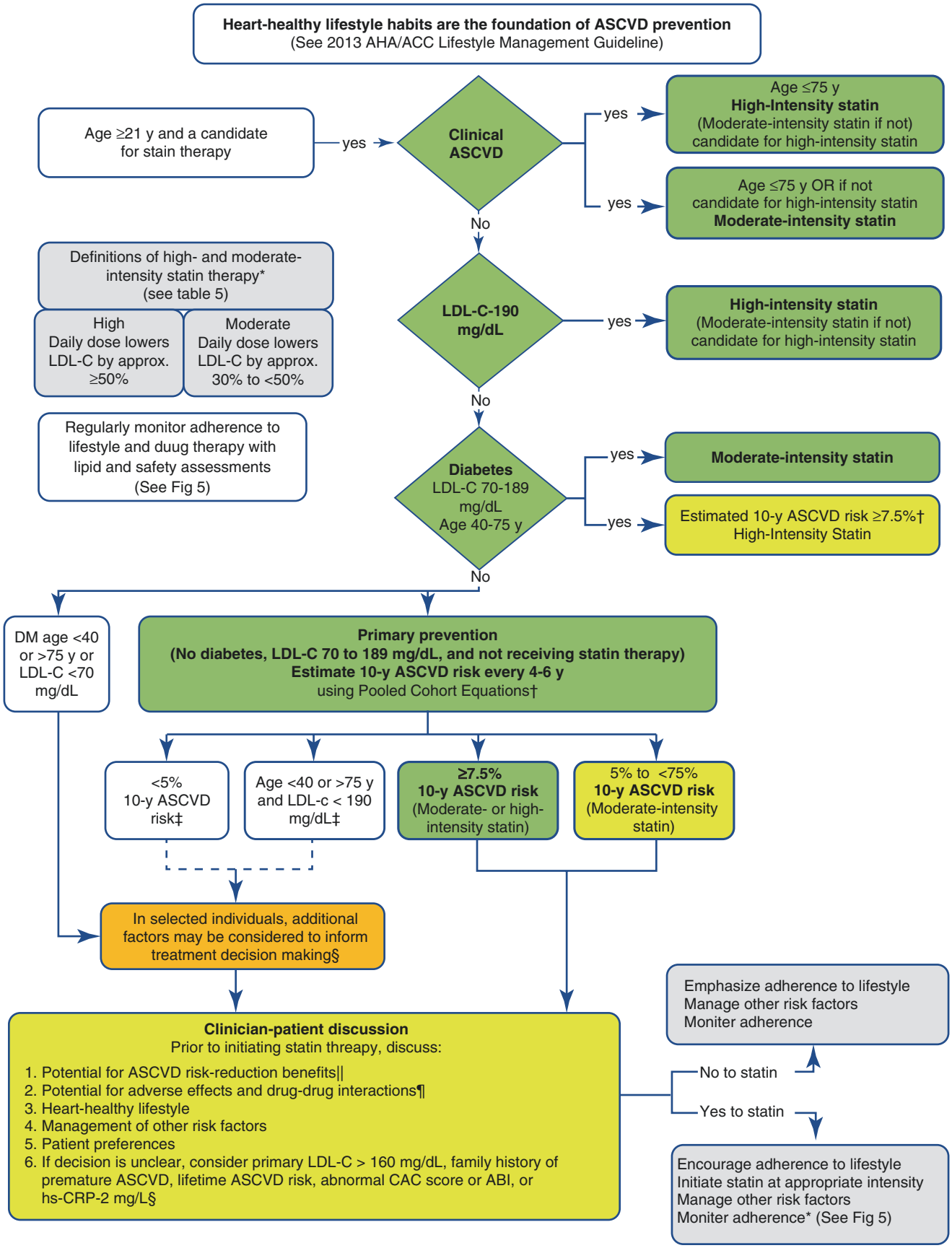
Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)
Age ≥21 y and a candidate for stain therapy
yes
Clinical ASCVD
yes
Age ≤75 y
High-Intensity statin
(Moderate-intensity statin if not) candidate for high-intensity statin
yes
Age ≤75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
Definitions of high- and moderate-intensity statin therapy*
(see table 5)
High
Daily dose lowers LDL-C by approx. ≥50%
Moderate
Daily dose lowers LDL-C by approx. 30% to <50%
LDL-C-190 mg/dL
yes
High-intensity statin
(Moderate-intensity statin if not) candidate for high-intensity statin
No
Regularly monitor adherence to lifestyle and duug therapy with lipid and safety assessments
(See Fig 5)
Diabetes
LDL-C 70-189 mg/dL
Age 40-75 y
yes
Moderate-intensity statin
yes
Estimated 10-y ASCVD risk ≥7.5%†
High-Intensity Statin
No
DM age <40 or >75 y or LDL-C <70 mg/dL
Primary prevention
(No diabetes, LDL-C 70 to 189 mg/dL, and not receiving statin therapy)
Estimate 10-y ASCVD risk every 4-6 y
using Pooled Cohort Equations†
<5%
10-y ASCVD risk‡
Age <40 or >75 y and LDL-c < 190 mg/dL‡
≥7.5%
10-y ASCVD risk
(Moderate- or high-intensity statin)
5% to <75%
10-y ASCVD risk
(Moderate-intensity statin)
In selected individuals, additional factors may be considered to inform treatment decision making§
Clinician-patient discussion
Prior to initiating statin threapy, discuss:
1. Potential for ASCVD risk-reduction benefits||
2. Potential for adverse effects and drug-drug interactions¶
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C > 160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP-2 mg/L§
Emphasize adherence to lifestyle
Manage other risk factors
Moniter adherence
No to statin
Yes to statin
Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Moniter adherence* (See Fig 5)

Table 6.1 ASCVD Statin Benefit Groups

Group	Description	Recommendations
Clinical ASCVD	Acute coronary syndrome History of MI Stable or unstable angina Coronary or other arterial revascularization Stroke TIA Other peripheral arterial disease presumed to be of atherosclerotic origin	1. At age ≤ 75 years, high-intensity statin recommended 2. At age > 75 years, or if not a candidate for high-intensity statin, moderate-intensity statin
LDL-C >190 mg/dL		1. High-intensity statin (moderate-intensity statin if not a candidate for high-intensity)
Diabetes	Type 1 or 2 Age 40–75 years	1. Moderate-intensity statin 2. High-intensity statin if estimated 10-year ASCVD risk ≥7.5%
≥ 7.5% estimated 10-year ASCVD risk and age 4–75 years		1. Moderate-to-high intensity statin

Data from [17]

Potential side effects of statin therapy are hepatic dysfunction and myopathy. Reports of severe hepatic dysfunction are rare. In 2012, the US Food and Drug Administration revised its labeling information to recommend liver function testing prior to statin initiation and only if clinically indicted subsequently. Muscle symptoms are a concern with statin use and range from myalgia to asymptomatic and symptomatic myopathy to rhabdomyolysis. Hypothyroidism and drug-drug interactions (particularly drugs that interfere with CYP3A4) can increase the risk of myopathy. Gemfibrozil, protease inhibitors and cyclosporine require care in the choice and dosage of statin therapy.

Bile acid resins are second-line cholesterol lowering agents. They are colesevelam, cholestyramine, and colestipol. They decrease LDL, do not affect HDL and may increase triglycerides. They act within the intestine to bind bile acids and interrupt the enterohepatic circulation of bile acids; as bile acids are produced, LDL receptor activity on the hepatocyte is increased. This enhances the clearance of LDL from the plasma, decreasing LDL levels. Bile acid resins can decrease LDL by 28%. Their effects on LDL are additive to statins. Their most common side effects are constipation, bloating and heartburn.

Ezetimibe is a cholesterol absorption inhibitor. It blocks the uptake of dietary and biliary cholesterol by intestinal enterocytes. Ezetimibe decreases LDL by 18%, increases HDL by 1%, and decreases triglycerides by about 2%. The effects of ezetimibe are additive to statins.

The most commonly used fibrates are gemfibrozil and fenofibrate. They are primarily used for hypertriglyceridemia. Their mechanism of action is to activate PPAR-alpha. They decrease VLDL and raise HDL. They decrease triglycerides by 20–70%. Fibrates may modestly decrease LDL, but in hypertriglyceridemic patients, LDL may rise. Fibrates may result in gallstones.

Nicotinic acid (niacin) is a vitamin B derivative. Niacin can reduce LDL by 20–25%, reduce triglycerides by 20–25%, and increase HDL by 25–50%. Niacin can decrease lipoprotein(a). In clinical trials, niacin has been shown to reduce total mortality, coronary heart disease mortality, and nonfatal myocardial infarction. Side effects of niacin include

Fig. 6.1 American Heart Association-American College of Cardiology Statin Initiation guidelines for the treatment of blood cholesterol to reduce ASCVD risk in adults. Colors correspond to the classes of recommendation (*green* = class 1, *yellow* = class 2a, *orange* = class 2b). ∗Percent reduction in LDL-C can be used as an indication of response and adherence to therapy but is not in itself a treatment goal. †The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. The estimator within this application should be used to inform decision making in primary prevention patients not on a statin. ‡Consider moderate-intensity statin as more appropriate in low-risk individuals. §For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C 160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, hs-CRP 2 mg/L, CAC score 300 Agatston units, or 75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. ‖Potential ASCVD risk-reduction benefits. The absolute reduction in ASCVD events from moderate- or high-intensity statin therapy can be approximated by multiplying the estimated 10-year ASCVD risk by the anticipated relative risk reduction from the intensity of statin initiated (approx. 30% for moderate-intensity statin or approx. 45% for high-intensity statin therapy). The net ASCVD risk-reduction benefit is estimated from the number of potential ASCVD events prevented with a statin, compared to the number of potential excess adverse effects. ¶Potential adverse effects. The excess risk of diabetes is the main consideration in approx. 0.1 excess cases per 100 individuals treated with a moderate-intensity statin for 1 year and approx. 0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. In RCTs, both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin therapy should be evaluated. *ABI* indicates ankle-brachial index, *ASCVD* atherosclerotic cardiovascular disease, *CAC* coronary artery calcium, *hs-CRP* high-sensitivity C-reactive protein, *LDL-C* low-density lipoprotein cholesterol, *MI* myocardial infarction, *RCT* randomized controlled trial. (Data from open source reference Stone et al. [17])

Table 6.2 Lipid-lowering therapies

Medication	Mechanism of action	Cholesterol effects	Side effects
HMG-CoA reductase inhibitors	Inhibit HMG-CoA reductase	↓ LDL 30–63% ↑ HDL 5% ↓ TG 20–40%	Hepatic dysfunction Myopathy
Bile acid resins	Interrupt enterohepatic circulation, increasing bile acid production, which increases LDL clearance, and decreases plasma LDL levels	↓ LDL 28% ↑ HDL 4–5% Can ↑ TG	Constipation Diarrhea Gas Impairment of fat soluble vitamins
Ezetimibe	Cholesterol absorption inhibitor	↓ LDL 18% ↑ HDL 1% ↓ TG 2%	
Fibrates	Activate PPAR-alpha 1. Increases LPL activity, thereby increasing TG catabolism in VLDL and chylomicrons) 2. Increases HDL 3. Decreased VLDL 4. Decrease Apo CIII	↓ TG 20–70% ↑ or ↓ LDL (in hypertriglyceridemic patients, can ↑ LDL)	GI upset Can interact with statins to ↑ risk of rhabdomyolysis
Niacin	1. Decrease free fatty acid mobilization, leading to a decrease in VLDL 2. Decrease Apo B production 3. Increase HDL	↓ LDL up to 40% ↓ TG 20–25% ↑ HDL 25–50%	Flushing Hepatotoxicity
Omega-3 fatty acids		↓ TG;↑ LDL in hypertriglyceridemic patients	

Table 6.3 High-, moderate- and low-intensity statins

Statin intensity	Description	Name of drug and dose
High-intensity statin therapy	Daily dose lowers LDL-C by approximately 50%	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg
Moderate-intensity statin therapy	Daily dose lowers LDL-C by approximately 30% to <50%	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg
Low-intensity statin therapy	Daily dose lowers LDL-C by <30%	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

Data from [17]

flushing, dry skin, nausea and abdominal pain. Aspirin given a half hour prior to niacin reduces the flushing reaction. The flushing reaction generally improves with time.

Omega-3 fatty acids are useful in patients with hypertriglyceridemia. With high doses of omega-3 fatty acids, triglycerides can fall by 75%. In hypertriglyceridemic patients, omega-3 fatty acids can raise LDL.

A highly anticipated new class of medications is awaiting approval by the Food and Drug Administration. These are the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. They act to inhibit PCSK9, which, when uninhibited, binds to the LDL-receptor, inducing degradation, which results in decreased metabolism of LDL and hypercholesterolemia. Phase II clinical trials have demonstrated dramatic additional lowering of the LDL by 50% when added to a statin. They may be particularly useful in patients with heterozygous familial hypercholesterolemia, patients who are high risk for CVD and not at a desirable LDL level and those who are statin intolerant.

Hypertension

Hypertension is present in about 76.4 million adults in the United States and is a major causal risk factor for CVD, hypertensive heart disease and heart failure, and stroke. A considerable percentage of adults with hypertension have associated obesity and glucose intolerance. The major benefit of antihypertensive therapy is a reduction in stroke and in the consequences of hypertensive heart disease. The reduction of coronary events is less than that anticipated from coronary risk models. Treatment of hypertension requires that the arm blood pressure be obtained in a standardized manner. This includes (a) an appropriate sized cuff; (b) sitting with the arm supported at the level of the heart; (c) inflating the cuff to at least 50 mmHg above expected pressure or 200 mmHg; (d) measuring the pressure in each arm at least once, the final pressure being the higher of the two; (e) repeating the measurement in 2 min and, if there is a significant systolic difference of more than 10 mmHg, repeating again 5 min later; and (f) averaging the second and third measurements. The systolic pressure is the first audible sound heard when the occluding pressure is slowly reduced,

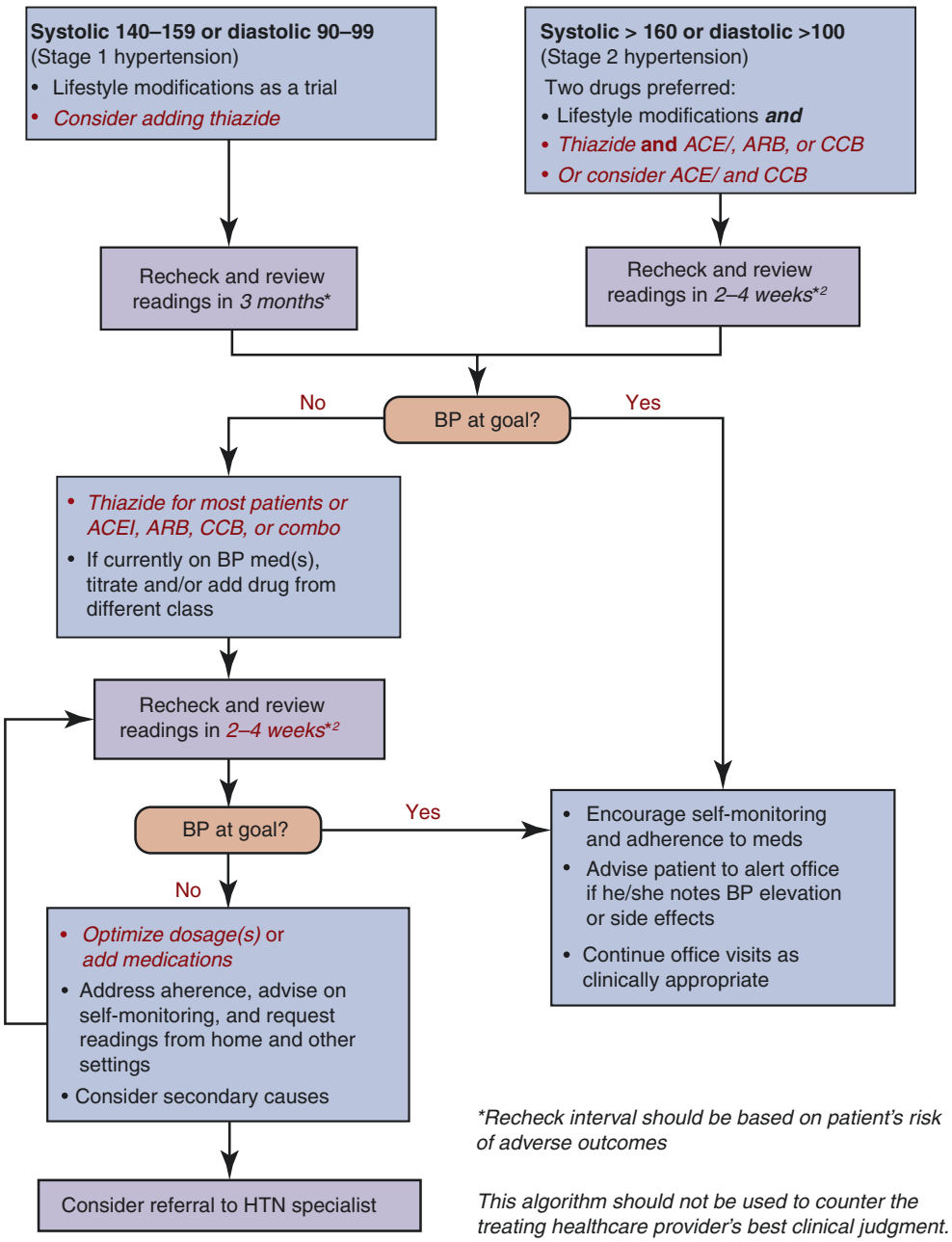

Fig. 6.2 American Heart Association-American College of Cardiology Treatment algorithm for controlling hypertension in adults. (Data from open source reference Go et al. [46])

and the change in sound identifies the diastolic pressure. A continuous increase in CVD risk is attributable to systolic pressures exceeding 120 mmHg and diastolic pressures exceeding 80 mmHg. The definition of hypertension is at 140/90 mmHg or higher (Fig. 6.2).

The JNC VII guidelines recommended screening every 2 years for normotensive and annually for those classified as prehypertensive [32]. Blood pressure control is defined as systolic and diastolic blood pressures <140 and < 90 mmHg, respectively. The recently released JNC VIII guidelines departed from tighter blood pressure limits set in JNC VII in the general population and in the subset of diabetics and elderly (age ≥ 60) [33]. A general target of blood pressure of ≤140/90 has now been applied to (1) those <60 years of age without diabetes or chronic kidney disease and (2) individuals with diabetes and or chronic kidney disease, regardless of age. Individuals >60 years of age without diabetes or chronic kidney disease have a target blood pressure < 150 systolic and < 90 diastolic.

Diabetes Mellitus

Patients with type 2 diabetes without a prior myocardial infarction are at the same risk for myocardial infarction and coronary mortality as patients without diabetes who had a

Table 6.4 Features of the metabolic syndrome

Risk factor	Defining level
Abdominal obesity	
Men	≥40 in. or 102 cm
Women	≥35 in. or 88 cm
Triglycerides	≥150 mg/dL
High-density lipoprotein cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥80 mmHg
Fasting blood glucose	≥100 mg/dL

prior myocardial infarction [34]. In addition to the increased prevalence of CHD among diabetic patients, the extent of the disease is greater at autopsy [35]. In comparison with non-diabetic patients, diabetic men and women have a higher incidence of two- and three-vessel disease (e.g., 83% vs. 17%). The 2013 ACC/AHA Blood Cholesterol guidelines recommend treating individuals aged 40–75 years with diabetes with a moderate to high intensity statin, based on the level of the ASCVD risk score [17].

The *metabolic syndrome,* or the insulin resistance syndrome, is a very common inherited or acquired metabolic trait in which there is insulin receptor insensitivity of all tissues, which results in increasing levels of circulating insulin and an "atherogenic lipid phenotype" of low HDL, high triglyceride levels, increase in LDL and ApoB levels, and small LDL particles [19] (Table 6.4). Persons with any three of the five criteria are characterized as having the metabolic syndrome. A family history of diabetes, hypertension, high triglyceride levels, and abdominal obesity should be considered risk factors for the metabolic syndrome. The metabolic syndrome predisposes to accelerated atherosclerosis, MI, and stroke by the interaction between several associated risk factors, endothelial dysfunction, and a prothrombotic state. The features of the metabolic syndrome are present in diabetic persons 5 to 15 years before carbohydrate intolerance. The characteristic phenotype of the metabolic syndrome may be acquired through long-term obesity, and men with a waist larger than 37 in. should be counseled that they could be genetically predisposed. The importance of early identification of the traits of the syndrome cannot be overemphasized. Regular exercise increases insulin sensitivity and, when combined with weight loss and reduction in body fat by appropriate number and selection of calories, can delay the onset of diabetes and reverse many of the risk factors, including low HDL, hypertension, and elevated triglyceride levels.

Other Considerations

Obesity is not a major independent risk factor, but it contributes significantly to a number of the causal factors. Body mass index (BMI) is the body weight divided by the height squared (kg/m^2). Overweight is defined as a BMI >25 kg/m^2. The risk attributable to obesity is very high with a BMI higher than 40 kg/m^2.

Obesity is generally associated with excessive dietary calories, fat calories, saturated fat, and sugars in the diet and with physical inactivity [36]. Contrary to common beliefs, the energy imbalance leading to weight gain in middle-aged persons is relatively small. The central distribution of body fat ("gut" fat) is a classic coronary phenotype associated with a cluster of risk factors (hypertension, low HDL, small LDL particles, carbohydrate intolerance). Together they are the most virulent contributors to coronary events, stroke, PVD, and end-stage renal disease. The waist circumference is an excellent measure of abdominal fat and is correlated highly with serum insulin level and insulin resistance. Insulin resistance or the metabolic syndrome should be suspected in a patient with a rapidly increasing abdominal girth without much change in weight, in a man with a waist circumference of more than 40 in. (102 cm), and in a woman with a waist circumference of more than 35 in. (88 cm). Weight loss requires restriction of total calories, proper selection of calories, reduction of simple sugars, and exercise. The metabolic syndrome identifies a high risk group for whom life style changes may be very helpful for preventing both CVD and diabetes. Patients should be encouraged to set their own goals for caloric intake and distribution, snacking, and exercise. Severe calorie restrictions are not necessary or sustainable. Exercise should be part of every weight-loss program. Weight reducing medications include sympathomimetics, anorexiants, serotonin-inhibtors, glucagon-like peptide 1 receptor agonists and fat aborption blockers. Examples of anti-obesity medications approved subsequent to 2012 include lorcaserin, phentermine HCL/topiramate extended release, naltrexone HCL/bupropion HCL extended release, and liraglutide. The key to weight loss is moderate caloric restriction (e.g. reduce to 10 cal/pound at ideal body weight) and limiting processed flours and simple carbohydrates and calories from saturated fats.

Physical inactivity is a risk factor for coronary disease, and a high level of fitness is associated with a 30–45% reduction in risk in all-cause and CVD mortality, respectively [37]. A moderate amount of regular exercise reduces CHD risk in previously sedentary men and women. The benefits attributable to regular exercise include improved well-being, lower blood pressure, decreased body fat, increased HDL, lower triglyceride levels, improved carbohydrate tolerance and insulin sensitivity, improved endothelial function, enhanced fibrinolysis, and decreased thrombosis. The ACC and AHA recommend at least 150 min/week of moderate-intensity physical activity, or 75 min/week of vigorous-intensity aerobic physical activity or a combination of both, performed in episodes of at least 10 min, preferably spread throughout the week [38]. The American College of Sports Medicine recommends 30 to

60 min of moderate-intensity exercise 5 days/week or 20 to 60 min of vigorous-intensity exercise 3 days/week) [39]. Walking, in forms such as parking farther away, taking stairs, and using a pedometer (approximately 2000 steps equal one mile), is the most common type of moderate-intensity exercise and has significant health benefits.

Aspirin

Various guidelines have been published in regards to the use of aspirin in the primary prevention of CVD. There is no general consensus and clinician judgment with respect to the benefits of aspirin must be weighed against the potential harms of bleeding. The 2009 United States Preventive Service Task Force (USPSTF) guidelines recommended that in men, ages 45–79 years of age, aspirin use is recommended when myocardial infarction prevention benefit is greater than bleeding risk [40]. However, in women, ages 55–79 years of age, aspirin is recommended when stroke prevention benefit outweighs bleeding risk; cut points are published in these guidelines where benefit of aspirin outweighs risk. The 2009 ACCF/AHA Performance Measures for Primary Prevention of Cardiovascular Disease in Adults guideline recommends that aspirin be used as preventive therapy for men with a 10-year coronary heart disease risk of 10% or more and for women with a 10-year CHD risk of 20% or more [41]. The ADA/AHA/ACCF 2010 Scientific Statement for Aspirin Use for Primary Prevention of Cardiovascular Events in People with Diabetes recommended low dose aspirin for primary prevention of CVD in diabetics who have a 10 year CVD risk of ≥10% and it may be considered in those at intermediate risk [42].

Postmenopausal Estrogens

Estrogen or estrogen/progestin replacement therapy (collectively, hormone replacement therapy) has been shown to reduce cardiac events in observational studies, but benefit was not found in randomized trials in which there was an increased risk of MI, deep vein thrombosis and pulmonary emboli [43]. Hormone replacement therapy should not be prescribed for coronary prevention.

Diet and Nutrient Supplements

Nutrition

The 2013 ACC/AHA Guideline of Lifestyle Management to Reduce Cardiovascular Risk recommends a diet that emphasizes intake of vegetables, fruits and whole grains, includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts and limits intake of sweets, sugar-sweetened beverages and red meats [38]. Achievement of this pattern is recommended by following plans such as the DASH dietary pattern, the USDA Food pattern or the AHA diet. The Mediterranean-style diet, which is moderate in fat, relatively low in saturated fat, high in fiber from fruits and vegetables, and lower in processed flours and simple sugars was shown to reduce CVD risk [44].

Vitamins

Lipid peroxidation is clearly a significant contributor to endothelial dysfunction and the pathogenesis of atherosclerosis, but there is little to no evidence in support of the claims of cardiovascular benefit for supplements of vitamin E, vitamin C, or beta-carotene [45].

Alcohol and Coronary Risk

Moderate alcohol intake is associated with a lower risk of MI in both men and women in observational studies, however there are no randomized control trials evaluating its effect. The benefit seems related to increasing HDL, but also may be an effect of potent antioxidants including bioflavinols (polyphenols) from grape skins. Moderate alcohol intake is defined as 1 drink equivalent of spirits, wine, or beer in women and 2 in men.

Summary

The concept of primary prevention for CHD and atherosclerosis is entrenched in evidence-based trials. Much is known, and there are many more possible targets for therapy according to the current understanding of the pathobiology of atherosclerosis. Management of cholesterol and risk reduction of CVD is detailed in guidelines by the ACC/AHA.

Practical Points

- Atherosclerosis is a systemic vascular inflammatory disease process present in nearly all adults and at least 25% of youths and is triggered by endothelial injury by one or more coronary risk factors.
- *Coronary risk factors* are factors whose presence are associated with or are correlated with an increased likelihood that atherosclerotic coronary disease will be present at a later time.
- The majority of acute coronary events result from rupture of a nonocclusive vulnerable plaque. Prevention strategies are intended to reduce the atherosclerotic burden and increase plaque stability.

- Primary prevention of coronary disease is guided by the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults.
- Detection of coronary calcification by CAC, determination of family history, ABI and hsCRP can be used to supplement risk assessment.
- Evidence-based primary prevention strategies include antiplatelet therapy with aspirin, blood pressure control, and lowering LDL with drugs and with diet, exercise, and smoking cessation.

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Secondary Prevention of Coronary Artery Disease

7

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Introduction

The secondary prevention of coronary artery disease can be defined as a long-term management strategy for patients who have sustained an acute coronary syndrome or have chronic coronary heart disease. Goals of secondary prevention include: (1) long-term survival, (2) enhanced quality of life by restoring and maintaining normal activities and psychosocial function, (3) prevention of recurrent coronary events, and (4) reduction of new lesion formation and rate of coronary disease progression.

Cardiology in the modern era is fortunate to have a large number of well-designed randomized clinical trials, which have addressed many of the issues surrounding coronary disease management, and which can serve to guide rational therapy choices. This chapter will be divided into segments covering each of the strategies and major therapeutic drug classes used in secondary prevention, with specific sections on preventive cardiology services, the elderly, women, diabetes, and compliance.

Rationale for Secondary Coronary Prevention

The pathogenesis of atherosclerosis includes injury to the endothelium or vessel wall and the thrombotic and inflammatory responses to that injury. The degree of injury, the development of occlusive plaque, and the characteristics of the plaque are dependent upon the interaction between lifestyle factors and genetic predisposition that are collectively the "coronary risk factors". Each of the major risk factors and several new risk factors have been associated with abnormal endothelial function in the absence of occlusive coronary disease, and most are risk markers for future coronary events. That the majority of known risk factors associated with acute coronary events and rate of plaque progression are modifiable is the basis for the success of medical management of coronary artery disease (CAD) known as secondary prevention.

The sentinel observations by Dr. Michael Davies in England in the mid-1980s [1] and Dr. Peter Libby in the United States 10 years later [2] have provided extraordinary clarity regarding the pathobiology of acute coronary syndromes. The concept of "rupture of the vulnerable plaque" and the characteristics of the vulnerable plaque initially observed in gross and microscopic pathologic studies have been supported by innumerable studies of ST-segment elevation and non-ST-segment elevation myocardial infarction (MI) and unstable angina using coronary angiography, intravascular ultrasound, and intracoronary angioscopy. The preponderance of coronary events is due to an occlusive or mural thrombus superimposed upon plaque fissuring or rupture of coronary lesions. The characteristics of the vulnerable plaque include a thin fibrous cap, a large lipid pool, decrease in the ratio of smooth muscle and collagen matrix to lipid pool, and a large number of inflammatory cells capable of secreting the matrix metalloproteinases considered a major source of plaque instability. The probability of a clinical event depends on the total plaque burden and the individual response to plaque instability. Each of the evidence-based secondary prevention strategies is designed to reduce thrombosis and enhance thrombolysis, decrease plaque growth and increase plaque stability.

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Clinical Risk Stratification

The risk factors associated with coronary disease are important predictors of long-term prognosis in established coronary disease. The major risks include age, smoking, hypertension, diabetes, total cholesterol, low density lipoprotein cholesterol (LDL), and high density lipoprotein cholesterol (HDL).

Evidence-Based Secondary Prevention Strategies (Table 7.1)

Antiplatelet Agents

The risk of acute coronary syndromes is increased with increasing levels of fibrinogen, platelet count and aggregation, plasminogen activator inhibitor-1 (PAI-1), and tissue plasminogen antigen, and inversely related to plasminogen activator activity. It is therefore not surprising that there is a strong, consistent reduction in MI and stroke risk with antiplatelet medications in CAD. Aspirin, a cyclooxygenase inhibitor, is irreversibly bound to platelets and blocks the formation of platelet thromboxane A2, the potent stimulus for platelet aggregation. Another powerful class of antiplatelet medications are the platelet P2Y12 receptor blockers (clopidogrel, ticlopidine, ticagrelor, prasugrel and cangrelor) which block the binding of adenosine phosphate to a specific platelet report P2Y12, thereby inhibiting the activation of the glycoprotein (GP) IIb/IIIa complex and platelet aggregation. Ticlopidine is rarely used due to its risk of thrombocytopenia, neutropenia and gastrointestinal intolerance.

The benefit of aspirin in secondary prevention was shown in a large meta-analysis by the Antithrombotic Trialists' Collaboration which showed that in patients with acute or prior vascular disease, there was significant benefit in the use of aspirin. Absolute reductions in the risk of having a serious vascular event were 36 per 1000 treated for 2 years among patients with previous myocardial infarction and 38 per 1000 patients treated for 1 month among patients with acute myocardial infarction [3].

Table 7.1 Medications for Secondary Prevention [9, 29]

Medication	Recommendation
Aspirin	1. Aspirin 75–162 daily mg is recommended in all patients with coronary artery disease unless contraindicated 2. Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin
P2Y12 receptor antagonist	1. P2Y12 receptor antagonist in combination with aspirin is indicated in patients after acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) with stent placement 2. For patients receiving a bare-metal stent or drug-eluting stent during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months
ACE inhibitors	1. ACE inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction ≤40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated 2. The use of ARBs is recommended in patients who have heart failure or who have had a myocardial infarction with left ventricular ejection fraction ≤40% and who are ACE inhibitor intolerant 3. It is reasonable to use ACE inhibitors in all other patients
Aldosterone blockade	1. Use of aldosterone blockade in post-myocardial infarction patients without significant renal dysfunction or hyperkalemia is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and beta-blocker who have a left ventricular ejection fraction ≤40% and who have either diabetes or heart failure
Beta-blockers	1. B-blocker therapy should be used in all patients with left ventricular systolic dysfunction (ejection fraction ≤40%) with heart failure or prior myocardial infarction, unless contraindicated. (use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce mortality.) 2. Beta-blocker therapy should be stated and continued for 3 years in all patients with normal left ventricular function who have had a myocardial infarction or ACS 3. It is reasonable to continue beta-blockers beyond 3 years as chronic therapy in all patients with normal left ventricular function who have had myocardial infarction or ACS 4. It is reasonable to give beta-blocker therapy in patients with left ventricular systolic dysfunction (ejection fraction ≤40%) without heart failure or prior myocardial infarction
Statins	1. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men <75 years of age who have clinical ASCVD, unless contraindicated 2. In individuals with clinical ASCVD, in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated 3. In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it

Aspirin therapy is one of the most intensively studied and well-accepted strategies for the prevention of recurrent cardiovascular events. In the Antithrombotic Trialists' Collaboration meta-analysis, there was no difference in efficacy or safety between doses of 75 to 150 mg/day (called low-dose aspirin) and 160 to 325 mg/day (called medium-dose aspirin) [3]. Enteric coating and lower doses may reduce the risk of peptic symptoms, gastritis, peptic ulcers, and gastrointestinal (GI) bleeding. A valuable, but often overlooked, recommendation in the event of symptoms of myocardial infarction, is chewing a 325 mg ASA, that can be easily carried as four "baby" ASA or one or two ASA in a packet.

In the setting of acute coronary syndrome, a loading dose of 162 to 325 mg of aspirin is recommended, which was demonstrated to be of benefit in the Second International Study of Infarct Survival [4] Subsequently, a lower dose of 75 to 162 mg/day of aspirin indefinitely is recommended based on CURRENT OASIS 7 data [5]. In the CURRENT-OASIS 7 trial, there was a prespecified subgroup analysis of the 17,263 acute coronary syndrome patients who underwent early PCI and there was no significant difference in the primary outcome of cardiovascular death, MI or stroke at 30 days, between those who were randomly assigned for 30 days a dose of 300 to 325 mg compared to those given 75 to 100 mg (4.1 versus 4.2 respectively) [6].

Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin.

A P2Y12 receptor antagonist, in combination with aspirin is indicated in patients after ACS or PCI with stent placement. For patient receiving bare-metal stent or drug-eluting stent placement during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily or ticagrelor 90 mg twice daily should be given for at least 12 months [7]. The recommended daily dose of aspirin with ticagrelor is 81 mg. After drug-eluting stent placement for stable coronary disease (in the non-ACS population), clopidogrel is recommended for 12 months if patients are not at high risk for bleeding. In patient receiving bare metal stents for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months [8].

Anticoagulants

Long-term anticoagulation after acute MI is generally limited to a subset of patients at high risk for embolic events. The administration of oral anticoagulation and dual antiplatelet therapy is referred to as triple oral antithrombotic therapy. Patients with chronic atrial fibrillation after myocardial infarction, should be treated with anticoagulation to reduce the risk of embolic events. In addition, patients with prosthetic heart valves and those receiving preventative management or treatment of venous thromboembolism, such as deep vein thrombosis and pulmonary embolism should receive anticoagulation. In patients who are at high risk for embolization post-MI, it is reasonable to begin anticoagulation. These types of patients are those with an acute LV thrombus identified after an MI, or those with an anterior MI and an LVEF <30%.

ß-Adrenergic Blockers

Beta-blockers should be used in all patients with left ventricular systolic dysfunction (ejection fraction <40%) with heart failure or prior myocardial infarction, unless contraindicated. Beta-blockers to be used are carvedilol, metoprolol succinate and bisoprolol, which have been shown to reduce mortality [9]. Beta-blocker therapy should be started and continued for 3 years in all patients with normal left ventricular function who have had myocardial infarction or acute coronary syndrome; it is reasonable to continue beyond 3 years. Beta-blockers may be considered as chronic therapy for all other patients with coronary or other vascular disease. Beta-blockers are effective at reducing the severity and frequency of angina attacks in patients with stable ischemic heart and should be used for this purpose. However, there is no high quality evidence that beta blocker use lowers the risk of death in patients with stable coronary heart disease in the absence of recent MI or heart failure. Two observational studies have found no difference in mortality in this patient population. In the international REACH registry of patients with established CVD, patients were followed for up to 4 years; patients were matched to those with known coronary disease without prior MI who were and were not taking a beta-blocker. After a median follow-up of 44 months, there was no difference in the primary outcome (12.9 versus 13.6 percent) [10]. In a study involving approximately 27,000 patients discharged after a first coronary heart disease event (acute coronary syndrome or coronary revascularization), approximately 20,000 individuals started beta-blockers within 7 days of discharge. During an average of 3.7 years of follow-up, beta-blocker treatment was associated with a 10% lower risk of death in the entire cohort. However, among those without prior MI, there was no difference in the risk of death [11].

Renin Angiotensin Aldosterone System Blockers

Angiotensin converting enzyme inhibitors (ACE) and angiostensin receptor blockers (ARB) decrease cardiovascular mortality in post-MI patients with systolic dysfunction. ACE-inhibitors and ARBs also slow the rate of progression

of proteinuric chronic renal failure, which is more common in diabetics post-MI.

In patients who are s/p acute MI, there is evidence from randomized control trials that ACE inhibitors or ARBs compared to placebo demonstrate an improvement in mortality. A meta-analysis of nearly 100,000 patients from four randomized trials in which ACE inhibitor was started within 36 h of MI, 30-day mortality was significantly lower in treated patients compared to controls [12].

ACE inhibitors are recommended to treat heart failure due to systolic dysfunction because multiple, large prospective, randomized trials have consistently demonstrated a significant reduction in mortality [13]. In addition, ACE inhibitors reduce protein excretion by about 30–35% in patients with nondiabetic or diabetic CKD [14].

Accordingly, the 2011 AHA/ACCF Secondary Prevention Guidelines recommend that ACE inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction <40% and in those with hypertension, diabetes, or chronic kidney disease as a Class I indication [9]. ARBs may be substituted in those who are ACE-intolerant. The routine use of ACE-I in all other patients with CVD or CVD risk factors is debated. Older trials such as HOPE [15] and EUROPA [16] demonstrated an approximately 20% risk reduction in CV events that was not solely dependent on blood pressure lowering effects. However, more recent data are equivocal in terms of CV risk reduction with ACE-I [17]. Therefore, the 2011 AHA/ACCF Secondary Prevention Guidelines recommend that it is reasonable to use ACE inhibitors in all other patients.

Aldosterone blockade benefits patients with systolic heart failure, possibly due to the effects of increasing the potassium levels and blockade of the deleterious effects of aldosterone on the heart. The 2011 AHA/ACCF Secondary Prevention Guidelines recommend that aldosterone blockade be used in post-MI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and beta-blocker who have a left ventricular ejection fraction of ≤40% and who have either diabetes or heart failure. These recommendations arise from the RALES [18] trial (which found benefit to spironolactone in NYHA class III or IV heart failure patients with LV EF ≤35%), the EMPHASIS-HF [19] trial, which found benefit of eplernone in patients with NYHA class II heart failure and low EF, and the EPHESUS [20] trial, which found benefit to eplernone in patients who were status post recent MI and a left ventricular EF of ≤40%.

Lipid Management

The management of dyslipidemia in secondary prevention is described in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol. Individuals with known ASCVD (atherosclerotic cardiovascular disease) should be placed on a high intensity statin, if under the age of 75 years (over 75 years, a moderate intensity statin is recommended). Clinical ASCVD is defined by the inclusion criteria for the secondary prevention randomized control trials and is defined as acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA or peripheral arterial disease presumed to be of atherosclerotic origin.

A large body of evidence from randomized control trials, spanning many years, demonstrates the benefit of statins in the secondary prevention population in reduction of CVD events and mortality [21–28].

The 2013 ACC/AHA Blood Cholesterol guidelines [29] represent a major departure from the prior set of guidelines, The National Cholesterol Education Guidelines Adult Treatment Panel III (NCEP ATP III) from 2004. No longer was an emphasis placed on lowering LDL to target levels as the authors felt there was insufficient data to target specific LDL (or non-HDL) goals. Rather four "statin benefit groups" were identified and doses of statin medications were recommended, based on statin benefit group. These statin benefit groups are (1) patients with clinical ASCVD, (2) primary prevention in patients with LDL >190 mg/dL, (3) patients with diabetes age 40–75 years, (4) patients without diabetes aged 40–75 years, with a Pooled Cohort Equation assessment of 10-year ASCVD risk ≥7.5% and an LDL 70–189 mg/dL. The 2013 ACC/AHA Blood Cholesterol guidelines drew as its source only data from randomized control trials as opposed to observation data.

Furthermore, the use of non-statin medications to high-intensity statin therapy was discouraged in the 2013 ACC/AHA Blood Cholesterol guidelines, given insufficient data to prove its use. In AIM-HIGH [30], the addition of niacin proved futile in individuals with low HDL and high triglycerides and ACCORD demonstrated the futility of adding fenofibrate in persons with diabetes [31]. Accordingly, pharmacologic intervention to raise HDL is not currently recommended. The 2013 ACC/AHA Blood Cholesterol guidelines do recommend that non-statin therapy, with the best evidence applicable, be considered in patients in whom the expected therapeutic response is not obtained or those who are unable to tolerate statins.

In 2014, the National Lipid Association (NLA) published a set of recommendations for patient-centered management of dyslipidemia. These recommendations differed from the 2013 ACC/AHA Blood in that the sources for its recommendations came from non-randomized control trial data. The NLA recommendations emphasize the causal relationship between LDL, non-HDL and CV risk. As such, LDL and non-HDL targets were retained; at increasing levels of risk, lower levels of cholesterol are recommended.

Similar to NCEP ATP III, a target LDL level of 70 mg/dL was recommended for those with established CVD, along with a non-HDL target of 100 mg/dL. In addition, diabetics with strong ASCVD risk are recommended to achieve LDL target of 70 mg/dL and non-HDL target of 100 mg/

dL. Accordingly, if goals are not met on patients on high-intensity statin, bile acid sequestrants or ezetimibe should be considered for LDL-C lowering.

Preventive Cardiology Services

Cardiac rehabilitation following MI, PCI, and CABG is a routine and necessary component of care. The following indications are now covered by the Center for Medicare and Medicaid Services and many third party payers [32]: (1) Acute MI within the preceding 12 months (2) CABG (3) Stable angina pectoris (4) Heart valve repair/replacement (5) Percutaneous coronary intervention with or without stenting (6) Heart or heart-lung transplant (7) Chronic heart failure. A 2011 meta-analysis of 34 trials that randomly assigned 6111 patients to exercise-based cardiac rehabilitation or no referral, the intervention was associated with a lower risk of all-cause death, a lower risk of reinfarction, improvement in risk factors, including smoking, blood pressure, body weight and lipid profile [33]. In addition to improving hard clinical endpoints, participation improves compliance with prescribed therapies, diminishes the emotional distress that often accompanies cardiac events, and improves overall quality of life. The benefits are seen in men and women of all ages, and studies have shown a particular benefit in the elderly.

Exercise also appears beneficial in patients with stable coronary artery disease. In a trial of 101 men with known coronary disease, participants were assigned to 20 min of exercise daily versus PCI with stenting; at 1 year there was a significant decrease in cardiac events in the exercise group [34]. In observational studies of patients who have undergone PCI, cardiac rehabilitation is associated with 30–50% improvement in mortality [35, 36].

Unfortunately, many barriers exist which lower participation of eligible patients in cardiac rehabilitation programs; only 10–15% of qualified patients participate, with particularly low rates for women [37]. Physicians in the US have traditionally been slow to refer patients to formal rehabilitation programs, and patients are unwilling or unable to participate for various reasons such as logistic or financial constraints, poor motivation, and lack of perceived benefit. Concerted efforts must be undertaken by physicians caring for post-MI patients to refer patients to these programs, facilitate enrollment and encourage compliance, and remove barriers to participation.

Hypertension

Hypertension is defined as systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg on two separate office visits [38]. Prehypertension is defined at systolic 120 to 139 mmHg or diastolic blood pressure 80 to 89 mmHg. An estimated 80 million adults >20 years of age have hypertension, with a prevalence of 32.6% of the United States population [39]. Nationally and internationally, hypertension is a major risk factor for death as it significantly contributes to myocardial infarction and stroke risk. The Eight Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-8 were recently released. In those <60 years of age without diabetes or chronic kidney disease and those of any age with diabetes or chronic kidney disease, a target blood pressure of ≤140/90 is recommended. Individuals >60 years of age without diabetes or chronic kidney disease have a target blood pressure of <150 systolic and < 90 diastolic [40]. The 2011 AHA/ACCF Secondary Prevention Guidelines recommend a target blood pressure of ≤140/90 with blood pressure management by beta-blockers and/or ACE inhibitors [9].

Physical Activity

The ACC/AHA 2013 Guideline on Lifestyle Management recommend at least 150 min/week of moderate-intensity physical activity or 75 min/week of vigorous-intensity aerobic physical activity or a combination of both, performed in episodes of at least 10 min, preferably spread throughout the week [41]. Walking, in forms such as parking farther away, taking stairs, and using a pedometer (approximately 2000 steps equal one mile) is the most common type of moderate intensity exercise and has significant health benefits.

Smoking Cessation

Tobacco use has been directly, causally linked to the development of CVD. The discontinuation of smoking is likely the single most beneficial intervention a patient may undertake in the prevention of CVD. Quitting smoking cuts one's risk of CVD in half [42]. The 2011 AHA/ACCF Secondary Prevention Guidelines recommend a goal of complete smoking cessation by using a strategy of asking, advising, assessing, assisting and arranging for follow-up for all smokers [9].

Diet

The 2013 ACC/AHA Guideline on Lifestyle Management recommends that for patients who would benefit from LDL-C lowering, a diet that emphasizes intake of vegetables, fruits and whole grains is recommended [41]. This should include low-fat dairy, poultry, fish, legumes, nontropical vegetable oils and nuts and limited intake of sweets, sugar-sweetened beverages and red meats. Calories from saturated fats should be limited to 5–6% and calories from trans fat should be reduced. For patients who would benefit from

blood pressure lowering, in addition to the preceding recommendations, a reduction in sodium (no more than 2400 mg of sodium) is recommended.

Weight Reduction

Obesity, particularly central obesity, is a risk factor for CVD. Goal body mass index (BMI) is 18.5 to 24.9 kg/m^2 and goal waist circumference is <35 in. for women, <40 in. for men, with lower cut points in South Asians and East Asians. Obesity is a major risk factor for hypertension, type 2 diabetes and dyslipidemia. In patients with known CVD, there is an obesity paradox such that being overweight or obese may be associated with better outcomes than normal weight.

Diabetes Management

The management of type 2 diabetes includes management of associated risk factors, including hypertension management, weight control, lipid management and the incorporation of adequate physical activity. The 2011 AHA/ACCF Secondary Prevention Guidelines recommend a hemoglobinA1c goal of <7%, keeping mindful to avoid hypoglycemia [9]. However, recent studies indicate that more stringent goals of hemoglobinA1c <6.5% did not result in CVD benefit and may lead to harm [43]. The 2013 American Diabetes Association (ADA) Position Statement recommends a goal <8% in secondary prevention patients [44]. Metformin is one of the only agents demonstrated to reduce CVD events in a randomized control trial [45]; the 2011 AHA/ACCF Secondary Prevention Guidelines recommend it as an effective first-line therapy [9].

Influenza

Patients with CVD should have an annual influenza vaccination. Randomized control trials FLUVACS [46] and FLUCAD [47] demonstrated benefit of the influenza vaccination in secondary prevention patients.

Psychosocial

The 2011 ACC/AHA Secondary Prevention Guidelines list a as a Class IIa recommendation, that for patients with recent coronary artery bypass graft surgery or myocardial infarction, it is reasonable to screen for depression if patients have access to case management, in collaboration with their primary care physician and a mental health specialist [9].

Hormone Replacement Therapy

For many years, hormone replacement therapy was given for the management of post-menopausal symptoms and for the belief that it would lead to the prevention of CVD (based on prior observational studies). However, the Heart Disease and Estrogen Replacement Study (HERS) reported no benefit of HRT on CVD events in secondary prevention, with a signal for harm [48]. Hormone replacement therapy is not recommended for the secondary prevention of CVD in women [49].

Summary

The understanding of the pathobiology of coronary disease has led to many clinical trials that have helped to establish an effective treatment paradigm. As with revascularization, the enthusiasm for prevention regimens must be tempered by rigorous clinical trials and cost analysis prior to wide spread acceptance.

Secondary prevention in stable coronary disease and following acute coronary syndromes involves a multifaceted strategy comprising pharmacologic therapy known to be of benefit, lifestyle and behavior modification, and continued interaction between patients and their physicians. Doctors must act as advocates as well as coaches for their patients in order to maintain adherence to therapeutic interventions.

Practical Points

- Goals of secondary coronary prevention are to increase long-term survival, improve quality of life, prevent recurrent coronary events, and reduce new lesion formation and rate of rupture.
- An understanding of the pathobiology of acute coronary syndromes forms the basis for developing treatment strategies, which can be effective for secondary prevention.
- Evidence-based strategies include pharmacologic therapy with aspirin, B-blockers, ACE inhibitors, a statin, a diet low in saturated fat and high in micronutrients, exercise, stress management, and smoking cessation.
- Treatment with a statin is a cornerstone of effective secondary prevention, because of both lipid and nonlipid effects. Lipid therapy must be individualized, with targeting of HDL-C and triglyceride levels with carefully administered combination in selected persons.
- Preventive cardiology services, including exercise programs, psychosocial interventions, and nutrition

counseling, have demonstrated benefit and are markedly underused in the United States.
- Smoking cessation through a stepped approach remains the most important intervention in secondary prevention of CAD.
- Hormone-replacement therapy with estrogen and with or without progestins for secondary prevention inpostmenopausal women is ineffective and should not be initiated for that purpose, and its discontinuation should be considered.
- Outcomes in the very elderly and in diabetic patients are worse than those in the general population; for that reason, proven therapies should be implemented aggressively in these patients.

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Stable Angina

8

Sharon Roble

Usual Causes

Angina occurs when there is an oxygen demand-supply mismatch in the myocardium. The most common cause of typical angina pectoris is atherosclerotic disease of the epicardial coronary arteries. Other, less common causes include epicardial coronary artery vasospasm, Kawasaki's disease, microvascular coronary disease, aortic stenosis, hypertrophic cardiomyopathy, coronary fistulas, anomalous coronary origins and intramyocardial location (bridging) of epicardial coronary vessels.

Presenting Symptoms and Signs

The definition of typical angina pectoris has three components: (a) substernal chest discomfort with a characteristic quality and duration that is (b) provoked by exertion or emotional stress and (c) relieved by rest or nitroglycerin (NTG). Atypical angina meets two of the three criteria, and noncardiac chest pain meets one or none of the criteria.

Typical angina pectoris is characterized as a feeling of constricting, squeezing, burning, or heaviness. The location of the discomfort may be substernal or interscapular, and it may radiate to the neck, jaw, shoulders, or arms. The typical duration of discomfort is 2–10 min. Discomfort that lasts less than 1 min is unlikely to be angina. Pain that lasts longer than 10 min may be indicative of unstable angina, myocardial infarction (MI), or noncardiac chest pain. Some patients may have dyspnea as an anginal equivalent. Typical angina may be provoked by physical exertion, emotional stress, cold weather, or after heavy meals.

The elderly and women, in particular, present with atypical symptoms more often. Coronary angiography may show insignificant disease but reduced coronary flow reserve may be a cause for inducible ischemia [1–3]. Diabetics are more prone to have episodes of silent ischemia and need intense care and evaluation. The Canadian Cardiovascular Society Classification System (CCS) is employed to grade angina pectoris (Table 8.1) [4]. The physical examination findings at rest are usually normal in patients with a history compatible with angina caused by chronic CAD. Patients with angina due to aortic stenosis or hypertrophic cardiomyopathy have a characteristic systolic ejection murmur. Auscultation during chest pain may reveal an S_3 gallop or a systolic murmur of mitral regurgitation secondary to papillary muscle dysfunction.

Table 8.1 Grading of angina pectoris by the Canadian Cardiovascular Society Classification system

Class I
Ordinary physical activity, such as walking or climbing stairs, does not cause angina
Angina (occurs) with strenuous, rapid, or prolonged exertion at work or recreation
Class II
Slight limitation of ordinary activity; angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, under emotional stress, or only during the few hours after awakening;
Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition
Class III
Marked limitations of ordinary physical activity; angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace
Class IV
Inability to carry on any physical activity without discomfort; anginal symptoms may be present at rest

Pathophysiology

Pathophysiology**:** Angina occurs when there is imbalance between oxygen supply and demand. Atherosclerotic plaque causing significant obstruction to flow occurs when luminal obstruction by the plaque is greater than 50% for the Left

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Main artery or greater than 70% for the remaining coronary vessels. Endothelial dysfunction and altered vasomotor reactivity is also present in coronaries affected with atherosclerosis. This leads to impaired vasodilation or even vasoconstriction in response to various stimuli including exercise [5, 6].

Helpful Tests

American College of Cardiology/American Heart Association Guideline Classification

The American College of Cardiology/American Heart Association (ACC/AHA) and the American College of Physicians–American Society of Internal Medicine (ACP-ASIM) jointly published guidelines for the management of patients with chronic stable angina in 1999 [4] and updated these guidelines in 2012 [7]. Diagnostic and therapeutic recommendations are categorized as Class I, II, or III. In Class I conditions, there is evidence or general agreement that a given procedure or treatment is useful and effective. In Class II conditions, there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of a procedure or treatment. For Class IIa, the weight of evidence or opinion is in favor of usefulness or efficacy, and for Class IIb, the usefulness or efficacy is less well established by evidence or opinion. In Class III conditions, there is evidence or general agreement, or both, that the procedure or treatment is not useful or effective and in some cases may be harmful.

The recommended indications for noninvasive testing and coronary angiography fall into two categories: to establish a diagnosis in patients with suspected angina and to risk-stratify patients with chronic stable angina. Left ventricular (LV) function, the presence of inducible ischemia (Table 8.2), and the anatomic extent and severity of CAD are key predictors of long-term survival of patients with chronic stable angina, and they influence decisions regarding revascularization. Left ventricular ejection fraction (LVEF) may be assessed noninvasively by echocardiography, radionuclide techniques, cardiac magnetic resonance imaging (MRI) and cardiac CT angiography or invasively with contrast-enhanced ventriculography during cardiac catheterization. Exercise testing provides additional prognostic information. For example, a low Duke Treadmill score, which combines parameters reflecting exercise capacity, symptoms, and ischemia, is predictive of 4-year survival in 99% of patients tested [4]. The guidelines recommend the inclusion of either an echocardiographic or radionuclide imaging technique in patients with resting ST segment depression, left bundle branch block, ventricular paced rhythm, ventricular pre-excitation or replorization changes from digoxin therapy. Also, patients with physical limitations, such as severe lung disease, arthritis, or peripheral vascular disease, should undergo pharmacologic stress testing in combination with an imaging modality.

Table 8.2 Noninvasive risk stratification

High risk (>3% annual mortality)
Resting or exercise LVEF <35%
Duke treadmill score ≤ −11
Large or multiple stress-induced perfusion defects
Stress-induced LV dilation or increased lung uptake of thallium 201
Echocardiographic evidence of ischemia involving more than two segments at HR <120 or dobutamine infusion ≤10 μg/kg/min
Intermediate risk (1–3% annual mortality)
LVEF 35%–49%
Duke treadmill score < 5 and > −11
Moderate stress-induced perfusion defect without LV dilation or increased lung uptake of thallium 201
Echocardiographic evidence of ischemia involving two or fewer segments at dobutamine infusion >10 μg/kg/min
Low risk (<1% annual mortality)
Duke treadmill score ≥ 5
No or small perfusion defect at rest or with stress
No stress-induced wall motion abnormalities

HR heart rate, *LV* left ventricular, *LVEF* left ventricular ejection fraction

Electrocardiography

A resting 12-lead electrocardiogram (ECG) should be obtained in all patients with symptoms suggestive of angina pectoris. The resting ECG is normal in approximately 50% of patients with chronic stable angina. ST-T changes are usually nonspecific. Q waves may indicate previous MI. LV hypertrophy may be caused by hypertension, aortic stenosis, or hypertrophic cardiomyopathy. Holter monitoring preferably with dual lead or event recording in patients with suspected vasospastic angina is helpful as these patients may have symptomatic or silent episodes of ischemia.

Echocardiography

The resting echocardiogram (Table 8.3) is useful for evaluating global and regional LV systolic function and regional wall motion as well as for identificating any underlying structural heart disease such as aortic stenosis or hypertrophic cardiomyopathy.

Computed Tomography

Electron beam computed tomography (EBCT) is a highly sensitive technique for detecting coronary artery calcification, an abnormality found in atherosclerotic arteries but not

Table 8.3 Indications for echocardiography or radionuclide ventriculography to establish diagnosis and to stratify risk according to Canadian Cardiovascular Society Classification system

Class I
Resting echocardiogram in patients with a systolic murmur suggestive of mitral regurgitation, aortic stenosis, or hypertrophic cardiomyopathy
Resting echocardiogram or radionuclide ventriculogram to assess LV function in patients with history of MI, Q waves, complex ventricular arrhythmias, or symptoms suggestive of congestive heart failure
Class IIb
Resting echocardiogram to diagnose mitral valve prolapse in patients with a click and/or murmur
Class III
Resting echocardiogram in patients with a normal ECG, no history of MI, and no symptoms or signs of heart failure, valvular heart disease, or hypertrophic cardiomyopathy

ECG electrocardiogram, *LV* left ventricular, *MI* myocardial infarction

normal arteries. An ACC/AHA Expert Consensus Document concluded that (a) EBCT has a high sensitivity, a much lower specificity, and overall predictive accuracy of 70% in a typical CAD patient population; (b) the predictive accuracy of EBCT is equivalent to alternative methods for diagnosing CAD; and (c) EBCT is not ideal for diagnosing CAD because of its low specificity [7]. The totality of evidence from the literature indicates that the total amount of coronary calcium predicts coronary disease events beyond standard risk factors. Calcium scoring may be useful (Class IIb, level of evidence B) in refining clinical risk in some patients with intermediate risk for CAD i.e. individuals with a 10–20% 10 year risk on the Framingham Risk Score (FRS). In addition, the Multi-Ethnic Study of Atherosclerosis (MESA) study looked at 10 year coronary heart disease risk in patients using calcium scoring in addition to traditional risk factors and a risk calculator is now available [8]. Patients in this latter category who have high calcium scores may thus qualify for more aggressive target values for lipid lowering therapies [9]. Coronary calcium assessment may also be reasonable in evaluation of (1) symptomatic patients who have equivocal stress tests, (2) patients with a cardiomyopathy of unknown etiology, and, (3) patients with chest pain, negative cardiac enzyme results and negative or equivocal ECGs (all Class IIb, level of evidence B). Asymptomatic persons with low risk scores on conventional risk stratification tools such as FRS, probably do not benefit from coronary calcium assessment (Class III, level of evidence B). Current data do not support serial EBCT studies to assess progression of coronary calcification (Class III, level of evidence C).

Given the invasive nature of cardiac catheterization and the significant number of patients referred for catheterization who have no or minimal epicardial coronary disease, there has been an impetus to explore alternative ways of defining the lumen and walls of the coronary vasculature. Therefore, interest in and use of multi-detector cardiac CT (MDCT) angiography has increased dramatically over the last few years. CT angiography is a reasonable tool to rule out obstructive epicardial coronary disease in symptomatic patients with a low-to-intermediate pre-test likelihood of disease (Class IIa, level of evidence B). Use of CT angiography is currently not deemed "appropriate" when used in asymptomatic persons for the detection of occult disease (Class III, level of evidence C) [9]. A significant limitation of CT angiography is variability in image quality due to motion artifacts (heart rate, ectopy, patient breathing), patient girth and calcification. Another concern with MDCT is the high radiation dose associated with these studies; however with the development of prospective gating techniques, the radiation dose associated with coronary CT angiography now approaches that of a diagnostic cardiac catheterization and remains much less than a radionuclide stress test.

Noninvasive Stress Testing

The predictive accuracy of noninvasive stress testing (Table 8.4) depends on the sensitivity and specificity of the test and the prevalence of the disease in the population studied—that is, the pretest probability of CAD. The exercise ECG is useful in patients with a normal resting ECG and an intermediate pretest probability of CAD, whereas it is less useful in patients with an abnormal resting ECG and/or either a low or high pretest probability of CAD. The inclusion of an imaging technique (i.e., echocardiography or myocardial perfusion imaging) increases the sensitivity and specificity of noninvasive stress testing. Pharmacologic stress testing (e.g., dobutamine echocardiography and adenosine or dipyridamole myocardial perfusion imaging) should be performed in patients who are unable to exercise adequately because of lung disease, peripheral vascular disease, or musculoskeletal disease.

Cardiac Catheterization and Coronary Angiography

Direct referral for diagnostic coronary angiography (Table 8.5) may be indicated in patients with chest pain and either a high pretest probability of severe CAD or a contraindication to noninvasive testing. Coronary angiography is usually accompanied by left-sided heart catheterization to rule out aortic stenosis and by contrast-enhanced ventriculography to assess regional and global LV function. Coronary angiography delineates the extent and severity of CAD and may reveal less common nonatherosclerotic causes of angina, such as Kawasaki's disease, intramyocardial bridging, vasospasm, coronary dissections, coronary fistulas or anomalous coronary arteries.

Table 8.4 Selected indications for noninvasive stress testing to establish diagnosis and to stratify risk according to Canadian Cardiovascular Society Classification system

Class I
Exercise ECG without imaging in patients with an intermediate pretest probability of CAD (see exceptions listed in Classes II and III)
Exercise myocardial perfusion imaging or echocardiography in patients who are able to exercise have an intermediate pretest probability of CAD, and one of the following baseline ECG abnormalities:
Preexcitation (Wolff-Parkinson-White) syndrome
>1-mm resting ST depression
Exercise myocardial perfusion imaging or echocardiography in patients with prior PCI or CABG
Adenosine or dipyridamole myocardial perfusion imaging in patients with an intermediate pretest probability of CAD and one of the following baseline
ECG abnormalities:
Electronically paced ventricular rhythm
Left bundle branch block (LBBB)
Stress myocardial perfusion imaging or echocardiography to identify the extent, severity, and location of ischemia in patients who do not have LBBB or electronically paced ventricular rhythm, or to assess the functional significance of coronary lesions in planning PCI
Class IIa
Patients with suspected vasospastic angina
Class IIb
Exercise ECG in patients with high or low pretest probability of CAD
Exercise ECG in patients taking digitalis or with left ventricular hypertrophy and < 1-mm ST segment depression
Exercise or dobutamine echocardiography in patients with LBBB
Class III
Exercise ECG without imaging in patients with the following baseline ECG abnormalities:
Preexcitation (Wolff-Parkinson-White) syndrome
Electronically paced ventricular rhythm
>1-mm resting ST depression
Complete LBBB
Patients with severe co morbidity that is likely to limit life expectancy or prevent revascularization

CABG coronary artery bypass graft, *CAD* coronary artery disease, *ECG* electrocardiogram, *PCI* percutaneous coronary intervention

Intracoronary ultrasound studies have demonstrated that diffuse coronary atherosclerosis may exit with a "false-negative" coronary angiogram. The hemodynamic significance of a coronary stenosis can be assessed with a Doppler wire or pressure-sensing wire to measure coronary flow reserve (FFR).

Differential Diagnosis

The differential diagnosis of chest pain includes numerous cardiac and noncardiac causes. Common cardiac causes of chest pain not attributable to myocardial ischemia are pericarditis and aortic dissection. Pulmonary causes include pulmonary embolism, pulmonary arterial hypertension, pneumothorax, pneumonia, and pleuritis. Gastrointestinal causes are esophagitis, esophageal spasm or reflux, esophageal tears, peptic ulcer disease, pancreatitis, and biliary tract diseases. Musculoskeletal causes of chest pain are muscular strain or spasm, costochondritis, fibromyalgia, rib fractures, cervical radiculopathy, and herpes zoster. Finally, chest pain may occur in patients with various psychiatric conditions, such as anxiety and affective disorders.

Table 8.5 Selected indications for coronary angiography to establish diagnosis and to stratify risk according to Canadian Cardiovascular Society Classification system

Class I
Patients with known or possible angina who have survived sudden death
Patients with CCS Class III or IV angina despite medical therapy
Patients with high-risk criteria shown on noninvasive testing regardless of anginal severity
Patients with angina and symptoms or signs of congestive heart failure
Class IIa
Patients with an uncertain diagnosis after noninvasive testing in whom the benefit of a more certain diagnosis outweighs the risk and cost
Patients who cannot undergo noninvasive testing because of disability, illness, or obesity
Patients with an occupation requirement for a definitive diagnosis
Patients with a high pretest probability of left main or three-vessel CAD
Patients with LVEF <45%, CCS Class I or II angina, and demonstrable ischemia but less than high-risk criteria shown on noninvasive testing
Class IIb
Patients with recurrent hospitalization for chest pain
Patients with greater than a low probability of CAD and an overriding desire for a definitive diagnosis
Patients with LVEF >45%, CCS Class I or II angina, and less than high-risk criteria shown on noninvasive testing
Class III
Patients with significant co morbidity in whom the risk outweighs the benefit
Patients with CCS Class I or II angina who respond to medical therapy and have no evidence of ischemia on noninvasive testing
Patients who prefer to avoid revascularization
Patients with a personal desire for a definitive diagnosis but a low probability of CAD

CAD coronary artery disease, *CCS* Canadian Cardiovascular Society, *LVEF* left ventricular ejection fraction

Complications

Stable angina can have significant adverse effects on patients' quality of life including negatively impacting an individual's exercise capacity and functional independence. In addition, the evaluation of chest pain has a substantial impact on the health care system both in the inpatient and outpatient setting. The medical complications of stable angina are primarily

those that may ensue from CAD, i.e. progression to unstable angina, myocardial infarction, ischemic cardiomyopathy, congestive heart failure, atrial and ventricular arrhythmias, and sudden death.

Therapy

The goals of treatment are to relieve symptoms and to reduce the risk of morbidity (e.g., MI) and death [1]. Ideally, successful treatment results in a functional capacity of CCS Class I. Contributing factors as anemia, hyperthyroidism and poorly controlled blood pressure should be identified and treated. The initial treatment program consists of the following:

- A: aspirin, ACE-Inhibitors, anti-anginal therapy (nitrates, calcium channel blockers, ranolazine).
- B: beta blockers.
- C: cigarette smoking cessation and cholesterol management.
- D: diet and diabetes therapy.
- E: education and exercise.

Pharmacologic Therapy

Anti-anginal Agents

Nitrates

Parker and Parker have published a detailed review of nitrate therapy (Table 8.6). Sublingual NTG tablets and spray are useful both for treating attacks of angina and for preventing episodes of exertional angina. Multiple long-acting nitrate preparations, including transdermal NTG, oral isosorbide dinitrate, and oral isosorbide mononitrate, have been shown to prolong the time to onset of ischemia during exercise testing. Tolerance, the major limitation of nitrate therapy, can be avoided by dosage regimens that provide a nitrate-free interval. Also, studies have suggested that antioxidant vitamins, such as vitamin C [10] and vitamin E [11], may counteract nitrate tolerance. There is no published evidence to suggest that nitrates change the incidence of death or MI in patients with chronic stable angina.

Table 8.6 Recommendations for pharmacotherapy according to Canadian Cardiovascular Society Classification system

Class I
Aspirin
Beta-blockers in patients with prior myocardial infarction
Calcium antagonists or long-acting nitrates when beta blockers are contraindicated or cause unacceptable side effects
Sublingual NTG or NTG spray for immediate relief of angina
Lipid-lowering therapy to achieve LDL <100 mg/dL
Class IIa
Clopidogrel when aspirin is contraindicated
Long-acting nondihydropyridine calcium antagonists instead of beta blockers
Class IIb
Low-intensity anticoagulation with warfarin in addition to aspirin
Class III
Dipyridamole
Chelation therapy

LDL low-density lipoprotein, *NTG* nitroglycerin

Beta Blockers

The Atenolol Silent Ischemia Study (ASIST) was a double-blind, placebo-controlled, randomized study of atenolol, 100 mg daily, versus placebo in 306 patients with Class I or II angina [12]. The entry criteria included evidence of ischemia during both exercise testing and Holter monitoring. Treatment with atenolol reduced the number and average duration of ischemic episodes recorded during 48 h of ambulatory ECG monitoring. Also, 1-year event-free survival rates were higher among the atenolol recipients than among the placebo recipients. Although ASIST was a relatively small trial, the results suggest that beta blockers may improve the prognosis of patients with chronic stable angina. Beta blockers are relatively contraindicated in patients with vasospastic angina as unopposed alpha receptor activity can induce or exacerbate coronary spasm.

Calcium Channel Blockers

The largest published placebo-controlled trial of a calcium channel blocker in patients with CAD was the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) [13]. The trial was designed to determine whether amlodipine retards progression of atherosclerosis in patients with CAD. Coronary angiography and carotid ultrasonography were performed in 825 patients at baseline and aftery 3 years. Of these patients, 69% had a history of stable angina. During the 3 years of follow-up, there were fewer hospitalizations for unstable angina and coronary revascularization among the amlodipine recipients. There were no differences in mortality or MI rates. Carotid artery atherosclerosis measured by ultrasonography progressed in the placebo recipients but not in the amlodipine recipients. There was no effect of amlodipine on progression of coronary atherosclerosis as measured by coronary angiography.

The Angina Prognosis Study in Stockholm (APSIS) was a long-term study of metoprolol or verapamil in 809 patients with stable angina [14]. Patients were randomly assigned in a double-blind manner to receive either metoprolol, 200 mg daily, or verapamil, 240 mg twice daily. After a median follow-up period of 3.4 years, there were no differences in total mortality, cardiovascular mortality, nonfatal cardiovascular events, or combined cardiovascular events.

The Total Ischaemic Burden European Trial (TIBET) was a long-term study of atenolol, nifedipine, and their combina-

tion in 682 patients with chronic stable angina [15]. Patients were randomly assigned to receive atenolol, 50 mg twice daily; nifedipine, 20 or 40 mg twice daily; or the combination. Exercise parameters improved and ambulatory ischemia decreased in each group, with no differences between the groups. Also, there were no significant differences in the frequency of clinical events.

Heidenreich et al. [16] performed a meta-analysis of trials that compared beta blockers, calcium channel blockers, and nitrates for stable angina. Trials that compared nitrates with either beta blockers or calcium channel blockers were too few to determine their relative efficacy. Although 72 studies that compared beta blockers with calcium channel blockers were identified, the APSIS and TIBET trials discussed previously were the only trials longer than 6 months, and they accounted for 103 of the 116 cardiac events that occurred in all of the trials. Short acting dihydropyridine Ca + antagonists should be avoided in patients with angina.

A more recent prospective double-blind randomized study, the CAMELOT trial, compared the effects of enalapril, amlodipine and placebo on cardiovascular events in patients with established CAD but normal blood pressures [17]. Amlodipine, but not enalapril, significantly reduced the incidence of cardiovascular events compared to placebo, HR = 0.69, p = 0.003. The IVUS substudy showed a significantly reduced rate of atherosclerosis progression (p = 0.02) in a subgroup of patients with systolic blood pressures greater than the mean i.e. 129/78 mmHg.

Ranolazine (Ranexa)

Ranolazine is a recently approved drug for treatment of angina in patients whose symptoms are refractory to conventional drugs and in whom the coronary anatomy is unsuitable for revascularization. There are two mechanisms of action of this drug: (A) prevention of Ca + overload in ischemic myocytes and thus prevention of diastolic tension, and (B) altered cardiac energy metabolism with partial inhibition of fatty acid oxidation with switch to glucose oxidation thus increasing cardiac metabolic efficiency [18]. Several large scale clinical trials have confirmed the efficacy of this drug either as monotherapy or when added to other anti-anginal agents i.e. beta blockers, calcium channel blockers and/or nitrates.

In the ERICA trial 565 patients with stable angina who were on amlodipine 10 mg a day and were allowed long acting nitrates but no B blockers were assigned to ranolazine 1000 mg a day or placebo [19]. Ranolazine significantly reduced the number of anginal episodes per week to 2.88 compared to 3.31 on placebo. In a larger trial consisting of 823 pts. (CARISA) who were either on atenolol or a Ca + channel blocker, Ranolazine significantly increased symptom limited exercise duration, time to ST segment depression compared to placebo [20]. The frequency of anginal episodes was reduced by 0.8 per week on 750 mg twice daily dose and by 1.2 episodes per week on 1000 mg twice daily dose of ranolazine compared to placebo. In the MARISA trial 191 patients were randomly assigned to placebo or monotherapy with three different doses of ranolazine 500, 1000, and 1500 mg twice daily. At all three doses, ranolazine significantly increased exercise duration compared to placebo [21].

Ranolazine can produce QT prolongation and is contraindicated in patients with prolonged QT as well as those on other drugs that can prolong QT interval. However, torsades de pointes ventricular tachycardia has not yet been reported. This drug should be used with caution in patients on digitalis glycosides or simvastatin as ranolazine may inhibit their metabolism. Caution should also be used in patients who are at risk for ventricular arrhythmias for other reasons such as ventricular dysfunction.

Antiplatelet Agents

Aspirin

Several clinical trials have demonstrated that aspirin improves outcome in patients with chronic stable angina. The Physicians' Health Study, a trial of aspirin (325 mg daily) among 22,071 male physicians, included 333 men with chronic stable angina at the time of enrollment [22]. After an average follow-up of 60 months, the incidence of MI was 7 in 178 among patients who received aspirin, in comparison with 20 in 155 among patients who received placebo (relative risk, 0.30; confidence interval, 0.04 to 0.42; $p < 0.001$). The Swedish Angina Pectoris Trial (SAPAT) randomly assigned 2035 patients with chronic stable angina to receive either aspirin, 75 mg daily, or placebo [23]. All patients were treated with sotalol for control of symptoms. After a median-duration follow-up of 50 months, the aspirin recipients had a 34% lower incidence of sudden death and nonfatal MI ($p = 0.003$). There was no significant difference in major bleeding. The guidelines recommend that aspirin, 75 to 325 mg, should be prescribed to all patients with angina and no contraindications [4].

Clopidogrel

Although there are no placebo-controlled trials of clopidogrel in patients with chronic stable angina, clopidogrel was superior to aspirin in patients with CAD who were enrolled in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial [24]. Therefore, patients who are intolerant of or truly allergic to aspirin should be treated with clopidogrel.

Lipid-Lowering Agents

Statins

The Scandinavian Simvastatin Survival Study (4S) was a randomized trial of simvastatin in 4444 patients with a history of angina pectoris or MI. Among the 21% of patients who had angina but no history of MI at the time of enrollment, there was a 26% reduction in the risk of major coronary events (coronary deaths, nonfatal MI, and resuscitated cardiac arrest), but analysis of this subgroup was not prespecified, and the difference did not achieve statistical significance ($p = 0.08$) [25]. The Regression Growth Evaluation Statin Study (REGRESS) was a randomized trial of the effects of pravastatin on progression and regression of CAD [26]. Enrollment included 768 male patients with stable angina, documented CAD, and serum cholesterol levels of 155 to 310 mg/dL. Forty-eight-hour ambulatory ECGs that were obtained before and after random assignment to receive pravastatin, 40 mg daily, or placebo demonstrated that pravastatin significantly decreased the frequency and duration of ischemic episodes.

The Reversal of Atherosclerosis with Aggressive lipid lowering (REVERSAL) trial compared intensive lipid lowering with 80 mg of atorvastatin to moderate lipid lowering with 40 mg of pravastatin on coronary artery atheroma burden assessed by Intra Vascular Ultra Sound measurements [27]. Patients undergoing diagnostic coronary angiography for a clinical indication were enrolled in whom IVUS study was performed at base line and following an 18 month period of treatment. Of the 654 pts. randomized 502 had IVUS studies on both occasions.). The mean baseline LDL was 150.2 mg/dL in both groups. It was reduced to 110 mg/dL in the Pravastatin group and to 79 mg/dL in the Atorvastatin group. Atheroma burden was unchanged (−0.4%, P = .98) in the Atorvastatin group suggesting no disease progression whereas it increased (+ 2.7%, P < .001) in the Pravastatin group suggesting progression of disease. There was also a significant decrease in CRP of 36.4% compared to baseline in high dose statin patients compared to only 5.2% in the moderate dose group. This latter finding raises the possibility that, to the extent that atherosclerosis is an inflammatory disease, the differences in the atheroma burden in the two groups are largely attributable to the differences in CRP reductions.

In the same manner as the REVERSAL study, the Treating To New Targets (TNT) trial provided further evidence that intensive lipid lowering with 80 mg daily of atorvastatin in patients with stable coronary heart disease (CHD) provided clinical benefit beyond that afforded with atorvastatin 10 mg daily [28]. In this trial, 10,001 patients with clinically evident CHD and LDL below 130 mg/dL were randomly assigned to atorvastatin 10 mg or 80 mg daily and followed for a mean of 4.9 years. Mean LDL in the 80 mg group was 77 mg/dL whilst in the 10 mg group it was 101 mg/dL. Although the high dose group had a significantly higher incidence of persistent liver aminotransferase level elevations (1.2% vs. 0.2%; ‘p < 0.001), patients in the 80 mg group had a 22% relative reduction (p < 0.001) in the rate of major cardiovascular events (death from CHD, non-fatal non-procedure related MI, resuscitation from cardiac arrest, or fatal or nonfatal stroke). There were no all-cause mortality differences.

The data from the PROVE-IT [29], REVERSAL, TNT and other such studies have given clinicians greater comfort in starting patients on high dose atorvastatin. The most recent National Cholesterol Education Program guidelines published in 2014 would now suggest starting patients on either a moderate or high dose statin therapy based on their risk factor profile as opposed to treating to an actual LDL value; however, this continues to be an area of active debate.

Fibrates

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated a 22% reduction in the relative risk of nonfatal MI or coronary death among patients with CAD and low levels of high-density lipoprotein (HDL) (less than 40 mg/dL) who received gemfibrozil [30]. Patients with a serum LDL cholesterol level higher than 140 mg/dL were excluded. Thirty-nine percent of the patients did not have a history of MI before enrollment, but the effect of gemfibrozil on outcomes in this subgroup was not reported.

Angiotensin-Converting Enzyme Inhibitors

On the basis of the results of trials such as the Study of Survival and Ventricular Enlargement (SAVE) [31] and the Studies of Left Ventricular Dysfunction (SOLVD) [32], angiotensin-converting enzyme (ACE) inhibitors are indicated for patients with a history of CAD and either congestive heart failure or asymptomatic LV dysfunction. The Heart Outcomes Prevention Evaluation (HOPE) Study was a double-blind, randomized trial with a two-by-two factorial design [33]. It evaluated the effects of an ACE inhibitor, ramipril *10* mg/day and vitamin E in 9541 patients at high risk of cardiovascular events. Of the subjects, 80% had a history of CAD, and 56% had a history of stable angina pectoris. The primary endpoint was a composite of MI, stroke, and death from cardiovascular causes. A total of 651 patients in the ramipril group (14.0%) reached the primary endpoint, in comparison with 826 patients in the placebo group (17.8%) [relative risk (RR), 0.78; $p < 0.001$]. Treatment

with ramipril reduced the rates of death from any cause (RR, 0.84; $p = 0.005$), death from cardiovascular causes (RR, 0.74; $p < 0.001$), MI (RR, 0.80; $p < 0.001$), stroke (RR, 0.68; $p < 0.001$), and revascularization procedures (RR, 0.85; $p = 0.002$). Among the 4759 patients with documented normal LVEF, treatment with ramipril was associated with significant reductions in the primary endpoint and each of its components.

In the PEACE (Prevention of events with ACE) trial 8290 patients with documented stable CAD and LVEF >40% were randomized to Trandolapril 4 mg. daily or placebo and followed for 4.8 years [34]. The primary end point was a composite of death, nonfatal MI or revascularization. No significant difference was found in the outcomes between the two groups. Some of the drawbacks in the trial were that at base line only 70% of ACE patients were on lipid lowering therapy and at 3 years only 51% of active treatment group were on target dose of 4 mg. of Trandolapril.

In the EUROPA (European trial on Reduction of cardiac events with Perindopril in stable CAD) study 12,218 patients with proven CAD and no clinical heart failure were randomized to Perindopril 8 mg. daily or placebo and followed for 4.2 years [35]. Primary outcome was combined cardiovascular death, MI or cardiac arrest. A significant reduction in the primary end point of 8% vs. 10% with relative risk reduction of 20% was noted in patients on ACE inhibitor.

The revised ACC/AHA guidelines in 2002 recommend that all patients with documented CAD by angiography or previous MI who have diabetes or LV dysfunction or other vascular disease should be on ACE inhibitors [36].

Antioxidants

The HOPE trial randomly assigned 4761 patients to receive vitamin E, 400 IU daily, and 4780 patients to receive placebo [37]. Treatment with vitamin E had no effect on cardiovascular events. Recently, Cheung et al. [38] reported the results of a small clinical study of patients with CAD and low levels of HDL. Lipoprotein changes over 12 months were studied in 153 patients who were randomly assigned to four treatment groups: antioxidants (vitamins E and C, beta-carotene, and selenium); simvastatin plus niacin; simvastatin, niacin, and antioxidants; or placebo. Simvastatin plus niacin increased HDL cholesterol and lipoprotein a-1, whereas the combination of antioxidant supplements blocked the HDL response to simvastatin plus niacin. In a preliminary report, the same study group wrote that the antioxidant combination also had deleterious effects on the progression of CAD as measured by quantitative coronary angiography [39]. Thus, patients with CAD should probably abstain from antioxidant vitamins.

Revascularization

The LVEF is a critical determinant of whether myocardial revascularization (Figs. 8.1 and 8.2) improves long-term survival of a patient with CAD. The angiographic extent of CAD affects the decision of whether to recommend medical therapy alone, percutaneous coronary intervention (PCI), or surgical revascularization. The presence of more than 50% stenosis of the left main coronary artery, more than 70% stenosis of the proximal left anterior descending coronary artery, or three-vessel CAD each is an indication for revascularize-

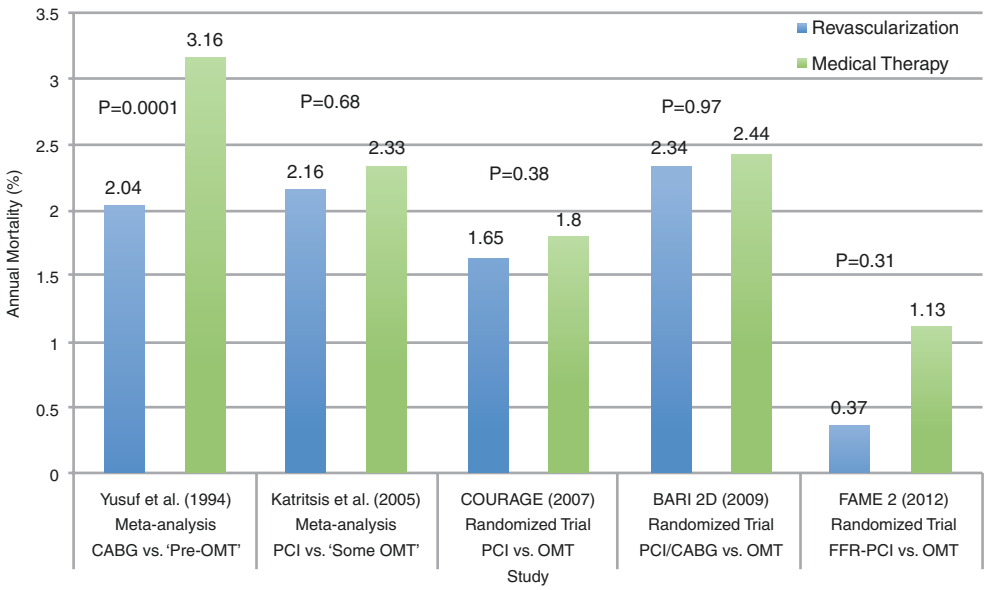

Fig. 8.1 Revascularization versus medical therapy impact on mortality. (From Patel and Bangalore [70]; with permission)

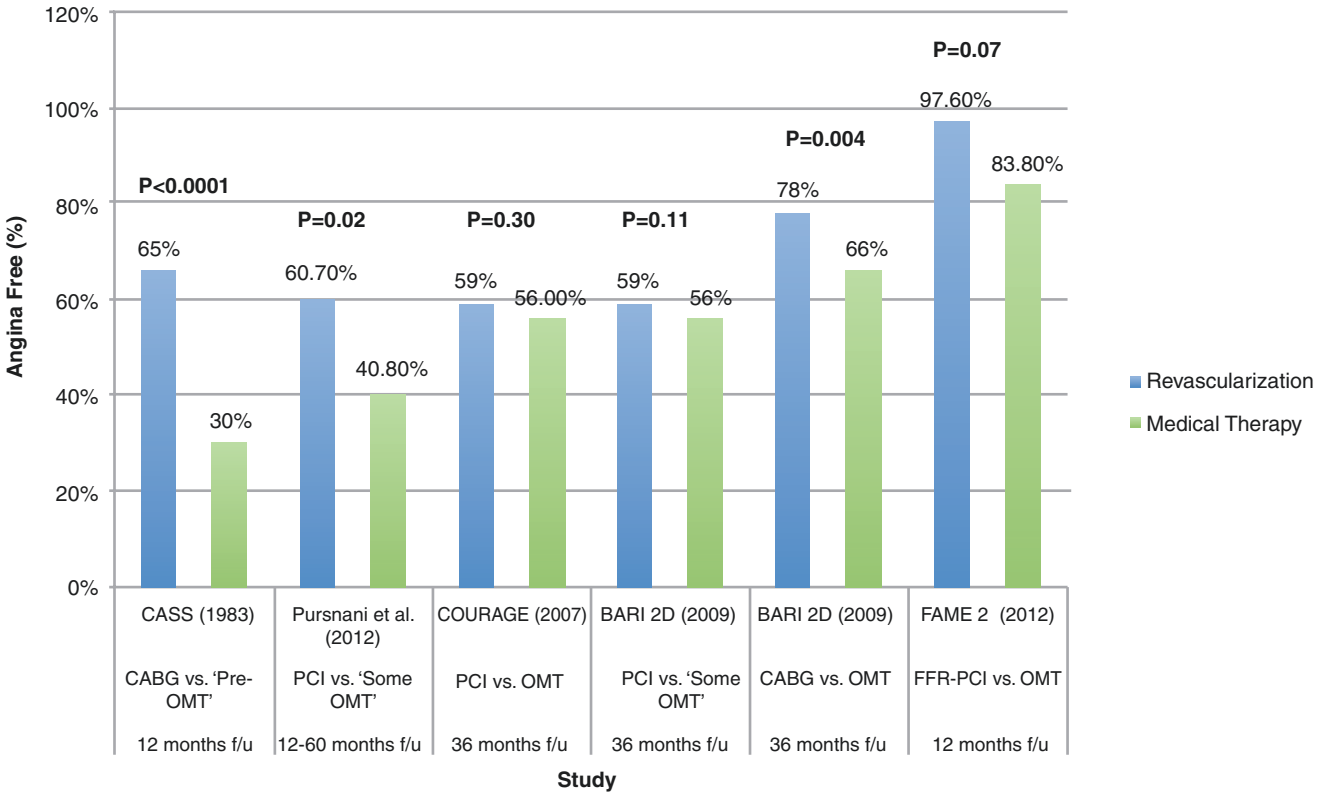

Fig. 8.2 Revascularization versus medical therapy: impact on angina. (From Patel and Bangalore [70]; with permission)

tion to improve survival. The appropriateness and optimal mode of revascularization are influenced by the medical history (i.e. severity/tolerability of symptoms and their response to medical therapy,) as well as prognostic information gleaned from stress testing results, coronary artery disease severity, LV systolic performance, diabetic status and concurrent noncardiac comorbidities. The Class I, II, and III recommendations for revascularization are listed in Table 8.7.

Coronary Artery Bypass Surgery

Patients with chronic stable angina were randomly assigned to undergo coronary artery bypass graft (CABG) or medical therapy in three major clinical trials: The Veterans Admininstration (VA) Cooperative Study, the Coronary Artery Surgery Study (CASS), and the European Coronary Surgery Study (ECSS). The general conclusions were that CABG prolongs survival of patients with stable angina who have the following characteristics: stenosis of more than 50% of the left main coronary artery; three-vessel CAD with LVEF of less than 50%; or two-vessel CAD with stenosis of more than 75% of the proximal left anterior descending coronary artery [40]. An overview of the 10-year results from all randomized trials of CABG versus medical therapy supported the conclusion that CABG prolongs survival in certain high-risk and medium-risk subgroups of patients with stable CAD but not in low-risk patients [41].

The survival benefit conferred by CABG in the current era may be underestimated by the randomized clinical trials conducted in the 1970s because operative mortality has decreased and arterial conduits are more frequently used. In comparison with placement of saphenous vein grafts as conduits, a single internal mammary artery (IMA) graft to the left anterior descending coronary is associated with lower operative mortality; greater graft patency; reduced frequency of MI, recurrent angina, and need for subsequent cardiac interventions; and increased long-term survival, among nonrandomized cohorts of patients [42]. The advantages conferred by IMA grafts presumably result from their greater patency rates in comparison with vein grafts. One surgical series reported long-term patency rates of 96% for IMA grafts [42]. In the CASS trial, 84% of the conduits were saphenous veins, and the cumulative graft patency rates 18 months and 5 years after CABG were only 85% and 82%, respectively [43]. A meta-analysis of 10 clinical reports concluded that bilateral IMA grafting provides better survival than does a unilateral IMA graft, but none of the 10 studies analyzed was a randomized trial [44].

The randomized trials of CABG versus medical therapy were performed before the availability of statins to treat hyperlipidemia. More recent studies indicated that statins and other lipid-lowering agents improve the long-term patency of saphenous vein bypass grafts [45, 46]. The largest trial was

Table 8.7 Recommendations for revascularization for chronic stable angina

Class I
CABG for significant left main stenosis
CABG for three-vessel CAD
CABG for two-vessel CAD with significant proximal LAD stenosis and either LVEF <50% or inducible ischemia
PTCA for two- or three-vessel CAD with significant proximal LAD stenosis if suitable anatomy, normal LVEF, and no diabetes
PTCA or CABG for one- or two-vessel CAD without proximal LAD stenosis if large area of viable myocardium and high-risk noninvasive criteria
CABG for one- or two-vessel CAD without proximal LAD stenosis for sustained VT or survivor of sudden death
CABG or PTCA for restenosis after PTCA if large area of viable myocardium or high-risk noninvasive criteria
PTCA or CABG if medical therapy unsuccessful and risk of revascularization acceptable
Class IIa
Repeat CABG if multiple graft stenoses
PTCA or CABG for one- or two-vessel CAD without proximal LAD stenosis if moderate area of viable myocardium and inducible ischemia
PTCA or CABG for one-vessel CAD with significant proximal LAD stenosis
Class IIb
PTCA for two- or three-vessel CAD with significant proximal LAD stenosis and diabetes or abnormal LVEF
PTCA for significant left main coronary artery stenosis if patient is not candidate for CABG
PTCA for one- or two-vessel CAD without significant proximal LAD stenosis for sustained VT or survivor of sudden death
Class III
PTCA or CABG for one- or two-vessel CAD without proximal LAD stenosis if symptoms mild, or inadequate trial of medical therapy, and small area of viable myocardium or no inducible ischemia
PTCA or CABG for 50–60% stenosis (other than left main coronary artery) and no inducible ischemia
PTCA or CABG for <50% stenosis
PTCA for patients who have significant left main stenosis and are candidates for CABG

CABG coronary artery bypass graft, *CAD* coronary artery disease, *LAD* left anterior descending artery, *LVEF* left ventricular ejection fraction, *PTCA* percutaneous transluminal coronary angioplasty, *VT* ventricular tachycardia

the National Heart, Lung, and Blood Institute's Post Coronary Artery Bypass Graft Clinical Trial [46]. The study enrolled 1351 patients with a history of CABG, at least one patent vein graft, and LDL cholesterol levels of 130 to 175 mg/dL. The patients were randomly assigned to undergo "aggressive" lowering of LDL, with a goal of 60 to 85 mg/dL, or to undergo moderate lowering, with a goal of 130 to 140 mg/dL. Treatment consisted of lovastatin, plus cholestyramine if needed. The mean LDL cholesterol level during treatment ranged from 93 to 97 mg/dL in the aggressive-treatment group, in comparison with 132 to 136 mg/dL in the moderate-treatment group ($p < 0.001$). Angiography was performed before and an average of 4.3 years after randomization. The rates of new graft occlusion were 6% for the aggressive-group and 11% for the moderate-treatment group ($p < 0.001$). The rates of new lesion formation in grafts were 10% for the aggressive-treatment group and 21% for the moderate-treatment group. There was a 29% lower rate of revascularization procedures in the aggressive-treatment group than in the moderate-treatment group ($p = 0.03$). The results strongly support the recommendation to treat elevated LDL cholesterol aggressively in patients who have undergone CABG.

Regardless of its effect on survival, CABG is an excellent therapy for relief of angina. The early randomized trials comparing CABG with medical therapy demonstrated excellent relief of angina after CABG but declining benefit after 5 years because of attrition of vein grafts. It is presumed that patients who receive arterial bypass grafts experience more durable relief of angina because of superior graft patency. The Bypass Angioplasty Revascularization Investigation (BARI) was a large trial that randomly assigned 1829 patients with stable angina to receive treatment with CABG or percutaneous transluminal coronary angioplasty (PTCA) [47]. At least one IMA graft was used in 82% of patients who underwent CABG. Of the patients who underwent CABG, 84% were free of angina 5 years after surgery [48].

Percutaneous Coronary Intervention

The benefits of PCI or medical therapy in patients with chronic stable angina have been examined in several clinical trials [49]. The relevance of some of these earlier studies is limited on account of several deficiencies including small sample sizes, inadequate clinical follow-up periods, small number of clinical events, poor definition and suboptimal use of medical therapy as well as use of outdated interventional techniques. However, with publication of the COURAGE trial in 2007, there was finally a large randomized trial comparing PCI to optimal medical therapy for stable coronary artery disease. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, randomly assigned 2287 patients with chronic stable angina to either optimal medical therapy alone versus PCI plus optimal medical therapy. Optimal medical therapy consisted of aspirin 81–325 mg daily, simvastatin alone or in combination with ezetimbie with a target LDL of 60–85 mg/dL, long acting metoprolol, amlodipine, and isosorbide mononitrate alone or in combination along with either Lisinopril or losartan as standard secondary prevention. Patients who underwent PCI were also on Plavix. In PCI group, a majority of intervention was performed.

Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Graft

Patients with chronic stable angina have been enrolled in numerous randomized trials of PTCA versus CABG. Pocock et al. [50] published a meta-analysis of 3371 patients who

were enrolled in eight randomized trials. There were 73 deaths in the CABG group and 79 in the PTCA group (RR, 1.08; 95% confidence interval, 0.79 to 1.50). One year after randomization, the prevalence of angina was higher among patients treated with PTCA (RR, 1.56; 95% confidence interval, 1.30 to 1.88), but 3 years after randomization, the difference was smaller (RR, 1.22; 95% confidence interval, 0.99 to 1.54). Another group of investigators performed a meta-analysis that included only five of the randomized trials and arrived at similar conclusions: The combined rate of mortality and nonfatal MI was not significantly different after PTCA or CABG at 1 to 3 years of follow-up, but CABG provided better relief of angina and was followed by fewer repeat revascularization procedures [51].

Each of the meta-analyses [50, 51] was performed before completion of the large randomized BARI study [47]. The BARI trial investigators randomly assigned 914 patients to undergo CABG and 915 patients to undergo PTCA. All patients had multivessel CAD; 41% had three-vessel disease. The mean LVEF was 57%. Of the patients who underwent CABG, 82% received at least one IMA graft. During the first 5 years of follow-up, 8% of the CABG patients underwent additional revascularization procedures, in comparison with 54% of the PTCA patients. The 5-year survival rates were 89.3% for CABG patients and 86.3% for PTCA patients ($p = 0.19$). Eight year results from the EAST trial [17] and 7 year data from the BARI trial [48] published in 2000 provided further support of the conclusions reached after 5 years in the BARI trial showing no survival difference in the overall study population.

Stent versus Coronary Artery Bypass Graft Trials

Several randomized trials have been performed to compare CABG with coronary stent placement [52, 53]. In the Stenting versus Internal Mammary Artery (SIMA) study, 123 patients with isolated *de novo* stenosis of the proximal left anterior descending coronary artery were randomly assigned to undergo coronary stent placement ($n = 62$) or CABG with an IMA graft ($n = 59$) [53]. One patient who received a stent experienced subacute stent thrombosis 4 days after the procedure and died of a massive cerebral hemorrhage after receiving a thrombolytic drug. One patient in the CABG group died of an anterior MI 10 days after CABG. After a mean follow-up period of 2.4 years, additional revascularization procedures were performed in 24% of the patients who underwent stent placement but in none of the patients who underwent CABG.

The Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multiple-Vessel Disease (ERACI) II study randomly assigned 450 patients with multivessel CAD to undergo either PCI ($n = 225$) or CABG ($n = 225$) [54]. Rates of mortality and freedom from MI were lower among patients randomized to PCI with stent placement than among patients randomized to CABG. The ERACI II study had numerous limitations, however, including relatively short duration of follow-up (mean, 18.5 months), small sample size, high postoperative mortality rate after CABG (5.7%), low use of glycoprotein IIb/IIIa inhibitors (28%), and use of a suboptimal stent design (Gianturco Roubin II) that has been associated with relatively high restenosis rates. Also, only 38 patients had stable angina before randomization.

In the ARTS trial, 1205 patients with multivessel CAD were randomly assigned to undergo CABG or stent implantation [52]. Among the 600 patients who underwent stent implantation, 57% had stable angina and 19% had diabetes; the mean LVEF was 61%; and 30% had three-vessel CAD and 68% had two-vessel CAD. Among the 605 patients who underwent CABG, 60% had stable angina and 16% had diabetes; the mean LVEF was 60%; and 33% had three-vessel CAD and 67% had two-vessel CAD. Among the patients who underwent CABG, 93% received at least one arterial conduit. After the procedure, creatine kinase values more than five times the upper limit of normal were found in 6.2% of the patients who underwent PCI, in contrast to 12.6% of the patients who underwent CABG ($p < 0.001$). After 1 year of follow-up, there was no significant difference between the two groups in the rates of death, stroke, or MI. Among patients who survived without a stroke or MI, repeat revascularization procedures were performed in 16.8% of the patients who underwent PCI, in contrast to 3.5% of those who underwent CABG. After 1 year, 90% of CABG patients were free of angina, in comparison with 79% of patients who underwent PCI. At 5 years, there were no significant differences in mortality or the incidence of stroke or MI but the stent group still had a higher rate of major adverse cardiac and cerebrovascular events 30.3 versus 8.8% ($p < 0.001$, RR = 3.46) in the CABG group [55].

The Stent or Surgery (SOS) trial randomly assigned 967 patients with multivessel CAD and severe angina refractory to medical therapy to undergo CABG ($n = 487$) or PCI ($n = 480$). After follow-up for 1 year, the rates of death and additional PCI or CABG were higher among patients who underwent PCI than among patients who underwent CABG.

The rapid evolution of PCI makes it difficult to apply the results of the randomized PCI versus CABG trials to clinical decision making today. After the early trials were completed, restenosis rates after PCI decreased dramatically because of the introduction of coronary stents. For example, a comparison of coronary artery stent placement with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery demonstrated restenosis rates of 19% after stent placement, in comparison with 40% after PTCA ($p = 0.02$) [56]. The 1-year rates of event-free survival were 87% after stent placement and 70% after PTCA ($p = 0.04$).

The last few years have witnessed a revolution in PCI techniques with the advent of drug-eluting stents that have dramatically reduced the incidence of clinical restenosis or target lesion revascularization when compared to PTCA or bare-metal stenting [57, 58]. This new generation of stents coated with antiproliferative agents (e.g., sirolimus, everolimus, zotarolimus, tacrolimus, paclitaxel) significantly reduces neointimal hyperplasia. To the extent that the historical superiority of CABG versus PCI was attributable primarily to greater angina relief and reduced number of repeat interventions for clinical restenosis, the drug-eluting stents have greatly diminished if not nullified this discrepancy between PCI and CABG revascularization. In the ARTS-II registry, the clinical outcomes of Cypher drug-eluting stents in 607 patients were compared to the 605 subjects who had undergone CABG in the surgical arm of the first ARTS trial, ARTS-I. Despite the Cypher stent group having significantly more diabetics, coronary lesions, 3-vessel CAD, hyperlipidemia and hypertension, there no significant differences in 1 year MACCE rates between the two groups, 10.2% Cypher DES vs. 11.6% for CABG [59]. For 1 year survival free from death, MI or CVA, the Cypher group had a significantly superior outcome 97.1% vs. 92.0% for CABG, $p < 0.001$.

The SYNTAX study, currently enrolling patients in multiple international sites, is a prospective randomized trial that will provide contemporary insights on the optimal revascularization strategy in patients with multivessel disease.

Recent observations on long term outcomes suggest that DES may be associated with an increase in late stent thrombosis but not necessarily death and MI. If these findings are confirmed, the pendulum may swing back in favor for CABG, or the use of more bare metal stents or both.

Percutaneous Coronary Intervention versus Coronary Artery Bypass Graft inDiabetics

Diabetic patients have higher rates of restenosis and target vessel revascularization procedures after both PTCA and coronary stent placement [60, 61]. Also, coronary artery occlusion and an associated decrease in LVEF are frequent manifestations of restenosis in diabetic patients, a possible explanation of the increased mortality rate after PTCA in diabetic patients [62]. A post hoc analysis of the 641 diabetics who were enrolled in the BARI trial revealed that the 5-year survival rate was greater among subjects who underwent CABG than among subjects who underwent PTCA (80.6% vs. 65.5%; $p = 0.003$). Among diabetic patients, the 7-year survival rates were 76.4% for those who underwent CABG and 55.7% for those who underwent PTCA ($p = 0.0011$) [33]. CABG greatly reduced the risk of death after Q wave MI. The mortality rate was 17% among patients who underwent CABG and subsequently suffered a Q wave MI, in comparison with 80% among patients who underwent PTCA [63]. The findings of a large prospective registry of 7159 diabetics with multivessel disease who required PTCA or CABG revascularization supported the BARI results demonstrating a mortality benefit with CABG in diabetics with 3-vessel CAD [64].

Interpretation of the BARI trial results is confounded by several concerns. Only 641 diabetic patients were enrolled in the BARI trial, and they did not constitute a prespecified subgroup. The survival advantage conferred by CABG among diabetic patients in the randomized component of the BARI trial was not observed among the diabetic patients who were eligible for BARI but declined random assignment and selected their mode of revascularization [65]. Most important, enrollment in the BARI trial was completed before the advent of stents and glycoprotein IIb/IIIa inhibitors, which appear to improve the short-term and long-term results of PCI, especially in diabetic patients [61, 66]. Inspired by the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT) study, a pooled analysis of the results of three randomized trials of abciximab versus placebo in patients undergoing PCI demonstrated that abciximab decreased 1-year mortality, especially among patients who underwent multivessel PCI [66]. The mortality rate among diabetic patients who underwent multivessel PCI was reduced from 7.7% to 0.9% with abciximab therapy ($p = 0.018$).

The Arterial Revascularization Therapies Study (ARTS) randomly assigned 1205 patients with multivessel CAD to undergo CABG or stent implantation [52]. It included 112 diabetic patients who received stents and 96 diabetic patients who underwent CABG [67]. IMA bypass grafts were placed in 99.7% of the nondiabetic and 89.3% of the diabetic patients who underwent CABG [67]. Diabetic patients who underwent CABG had a higher 1-year event-free survival rate than did diabetic patients who underwent coronary stent placement (84.4% vs. 63.4%; $p < 0.001$), primarily because of a 21.6% lower rate of repeat revascularization. This finding was unchanged at 5 year follow-up [55].

Further information on the merits of medical therapy versus revascularization strategies in diabetic patients with will be generated by the BARI-2D and FREEDOM trials.

Refractory Myocardial Ischemia

Some patients with chronic stable angina are not candidates for PCI or CABG and continue to have severe angina despite maximal medical therapy. Various investigational approaches have been explored to alleviate angina in this population of patients. Percutaneous transmyocardial laser revascularization was widely advocated but eventually abandoned. Enhanced external counterpulsation may reduce the frequency of anginal episodes in patients with angina pectoris.

Spinal cord stimulation and myocardial angiogenesis have also been reported with generally mixed clinical results.

Education and Exercise

Regular exercise improves functional capacity, endothelial function and decreases anginal episodes [36, 68]. In a randomized trial comparing PCI to exercise in patients with stable coronary artery disease, Hambrecht *et al.* reported fewer major adverse cardiac events and improved exercise capacity at 1 year in the exercise group [69]. Management of coronary artery disease is a lifelong endeavor which requires patient education and participation for the life style modification necessary for the attainment of symptomatic improvement and improved survival.

Prognosis and Follow-Up

The 5-year survival rate among patients receiving only medical treatment can be predicted from the extent of CAD (Table 8.8) [4]. The ACC/AHA and ACP-ASIM guidelines for the management of patients with chronic stable angina recommend follow-up evaluation every 4 to 12 months [4]. The guidelines recommend follow-up evaluations every 4 to 6 months during the first year of therapy and annual evaluations thereafter if the patient is stable and reliable. The guidelines recommend asking five questions during each follow-up evaluation (Table 8.9). Aggressive risk factor control should be pursued (see Chap. 7). The Classes I, II, and III indications for echocardiography, treadmill exercise testing, stress imaging studies, and coronary angiography during follow-up are summarized in Table 8.10. An assessment of LV function is advisable in patients with new or worsening heart failure or an interval MI. Stress testing is indicated for patients who have a significant change in clinical status. Coronary angiography is indicated for patients who develop Class III angina despite maximal medical therapy.

Table 8.8 Prognosis

Extent of coronary artery disease	5-Year survival rate (%)
One-vessel disease, 75%	93
>One-vessel disease, 50%–74%	93
One-vessel disease, ≥95%	91
Two-vessel disease	88
Two-vessel disease, both ≥95%	86
One-vessel disease, ≥95% proximal LAD	83
Two-vessel disease, ≥95%	83
Two-vessel disease, ≥95% proximal LAD	79
Three-vessel disease	79
Three-vessel disease, ≥95% in at least one	73
Three-vessel disease, 75% proximal LAD	67
Three-vessel disease, ≥95% proximal LAD	59

LAD left anterior descending (artery)

Table 8.9 Questions to ask at each follow-up visit

Has the patient decreased the level of physical activity since the last visit?
Have the patient's anginal symptoms increased in frequency and become more severe since the last visit?
How well is the patient tolerating therapy?
How successful has the patient been in reducing modifiable risk factors and improving knowledge about ischemic heart disease?
Has the patient developed any new comorbid illnesses, or has the severity or treatment of known comorbid illnesses worsened the patient's angina?

Table 8.10 Recommendations for noninvasive testing and coronary angiography during follow-up according to Canadian Cardiovascular Society Classification system

Class I
Chest radiograph for patients with evidence of new or worsening congestive heart failure
Assessment of LVEF and segmental wall motion in patients with new or worsening congestive heart failure or evidence of intervening MI by history or ECG
Echocardiography for evidence of new or worsening valvular heart disease
Treadmill exercise test for patients without prior revascularization who have a significant change in clinical status, are able to exercise, and do not have any of the ECG abnormalities listed in the next recommendation
Stress imaging for patients without prior revascularization who have a significant change in clinical status and are unable to exercise or have one of the following ECG abnormalities:
Preexcitation (Wolff-Parkinson-White) syndrome
Electronically paced ventricular rhythm
>1-mm resting ST depression
Complete LBBB
Stress imaging for patients who have a significant change in clinical status and required a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results
Stress imaging for patients with prior revascularization who have a significant change in clinical status
Coronary angiography in patients with Class III angina despite maximal medical therapy
Class IIb
Annual treadmill exercise testing in patients who have no change in clinical status, can exercise, have none of the ECG abnormalities listed in number 5 above, and have an estimated annual mortality >1%
Class III
Echocardiography or radionuclide imaging to assess LV function in patients with a normal ECG, no history of MI, and no evidence of congestive heart failure
Repeat treadmill exercise testing in <3 years in patients who have no change in clinical status and an estimated annual mortality <1% on their initial evaluation
Stress imaging for patients who have no change in clinical status and a normal rest ECG, are not taking digoxin, are able to exercise, and did not require a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results
Repeat coronary angiography in patients with no change in clinical status, no change on repeat exercise testing or stress imaging, and insignificant CAD on initial evaluation

CAD coronary artery disease, *ECG* electrocardiogram, *LBBB* left bundle branch block, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction

Practical Points

- Sublingual NTG or NTG spray is indicated for immediate relief of angina.
- Aspirin is indicated for all patients who can tolerate aspirin.
- Beta blockers are indicated as initial therapy in all patients who can tolerate them.
- Calcium channel blockers, long-acting nitrates, or both are indicated when beta blockers are contraindicated, are unsuccessful, or cause unacceptable side effects. Angiotensin Converting Enzyme Inhibitors should be considered in all patients with CAD especially those who have impaired LV systolic function, diabetes or hypertensive heart disease.
- Lipid-lowering therapy is indicated in patients with LDL cholesterol levels higher than 130 mg/dL.
- Coronary angiography should be performed in selected patients with chronic stable angina.
- Coronary revascularization in patients with chronic stable angina offers symptomatic relief and reduces mortality risk in certain subsets.

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Unstable Angina/Non-ST Elevation Myocardial Infarction

9

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Usual Causes

Unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) form part of the spectrum of acute coronary syndromes (ACS) that includes acute ST-segment elevation myocardial infarction (MI). These conditions are pathophysiologically related and may present in similar fashions. However, acute ST-segment elevation MI is identified by ST segment elevations on the electrocardiogram, while cardiac biomarkers are used to differentiate NSTEMI (biomarker positive) or UA (biomarker negative) in the setting of acute coronary syndrome without ST elevations on the ECG.

There are multiple, and not mutually exclusive causes of UA/NSTEMI (Table 9.1). The usual cause is disruption of the endothelium overlying an atherosclerotic plaque and formation of a non-occlusive thrombus. Plaques prone to rupture have a large lipid core, high macrophage and activated T-lymphocyte density, low smooth muscle cell density, and a thin fibrous cap characterized by disorganized collagen [1, 2]. The plaque shoulder, at its junction with the arterial wall, is mechanically the weakest point where most ruptures occur, exposing a lipid core that is a potent stimulator of platelet-rich thrombus formation [3, 4]. Two-thirds of plaque ruptures with thrombus have a <50% diameter stenosis before plaque rupture and 97% have <70% diameter stenosis [5]. Thrombus occurring on a ruptured or fissured plaque results from a complex series of interactions between the exposed lipid core, macrophages, smooth muscle cells, collagen, circulating blood products, and coagulation factors. Platelet surface receptors recognize the vascular matrix components (collagen, von Willebrand factor, vitronectin, and fibronectin), stimulating platelet activation and adhesion. Activated platelets secrete mitogenic, chemotactic, and vasoactive substances and undergo conformational changes with the recruitment and activation of glycoprotein (GP) IIb/IIIa receptors. The activated GP IIb/IIIa receptors mediate platelet aggregation by fibrinogen cross-linkage, forming the platelet-rich white thrombus on the surface of the plaque [6]. Tissue factor interacts with activated factor VII to initiate the coagulation cascade resulting in the generation of fibrin which traps red blood cells and forms the overlying red thrombus [7]. Myocyte necrosis in NSTEMI is believed to be due to temporary arterial occlusion or embolization of platelet-thrombus aggregates and plaque material into the microcirculation.

Table 9.1 Causes of unstable angina and non ST segment elevation MI[a]

1. Non occlusive thrombus on preexisting plaque
2. Dynamic obstruction (coronary artery spasm or vasoconstriction)
3. Progressive mechanical obstruction
4. Inflammation and/or infection
5. Spontaneous or iatrogenic dissection
6. Secondary unstable angina

Adapted from Braunwald [62]

[a]These causes are not mutually exclusive; some patients have ≥2 causes

Less common causes of UA/NSTEMI include dynamic obstruction (such as that associated with vasospasm), progressive atherosclerosis or restenosis, arterial inflammation, arterial dissection (spontaneous or iatrogenic) and secondary UA/NSTEMI. Vasoconstrictor substances acting on a segment of epicardial coronary artery with dysfunctional endothelium may lead to vasoconstriction or focal spasm [8, 9]. Progressive atherosclerotic obstruction can occur in stable calcified lesions or following percutaneous coronary intervention (PCI). Sites of plaque disruption usually exhibit features of inflammation [10].

Non-cardiac events can cause a mismatch in myocardial oxygen demand and supply, resulting in UA/NSTEMI. They may be caused by: (1) increased myocardial oxygen demand (fever, thyrotoxicosis), (2) reduced myocardial

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Table 9.2 Classification of MI according to the third universal definition of myocardial infarction

Type I MI: Spontaneous myocardial infarction related to plaque rupture with resultant intraluminal thrombus formation
Type II MI: secondary ischemia related to an imbalance between myocardial oxygen supply and demand
Type III MI: MI resulting in deal when biomarkers are unavailable
Type IVa MI: Myocardial infarction related to percutaneous coronary intervention
Type IVb: myocardial infarction related to stent thrombosis
Type V MI: MI related to coronary artery bypass surgery

Adapted from Thygesen et al. [11]

oxygen delivery (anemia, hypoxemia), or (3) reduced coronary blood flow (arrhythmia, hypotension). Although there may be co-existing coronary artery disease, it is usually stable and attention to the precipitating condition is prudent. When an MI is caused by a mismatch in myocardial supply and demand, it is referred to as a Type II MI by the Third Universal Definition of Myocardial Infarction [11]. According to this classification, tradition plaque rupture myocardial infarction is considered a Type I MI (Table 9.2).

Presenting Signs and Symptoms

The primary presentation of patients with UA and NSTEMI is new onset angina, either at rest, with minimal exertion, or with acute worsening of pre-existing angina [12] (Table 9.3). Classically, the pain is described as a pressure sensation in the chest that radiates to the left arm and neck. Associated with the chest pain in varying frequencies are the symptoms of diaphoresis, dyspnea, nausea, and vomiting. On occasion, particularly in women, diabetics, and the elderly, there may have no discernable chest pain. Instead, patients may complain of varying components of arm pain, neck pain, epigastric discomfort or a decrease in exercise threshold with worsening dyspnea on exertion. When these non-chest pain symptoms are related to physical or emotional stress and relieved by rest or nitroglycerin, they should be considered anginal equivalents. Accordingly, progression in frequency and intensity of these atypical symptoms should warrant the same degree of concern as with chest pain.

A careful history may identify features in the chest pain syndrome that make it less likely cardiac in origin. Pain that lasts for many hours to days, or on the other hand only a few seconds, is unlikely to be ischemic in origin. Pain that is clearly pleuritic or positional or located with the tip of one finger is also less likely to be cardiac in origin. The physician should document in the medical record whether there is a high, intermediate, or low likelihood of acute ischemia caused by coronary artery disease (Table 9.4).

Table 9.3 Three principle presentations of unstable angina

Rest angina	Angina occurring at rest and prolonged, usually >20 min
New-onset angina	New-onset angina of at least CCS[a] Class III severity
Increasing angina	Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by ≥1 CCS class to at least CCS Class III severity)

Adapted from Braunwald [12]
[a]Canadian Cardiac Society Classification. CCS I is angina with strenuous or prolonged exertion; CCS II is slight limitation of ordinary activity and angina with walking more than one flight of stairs or two level at a normal pace; CCS III is marked limitation of physical activity with angina at less one flight of stairs or before two level blocks at normal pace; CCS IV is severe limitation of physical activity, with potential rest symptoms

Table 9.4 Likelihood that signs and symptoms represent an ACS secondary to CAD

Feature	High likelihood Any of the following:	Intermediate likelihood Absence of high-likelihood features and presence of any of the following:	Low likelihood Absence of high- or intermediate-likelihood features but may have:
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age > 70 years Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (≥0.5 mm) or T-wave inversion (≥2 mm) with symptoms	Fixed Q waves ST depression 0.5–1 mm or T-wave inversion greater than 1 mm	T-Wave flattening or inversion in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

ACS acute coronary syndrome, *CAD* coronary artery disease, *CK-MB* creatine kinase MB, *ECG* electrocardiogram, *MI* myocardial infarction, *MR* mitral regurgitation, *TnI* troponin I, *TnT* troponin T
From Galvani et al. [23]; with permission

The physical examination in patients with UA/NSTEMI is many times fairly unremarkable. Still, it is very important that the exam be performed in a meticulous and structured fashion as non-cardiac (pleurisy, pneumothorax) and non-ischemic (valvular disease, pericarditis or pericardial effusion, and vascular emergencies) causes of chest pain may be revealed. Additionally, if acute coronary syndrome is suspected, serial exams are warranted and may identify troubling signs such as hypotension, bradycardia or tachycardia, pulmonary rales, a third heart sound, or a new or worsening murmur suggestive of a papillary muscle rupture. If identified, these findings demarcate a population requiring earlier and more aggressive therapy [13].

Helpful Tests

Electrocardiography

The ECG is important for both diagnosis and risk stratification. A 12 lead ECG should be performed and reviewed within 10 min of presentation to the Emergency Department. Persistent ST segment elevation is treated according to the STEMI guidelines, and this is reviewed separately in the Chapter on "Acute ST Segment Myocardial Infarction" [14].

ECG abnormalities most commonly found in patients presenting with NSTEMI include transient ST segment elevation (<20 min), ST segment depression, and T wave inversion [15]. More specifically, the characteristics and the magnitude of pattern abnormalities increase the likelihood of coronary artery disease. New or dynamic ST-segment depression (>0.5 mm) is suggestive of acute ischemia with an associated prothrombotic state [16]. Inverted T waves may also suggest ischemia or NSTEMI, although the risk is less than for ST-segment depression. Non-specific ST-segment changes (≤0.5 mm) and T wave changes (≤2 mm) are less specific and may also be related to drugs or repolarization abnormalities in association with left ventricular hypertrophy or conduction disturbances. Alternatively, the ECG may be normal, as is the case in 1–6% of patients with NSTEMI and >4% of patients with unstable angina [17].

In the GUSTO-IIb trial, the 30-day incidence death or myocardial infarction was 5.5% in patients with T-wave inversion, 9.4% in those with ST-segment elevation, 10.5% in those with ST-segment depression, and 12.4% in patients with ST elevation and depression [18]. All these ECG findings may be transient phenomena and this illustrates the importance of serial tracings, especially if symptoms recur. In fact, continous ST-segment monitoring may reveal episodes of otherwise undiagnosed ischemic episodes.

Biochemical Markers

Although many markers and assays that detect myocardial necrosis are available, the cardiac troponins T and I are the most commonly used, and have emerged as the markers of choice in acute coronary syndromes. They have achieved an important role in diagnostic, prognostic, and treatment pathways by virtue of their high degree of sensitivity and specificity and their relative ease of use and interpretation. In the appropriate clinical context of ACS, myonecrosis may be diagnosed when the maximal concentration of troponin T or I exceeds the decision limit (99th percentile for a reference group) on at least one occasion in a 24-h period [11]. Due to the improved sensitivity of the newer tropinin assays, troponin levels can be increasingly elevated in patients without a traditional plaque rupture MI, and thus troponin levels must be interpreted in the appropriate clinical context. Additionally, serial troponin levels may be helpful in differentiating troponin elevations from alternative causes. For example, in patients with congestive heart failure or renal failure, the troponin levels may be mildly elevated but the trend is flat, as oposed to the acute risk and fall of troponin values typically seen in ACS. Troponin I is more accurate with renal insuficiency [19].

Both troponin T and I are detectable around 4–6 h after myocardial injury and measurable for up to 2 weeks. Mortality risk is directly proportional to troponin levels in a manner incremental to the prognostic information provided by other clinical and electrocardiographic risk factors [20, 21]. Acute coronary syndrome without evidence of cardiac biomarker elavation from consecutive samples (at least 6 h apart) is classified as unstable angina.

CK-MB is less specific then troponin, being also present in skeletal muscle and in low levels in the blood of healthy persons, and is also less sensitive. Compared to troponin, CK-MB has a short half-life, making it useful in the identification of recurrent myocardial necrosis. Levels of CK-MB tend to return to normal within 36–48 h after initial release. With the newer troponin assays widely available, CK-MB is no longer considered useful for diagnosis of ACS [15].

Other biomarkers have been evaluated for their ability to risk-stratify and prognosticate in the setting of UA/NSTEMI. C-reactive protein levels in ACS appear to be related to long-term mortality in an independent and additive fashion to troponin levels [22]. B-Type natriuretic peptide is a neurohormone released in its precurser form proBNP when the ventricular myocardium is subjected to increased wall stress. Increasing serum levels of these neurohormones measured at first contact or early in the hospital stay are associated with higher short and long term mortality rates [23].

Whether a multi-faceted biomarker approach can favorably guide therapies and improve outcomes in UA/NSTEMI populaitons is of significant interest.

Noninvasive Testing

Echocardiography allows for the rapid determination of left ventricular function as well as wall motion abnormalities, and should be employed early in settings of uncertainty regarding the etiology of active, potentially anginal chest pain. Stress testing to risk stratify (Table 9.5) should be performed in low risk and intermediate risk patients who do not meet the threshold for coronary angiography [15]. The choice of stress test is based on the resting ECG, ability to exercise, and local expertise. Treadmill testing is suitable in low risk patients with good exercise tolerance in whom the ECG is free of ST-segment abnormalities, bundle branch block, left ventricular hypertophy, intraventricular conduction delay, paced rhythm, preexcitation, and digoxin effect. Echocardiographic or nuclear stress imaging should be added in patients with ECG abnormalities that prevent accurate interpretation. Pharmacological stress testing can be performed in patients who cannot exercise, or fail to achieve an adequate heart rate with exercise.

Table 9.5 Noninvasive risk stratification

High risk (>3% annual mortality rate)
1. Severe resting LV dysfunction (LVEF < 35%)
2. High-risk treadmill score (score ≤ −11)
3. Severe exercise LV dysfunction (exercise LVEF < 35%)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving >2 segments) developing at a low dose of dobutamine ($\leq$10 mg kg^{-1} min^{-1}) or at a low heart rate (<120 bpm)
9. Stress echocardiographic evidence of extensive ischemia
Intermediate risk (1–3% annual mortality rate)
1. Mild/moderate resting LV dysfunction (LVEF 35–49%)
2. Intermediate-risk treadmill score (−11 < score < 5)
3. Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium–201)
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤2 segments
Low risk (<1% annual mortality rate)
1. Low-risk treadmill score (score ≥ 5)
2. Normal or small myocardial perfusion defect at rest or with stress
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress

LV left ventricular, *LVEF* left ventricular ejection fraction

Table 9.6 American College of Cardiology/American Heart Association 2012 guidelines for invasive management of unstable angina/NSTEMI

Preferred strategy	Patient characteristics
Invasive	Recurrent angina or ischemia at rest or with low level activities despite intensive medical therapy Elevated cardiac biomarkers (TnT or TnI) New or presumably new ST-segment depression Signs or symptoms of HF or new or worsening mitral regurgitation High-risk findings from noninvasive testing Hemodynamic instability Sustained ventricular tachycardia PCI within 6 months Prior CABG High-risk score (eg, TIMI, GRACE) Mild to moderate renal dysfunction Diabetes mellitus Reduced LV function (LVEF < 40%)
Conservative	Low-risk score (eg. TIMI, GRACE) Patient or physician preference in the absence of high-risk features

CABG indicates coronary artery bypass graft, *GRACE* Global Registry of Acute Coronary Events, *HF* heart failure, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *TIMI* Thrombolysis In Myocardial Infarction, *TnI* troponin I, and *TnT* troponin T
Adapted from Amsterdam et al. [15]

Cardiac Catheterization

The combination of left heart catheterization and coronary angiography can define regional and global left ventricular function, valvular function, and coronary artery anatomy. It is routinely performed as part of an "invasive stategy" within 24–72 h of hospital admission, with an intent to revascularize the affected territory, and is further discussed below in the section under "Coronary Revascularization". The procedure should not be performed in patients who are clearly not revascularization candidates, in those who do not want catheterization, or in those who are at low risk. Indications for cardiac catheterization are listed in Table 9.6 [15].

Complications

If left untreated, 5–10% of patients with UA die and 10–20% suffer a non-fatal MI within 30 days. One quarter of patients with NSTEMI develop Q-wave MI, with the remaining having non-Q-wave MI. Arrhythmia, congestive heart failure, and cardiogenic shock are life-threatening complications. Recurrent ischemia may result in need for urgent coronary artery revascularization. The TIMI Risk Score [24] and GRACE Prediction score [25] are prognostic tools that predict death, MI, and need for urgent revascularization, and identify patients more appropriate for more aggressive therapy.

Differential Diagnosis

Chest pain, the main manifestation of ACS, may be the presentation of many non-ischemic conditions. The rapid evaluation and treatment that is warranted for acute coronary syndromes should not be done at the expense of potentially missing an alternative condition that would warrant a significantly different approach and treatment.

Causes of non-ischemic chest discomfort include: (1) musculoskeletal chest pain; (2) gastrointestinal discomfort (gastroesophageal reflux disease, peptic ulcer disease, biliary or pancreatic disease, or esophageal spasm); (3) cardiac non-ischemic pain (valvular heart disease, hypertrophic cardiomyopathy, pulmonary hypertension, pericarditis, aortic dissection); (4) pulmonary discomfort (pulmonary embolus, pneumothorax, pneumonia, COPD exacerbation); (5) anxiety. This list is not meant to be exhaustive, but demonstrates the spectrum of conditions and underscores the importance of a rapid and accurate diagnosis.

Therapy

Unstable angina results in more than two million hospital admissions per year and NSTEMI accounts for around two-thirds of all myocardial infarction admissions [26]. The goals of an effective treatment strategy are relief of ischemia and prevention of further MI, recurrent MI or death. These goals may be achieved by the accurate risk stratification, early initiation of appropriate therapy and selective coronary artery revascularization.

General Measures

Patients who present with a NSTEMI should be admitted to the hospital. Bed or chair rest is recommended in the presence of ongoing ischemia. Oxygen should be administered for patients with cyanosis, respiratory distress, high risk features, and with hypoxemia (SaO2 < 90%). Continuous electrocardiographic monitoring for arrhythmias allows for the prompt detection and treatment of potentially fatal rhythm disorders. ST-segment monitoring may have a role in detecting ongoing ischemia that may otherwise go undetected. Patients should be managed with antiplatelet, anticoagulation, and antianginal therapy. Morphine sulfate has analgesic, anxiolytic, and hemodynamic effects that are beneficial in patients with persistent symptoms despite nitroglycerin (Table 9.7).

Table 9.7 2012 American College of Cardiology/American Heart Association guidelines for pharmacologic management of unstable angina/NSTEMI

Therapy	Class I	Class IIA	Class IIB	Class III
Anti-ischemic	**Bed rest** **Continuous ECG monitoring** **NTG for relief of symptoms** **O_2 for hypoxia** **Morphine for persistent pain, CHF, agitation** **Beta-blocker** **Verapamil or diltiazem for recurrent pain if beta-blocker contraindicated** **ACE-I for CHF, HTN, DM**	**Long acting Ca^{2+} blocker for recurrent pain after NTG/beta-blocker ACE-I**	**Verapamil or diltiazem instead of beta-blocker** **Nifedipine plus beta-blocker**	**NTG within 24 h of sildenafil** **Nifedipine without beta-blocker**
Anti-platelet	ASA indefinitely Clopidogrel, Ticagrelor, prasugrel for up to 12 months GP IIb-IIIa antagonists if started previously	Eptifibatide or tirofiban for persistent pain, (+) troponin, high risk if PCI not planned Omit GpIIb/IIIa inhibitor if bivalirudin selected for PCI	Eptifibatide or tirofiban if no high risk features and PCI not planned Platelet function testing	Fibrinolytic therapy Abciximab if PCI not planned
Anti-coagulant	UFH or LMWH	Enoxaparin instead of UFH		
Discharge	Sublingual NTG Drugs required in hospital to control symptoms if no revascularization ASA 75–325 mg qd Clopidogrel 75 mg po q day for 9 months Beta-blocker Lipid lowering drugs until LDL <100 mg/dL ACE-I for CHF, LVEF < 40%			

ACE-I ACE inhibitor, *ASA* aspirin, *CHF* congestive heart failure, *DM* diabetes mellitus, *ECG* electrocardiogram, *GP* glycoprotein, *HTN* hypertension, *IABP* intraaortic balloon pump, *LDL* low density lipoprotein, *LMWH* low molecular weight heparin, *LVEF* left ventricular ejection fraction, *MSO_4* morphine sulphate, *NTG* nitroglycerin, *O_2* oxygen, *PCI* percutaneous coronary intervention, *UFH* unfractionated heparin

Anti-ischemic Agents (Table 9.8)

Nitrates

Nitrates dilate venous capacitance vessels and peripheral arterioles, reducing preload and to a lesser extent afterload, thereby alleviating myocardial wall stress and oxygen demand. In addition, by dilating epicardial coronary arteries and increasing collateral flow nitrates also increase myocardial oxygen supply. Although adequately-powered trials demonstrating symptom relief or reduced cardiac events are lacking, the physiological effects and extensive clinical experience of nitroglycerin serve as the basis for its routine use in UA/NSTEMI. In patients with signs and symptoms of ongoing ischemia after three sublingual nitroglycerin tablets, intravenous nitrogycerin should be started at 10 mcg/min and increased every 3–5 min until ischemia is relieved or there is a significant drop in blood pressure (systolic BP <110 mmHg or >25% decrease from starting). IV nitroglycerine is also useful in NSTEMI patients with heart failure or hypertension. Due to the phenomenon of nitrate tolerance, the dose may have to be increased periodically. In patients without refractory symptoms, intravenous nitroglycerin should be converted to an oral or topical form within 24 h, with nitrate-free periods to avoid tolerance. Use of sildenafil within 24-h or tadalafil within 48-h represents a strong contraindication to the use of nitrates in any form. Nitroglycerine is also contraindicated in patients with hypotension and should be avoided in patients with RV infarction.

Table 9.8 Anti-ischemic agents

Drug	Route	Dose
Nitrates NTG	Sublingual tablets	0.3–0.6 mg up to 1.5 mg
	Spray	0.4 mg as needed
	Transdermal	0.2–0.8 mg/h q 12 h
	Intravenous	10–200 mg/min
Isosorbide dinitrate	Oral	10–80 mg BID or TID
Isosorbide mononitrate	Oral	30–240 mg QD
Beta Blockers		
Propranolol	Oral	20–80 mg QID
Metroprolol	Intravenous	5 mg q 5 min × 3
	Oral	50–200 mg BID
Atenolol	Intravenous	5 mg q 5 min × 2
	Oral	50–200 mg QD
Esmolol	Intravenous	500 mcg/kg IV over 1 min repeated before each upward titration 50 mcg/kg infusion increased by 50 mcg/kg every 5 min up to 200 mcg/kg/min
Calcium Channel Blockers		
Diltiazem-CD	Oral	120–360 mg qd
Verapamil-SR	Oral	120–480 mg qd

Beta-Blockers

Beta-blockers decrease myocardial contractility, systolic blood pressure, and heart rate, with the net effect of decreasing myocardial oxygen demand. A meta-analysis of three double blind randomized trials suggested that beta-blocker treatment was associated with a 13% relative reduction in the risk of progression to MI [27]. There is no evidence of superiority for any member of this class over the others, although there is a general consensus that beta-blockers with intrinsic sympathomimetic activity should be avoided, and in patients with stable heat failure with systolic dysfunction one of the three beta blockers with proven mortality benefits should be used (sustained-release metoprolol succinate, carvedilol, or bisoprolol).

In general, oral therapy should be initiated within 24 h of admission, though intravenous use is reasonable in those with ongoing rest pain and hypertension if contraindications are meticulously excluded—as these may be clinically subtle. These contraindications include active asthma, severe conduction disturbances (PR interval > 0.24 s, second or third degree AV block), congestive heart failure with low output state, bradycardia, or hypotension. Careful attention to the signs and symptoms of heart failure is mandatory when considering beta-blocker therapy, and in the marginal patient they have been associated with cardiogenic shock.

Calcium Channel Blockers

These agents variably produce vasodilation, decreased myocardial contractility, AV block, and sinus node slowing. The dihydropyridine calcium channel blockers nifedipine, amlodipine, and felodipine have mostly vaso-dilatory properties, whereas verapamil and diltiazem have a greater effect on contractility and conduction. A meta-analysis of the use of this class in UA showed no effect on death and non-fatal MI [28]. Diltiazem and verapamil should not be used in patients with low ejection fractions or congestive heart failure and nifedipine should not be used without a beta-blocker and may cause an increase in mortality in ACS patients [29–31]. These agents are presently reserved for patients with coronary spasm, recurrent ischemia on nitrates and beta-blockers, or beta-blocker intolerance [15].

Anti-platelet Therapy (Table 9.9)

Aspirin

Aspirin, at doses ranging from 75 to 325 mg daily, irreversibly inhibits cyclooxygenase-1 blocking the formation of thromboxane A2 and reduces platelet aggregation. When used in UA, aspirin has repeatedly been associated with a reduction in the risk of cardiac death and non-fatal MI by approximately 50% [32, 33]. Consequently, aspirin is recommended at an early and initial dose of 162–365 mg in all

Table 9.9 Anti-thrombotic and anticoagulation agents

Class	Drug	Route	Dose
Cyclo-oxygenase inhibitor	Aspirin	Oral	325 mg, then 81 mg qd
ADP-receptor antagonists	Clopidogrel	Oral	300–600 mg, then 75 mg qd
	Ticlopidine	Oral	500 mg, then 250 mg BID
	Ticagrelor	Oral	180 mg, then 90 mg BID
	Prasugrel	Oral	60 mg, then 10 mg qd
GP IIb/IIIa receptor antagonists	Abciximab	Intravenous	0.25 mg/kg bolus, then 0.125 mcg/kg/min (max 10 mcg/min) for 12–24 h
	Eptifibatide	Intravenous	180 mcg/kg bolus, then 2 mcg/kg/min up to 72 h
	Tirofiban	Intravenous	0.4 mcg/kg for 30 min, then 0.1 mcg/kg/min up to 108 h
Heparins	Heparin	Intravenous	60–70 U/kg (max 5000 U) bolus, then 12–15 U/kg/h (max 1000 U/kg/h) titrated to aPTT 1.5–2.5 times control
	Dalteparin	Subcutaneous	120 IU/kg (max 10,000 IU) BID
	Enoxaparin	Subcutaneous	1 mg/kg BID (may start with 30 mg IV bolus)
Direct thrombin Inhibitors	Bivalirudin	Intravenous	0.1 mg/kg bolus, 0.25 mg/kg/h For PCI with no prior treatment 0.75 mg/kg bolus, 1.75 mg/kg/h infusion
Anti-Xa	Fondaparinux	Subcutaneous	2.5 mg sc once daily

patients with ACS. It should be continued indefinitely at a dose of 81 mg unless side effects are manifest, as higher doses of aspirin (160 mg and greater) are associated with higher bleeding risk without additional benefit [34]. Contraindications to its use are allergy and active bleeding. In patients with a history of gastrointestinal bleeding, acid suppression therapies (proton-pump inhibitors) are recommended with the intent of reducing subsequent bleeding events.

Adenosine-Diphosphate Receptor Inhibitors

The binding interaction between adenosine diphosphate (ADP) and its receptor ($P2Y_{12}$) mediates platelet aggregation. Many P2Y12 inhibitors have been developed, and they are among the thienopyridine (ticlopidine, clopidogrel and prasugrel) and non-thienopyridine (ticagrelor) classes. Ticlopidine was the first widely used P2Y12 inhibitor, and decreased the rate of fatal and non-fatal MI by 46% in one study [35]. However, the risk of neutropenia, thrombocytopenia, and gastrointestinal side effects has limited its widespread clinical use. Compared to ticlopidine, clopidogrel has a faster onset of action and fewer side effects, and has become the most commonly used thienopyridine for UA/NSTEMI. In the Clopidogrel in Unstable angina to Prevent ischemic Events (CURE) [36] trial, 12,562 UA/NSTEMI patients were randomized to aspirin alone or aspirin plus clopidogrel. There was a 20% reduction in the composite endpoint of cardiovascular death, MI, or stroke with only a slight increase in the risk of bleeding with combination antiplatelet therapy. A 300–600 mg loading dose is recommended initially. Loading with 600 mg results in a more rapid platelet inhibition compared to the 300 mg dose [15]. For patients with UA/NSTEMI clopidogrel therapy is recommended at a maintenance dose of 75 mg daily for at least 1 month and ideally for up to 1 year in those treated medically or with a bare-metal stent. In patients who have received a drug eluting stent, clopidogrel should be continued for at least 1 year uninterrupted. This is in addition to lifelong recommended aspirin therapy [15].

The newest thienopyridine is prasugrel. It has the fastest onset of all P2Y12 inhibitors (30 min), and is less dependent on CYP2C19 biotransformation—a feature that theoretically reduces the individual heterogeneity observed with clopidogrel. In TRITON-TIMI 38, 13,608 patients with ACS and planned percutaneous intervention were randomized to prasugrel (loading dose of 60 mg, followed by 10 mg daily) or clopidogrel (loading dose 300 mg followed by 75 mg daily); both in addition to aspirin. At a median follow up of 14.5 months, prasugrel was associated with a lower incidence of non-fatal MI and stent thrombosis, which powered a significant reduction in the composite endpoint which also included cardiovascular death and stroke. This favorable effect came at the expense of increased life-threatening and fatal bleeding [37]. There was net harm in patients with a history of a previous CVA and prasugrel is contraindicated in this population. It was also shown to be of no clinical benefit in patients older than 75 years of age, and in those with body weight < 60 kg [38]. Prasugrel is not indicated in NSTEMI "upstream" of planned early coronary angiography, or when NSTEMI is treated with medical therapy alone [39, 40].

Ticagrelor is the only clinically available non-thienopyridine P2Y12 inhibitor. It is a reversible P2Y12 inhibitor, requires no conversion to its active metabolite and provides more rapid and uniform platelet inhibition than either clopidogrel or prasugrel. In the PLATO trial, 18.624 patients with ACS were randomized to ticagrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel, both in addition to aspirin. At 12 months, ticagrelor was associated with a significant 16% reduction in the composite primary endpoint of vascular

death, myocardial infarction or stroke, and a 22% decrease in all cause mortality. These comparative benefits were not associated with a significantly increased risk of composite major bleeding [41]. Ticagrelor can cause dyspnea in ~15% of patients, although rarely significant enough to cause discontinuation, and this often improves over time. Also, bradycardia can be seen. When using ticagrelor, only aspirin 81 mg should be used, as the benefit over clopidogrel is not seen with higher doses of aspirin [42].

In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued at least 5 days prior to surgery, and prasugrel discontinued at least 7 days prior to surgery [15]. In patients in whom received clopidogrel, but the risk of waiting 5 days is elevated, it may be reasonable to perform a CABG between days 1 and 4 after clopidogrel discontinuation. While there is higher rate of non-life threatening bleeding and transfusion requirements, a higher rate of life threatening bleeding has not been demonstrated [43].

Glycoprotein IIb/IIIa Inhibitors

The binding of fibrinogen to GP IIb/IIIa receptors on different platelets is the final event in platelet aggregation. GP IIb/IIIa antagonists occupy these receptors, preventing fibrinogen from cross-linking platelets, thereby preventing platelet aggregation. There are currently three intravenous agents approved for clinical use: abciximab, a monoclonal antibody; eptifibatide, a cyclic heptapeptide; and tirofiban, a non-peptide mimetic. These agents have been used both as medical therapy and as adjuncts to PCI. Three large older studies using the different agents have each shown a significant early reduction in death and MI that was sustained at 30 days [44–46]. In a meta-analysis of the 12,296 patients enrolled in these studies, there was a 34% relative reduction in the rates of death or MI during a 24-h period of medical management without revascularization (2.5% vs 3.5%; $p = 0.001$) [47]. This benefit is most pronounced in high-risk patients and is further amplified in patients who underwent PCI as part of an early invasive strategy.

However, most of the trials that established the effectiveness of Gp IIb/IIIa inhibitor therapies in UA/NSTEMI were performed prior the demonstrated benefits of oral ADP-receptor antagonists. The routine use of early "triple therapy" with aspirin, ADP-receptor and Gp IIb/IIIa antagonists has been associated with increased bleeding without a significant reduction in MI and death when used prior to percutaneous coronary intervention [48]. As a result, Gp IIb/IIIa antagonists are presently reserved for selected patients with breakthrough ischemia and a lower risk of bleeding. They are preferentially initiated in the cath lab and are particularly useful in patients who have not been preloaded with dual antiplatelet therapy. In patients undergoing an initial non-invasive strategy, ADP receptor inhibitors are preferable to GP IIb/IIIa receptor inhibitors.

Anticoagulation (Table 9.9)

In patients with a NSTEMI, anticoagulation, in addition to antiplatelet therapy, is indicated for all patients, irrespective of the initial treatment strategy chosen [15].

Unfractionated Heparin

Heparin is a glycosaminoglycan made up of multiple different polysaccharide chain lengths with different anticoagulant activity. Anti-thrombin III undergoes a conformational change when bound to heparin that accelerates its inhibition of thrombin and factor Xa. Heparin also binds competitively to other plasma proteins (acute phase reactants), blood cells, and endothelial cells which have varying concentrations, thus affecting its bioavailability. Another limitation of heparin is its lack of effect against clot-bound or platelet-rich thrombus and its degradation by platelet factor 4.

In a meta-analysis of six small trials in UA, the addition of unfractionated heparin to aspirin reduced risk of death or myocardial infarction by 33% compared with aspirin alone [49]. However, due to variable protein binding and bioavailability, heparin therapy requires frequent monitoring to assure that a safe therapeutic range is maintained. The target activated partial thromboplastin time (aPTT) should be 1.5–2.5× control and should be checked every 6 h after a dose change and every 24 h after 2 consecutive therapeutic values. Serial platelet counts are also recommended to monitor for heparin-induced thrombocytopenia.

Low Molecular Weight Heparin

Low molecular weight heparin is prepared by depolymerization of the polysaccharide chains of heparin [50]. The majority of chains contain <18 saccharide units and inactivate only factor Xa, in contrast to the longer chains which inhibit both factor Xa and thrombin (factor IIa). This results in more potent inhibition of thrombin generation. Compared with unfractionated heparin, low molecular weight heparin has lower plasma protein binding (and as a result does not require routine monitoring), greater bioavailability, more resistance to neutralization by platelet factor 4, greater release of tissue factor pathway inhibitor (TFPI), and a lower incidence of thrombocytopenia. Disadvantages are there may be an increased risk of minor bleeding particularly when switching from enoxaparin to UFH at the time of a PCI, it is more difficult to titrate and monitor during PCI, and it is really cleared. Enoxaparin is given 1 mg/kg subcutaneously every 12 h (in patients with CrCl >30 mL per minute). Overall the efficacy is similar to slightly improved compared to unfractionated heparin [51, 52].

Direct Thrombin Inhibitors

Direct thrombin inhibitors have the theoretical advantage over heparin of inhibiting clot bound thrombin and not being inhibited by circulating plasma proteins and platelet factor 4

[53]. The activated clotting time can be used to monitor anticoagulation activity, but usually is not necessary. Hirudin was shown in several trials to be associated with a small short-term reduction in death and MI, but bleeding was increased [54]. More recently, bivalirudin has been developed and clinically employed. The ACUITY trial randomized patients with UA/NSTEMI to bivalirudin compared to heparin with GP IIb/IIIa inhibition. Bivalirudin alone was associated with comparable short- and long-term ischemic outcomes, with a lower risk of major bleeding at 30 days (3.0% vs 5.7%), Bivalirudin is approved as a substitute for unfractionated heparin in patients with UA/NSTEMI undergoing PCI, and is the preferred agent in place of heparin in patients with heparin-induced thrombocytopenia.

Factor Xa Inhibitors

By inhibiting factor Xa upstream in the coagulation cascade this class of drugs reduce thrombin generation. Fondaparinux has dose-independent clearance, and a long half-life allowing for a more predictable and sustained anticoagulation with a fixed-dose once daily administration (2.5 mg subcutaneous once daily). Fondaparinux, when compared to enoxaparin in patients with NSTEMI, showed there was no difference in short term composite ischemic endpoint, but there was a lower risk of bleeding with fondaparinux [55]. As a result, it is approved for use in patients with UA/NSTEMI when an initial conservative strategy is employed, and is also the preferred agent in patients in whom a conservative strategy is selected and who have an increased risk of bleeding. It has been shown, however, to be associated with catheter thrombus formation, and if undergoing PCI an alternative anticoagulant should be used [15]. It is excreted by the kidneys and it is contraindicated with a CrCl of <30 mL/min.

Coronary Revascularization

In patients who present with a NSTEMI, there are generally two initial pathways for which to triage: (1) an invasive strategy in which coronary angiography is planned, and (2) an initial "ischemia-guided" or "conservative strategy". More recent studies, including a meta-analysis, suggest that intermediate to high risk patients (elevated troponins, ST depression on ECG, elevated TIMI or Grace scores), benefit from an invasive strategy [56–58] (Table 9.6). These studies have shown a reduction in death and MI, with less angina and rehospitalizations in patients triaged to coronary angiography with intent on revascularization. Particularly notable is the effect on decreasing recurrent MI, especially in high risk patients (GRACE scores > 140).

While the exact timing for the coronary angiography after presentation when an invasive strategy has not been delineated, an "early invasive" approach is considered within 24 h, and a "delayed invasive" angiography is within 25–72 h. It is reasonable to choose an early invasive strategy over a delayed invasive strategy for patients who are stabilized but considered high risk [59]. A more delayed strategy, however, is certainly reasonable in low to intermediate risk patients, particularly patients with renal insufficiency. An "urgent/immediate" (within 2 h) invasive strategy with intent to perform revascularization is indicated for NSTEMI patients without contraindications, who have refractory angina, or hemodynamic or electrical instability [15].

An ischemia-guided strategy is reasonable in low to intermediate risk patients, as defined by a TIMI score of 0–1, GRACE score < 109, no ST depression on ECG, and negative troponins. This strategy may particularly be preferred in women [60]. When this strategy is chosen, in order to detect ischemia and estimate prognosis, a noninvasive stress test should be considered prior to discharge, as long as the patient has been free of angina for 12–24 h. Patients with recurrent angina or ischemia despite intensive medical therapy, those with high risk findings on non-invasive testing, and those with LV dysfunction found on noninvasive testing, should then be referred to coronary angiography with intent on revascularization.

The choice of PCI with stent placement versus CABG is outside the scope of this chapter. Factors that may suggest benefit from CABG, however, include complex, multivessel coronary artery disease, diabetes, and systolic dysfunction. Technological advances, high success rates, and relatively low complication rates, however, have increasingly made PCI a revascularization alternative, particularly in patients with preserved left ventricular function, one or two vessel disease, or contraindications or high risk for surgery. A "heart team" approach that involves interventional cardiology and cardiothoracic surgery, and of course patient preference should be at the center of the decision making.

Prognosis and Follow-Up

In patients with NSTEMI, ongoing plaque instability and endothelial dysfunction persist for weeks as the healing process is taking place. There is also evidence of continued inflammation and a prothrombotic state. Several clinical and electrocardiographic features have been shown to increase the risk of death at 1 year after NSTEMI, and they include persistent ST-segment depression, congestive heart failure, advanced age, ST-elevation, severe COPD, positive troponin, prior CABG, renal insufficiency, and diabetes. In some studies, mental depression is also included as an independent risk factor for adverse events at 1 year.

Most patients are discharged on an anti-ischemic regimen that is similar to their in-patient regimen. The medications that are considered to have a class I indication in the ACC/

AHA guidelines for UA/NSTEMI are listed in Table 9.7 [15]. Patients should be given sublingual or spray nitroglycerine to be taken as needed.

After discharge patients should be seen in the outpatient setting within 1–2 weeks. They should be reassessed for the need for cardiac catheterization and revascularization if not undertaken at the index hospitalization, or if there was incomplete revascularization [56]. There will need to be extensive education on post discharge medications, especially antiplatelet therapy. While aspirin should be continued indefinitely, the duration of dual antiplatelet therapy will need to be a discussion between the patient and their cardiologist. Discontinuation of dual antiplatelet therapy should only be considered if the risks of bleeding outweigh the benefits from reduction in in-stent thrombosis. Continuing dual antiplatelet therapy >12 months after PCI may be considered in patients with low bleeding risk [15].

Aggressive lifestyle and risk factor modification should be employed in all patients, and is the cornerstone for secondary prevention. The goals should be: (1) effective glycemic control in diabetics (HbA1c <7.0); (2) hypertension control to a goal blood pressure <130–140/80 mmHg; (3) high dose statin therapy [61]; (4) smoking cessation; (5) initiation of a daily exercise program, preferably with cardiac rehab; (6) low-saturated-fat diet; (7) maintenance of optimal weight.

Practical Points

- The usual cause of UA/NSTEMI is atherosclerotic plaque disruption and non-occlusive thrombus formation.
- The history, physical examination, ECG, and troponin values provide critical information for early risk stratification.
- Initial pharmacotherapy should include aspirin, ADP-receptor antagonist, anticoagulation (heparin or low molecular heparin, or Xa inhibitors), nitrates, and the cautious use of beta-blockers.
- An early invasive strategy should be followed in high risk patients who are willing to undergo coronary revascularization. An early conservative strategy may be appropriate for low risk patients.
- Coronary artery revascularization should be performed in appropriate candidates.
- Long-term pharmacotherapy should include aspirin, an ADP-receptor antagonist, beta-blocker, statin, and an ACE inhibitor if indicated.
- Aggressive risk factor control to goals should be pursued.

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Acute ST Elevation Myocardial Infarction

10

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Acute myocardial infarction (AMI) remains a major public health issue and is the leading cause of death in the United States. ST elevation myocardial infarction is a syndrome that is comprised of clinical signs and symptoms of myocardial ischemia, electrocardiographic changes of ST elevation in two or more contiguous leads of at least 2 mm in men and at least 1.5 mm in women in leads V2/V3 or at least 1 mm in all other contiguous leads, and elevations in cardiac biomarkers, frequently troponin [1]. In 2009, roughly 680,000 patients were discharged from U.S. hospitals after an AMI [2]. Coronary occlusions associated with ST-elevation on electrocardiography account for about 30–45% of the AMI cases [3]. Although there is substantial overlap in diagnostic and therapeutic approaches, other forms of AMI are addressed in detail elsewhere under acute coronary syndromes.

Usual Causes

Atherosclerotic coronary artery disease and plaque rupture with resultant thrombosis remains the most common cause of AMI [4]. Other, less common causes include arteritis, trauma, embolization, congenital anomalies, hypercoagulable states, and substance abuse. Table 10.1 lists a number of pathologic processes other than atherosclerosis that may cause AMI [5].

Table 10.1 Non-atherosclerotic causes of acute myocardial infarction

Arteritis
Takayasu's disease
Polyarteritis nodosa
Mucocutaneous lymph node (Kawasaki's) syndrome
Systemic lupus erythematosus
Rheumatoid arthritis
Ankylosing spondylitis
Trauma to coronary arteries
Metabolic diseases with coronary artery involvement
Mucopolysaccharidoses (Hurler's syndrome)
Homocystinuria
Fabry's disease
Amyloidosis
Luminal narrowing by other mechanisms
Spasm
Dissection of the aorta extending into coronary artery
Emboli to coronary arteries
Infective endocarditis
Nonbacterial thrombotic endocarditis
Prosthetic valve emboli
Cardiac myxoma
Paradoxical emboli
Papillary fibroelastoma of the aortic valve
Congenital anomalies
Anomalous origin of the left coronary from the pulmonary artery
Left coronary from anterior sinus of Valsalva
Miscellaneous
Carbon monoxide poisoning
Polycythemia vera
Thrombocytosis
Cocaine abuse

Adapted from Cheitlin et al. [5]

Presenting Symptoms and Signs

History

A well-documented history is extremely important in establishing the diagnosis of AMI. The classic symptom is crushing retrosternal chest discomfort with radiation to the

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left arm [6]. Patients may also present with neck, jaw, back, shoulder, or right arm pain as the sole manifestation. Other associated symptoms include diaphoresis, dyspnea, fatigue, weakness, dizziness, palpitations, acute confusion, nausea, or emesis. Nausea and emesis are seen more frequently with inferior wall MI. Some individuals may present with epigastric pain, which can lead to the misdiagnosis of heartburn or another abdominal disorder. Elderly individuals may not have any chest discomfort but may present with symptoms of left ventricular failure, marked weakness, or syncope [7]. Postoperative patients and diabetic patients are other subgroups that may not experience classic symptoms with AMI.

Physical Examination

Patients presenting with AMI often appear anxious and in distress and a detailed physical exam is important in excluding other diagnoses and in risk-stratifying patients. A fourth heart sound is almost universally present in patients who are in sinus rhythm. All patients should have a thorough cardiac examination as a baseline to monitor for mechanical complications that may develop. Age, systolic blood pressure, heart rate, rales, and a third heart sound are important prognostic determinants in patients with AMI [8, 9]. A thorough baseline neurologic and peripheral vascular examination is also important and serves as a baseline to monitor for post intervention complications such as stroke or arterio-venous fistula.

Helpful Tests

Electrocardiography

The electrocardiogram (ECG) is a valuable clinical tool for the diagnosis and localization of AMI [10]. The electrocardiographic diagnosis of AMI requires at least 2 mm of ST elevation in V2/V3 in males, 1.5 mm in females, or at least 1 mm of ST elevations in at least two other contiguous leads in both males and females [1]. The presence of prior left bundle branch block may confound the diagnosis of AMI, but striking ST segment deviation that cannot be explained merely by conduction abnormality is suggestive of AMI. Sgarbossa et al. [11] validated three electrocardiographic criteria with independent value in the diagnosis of AMI in patients with left bundle branch block: ST segment elevation of 1 mm or more that was concordant with (in the same direction as) the QRS complex; ST segment depression of 1 mm or more in lead V_1, V_2, or V_3; and ST segment elevation of 5 mm or more that was discordant with (in the opposite direction from) the QRS complex.

Table 10.2 Biochemical markers for detecting myocardial necrosis

1. Any elevation of troponin T or I during the first 24 h after the index clinical event
2. Any elevation of CK-MB in two sequential samples
3. CK-MB twice upper reference limit at any time
4. CK-MB should rise and fall, stable elevated values are never due to MI
5. CK twice upper reference limit (less satisfactory)

CK creatine kinase, *MB* muscle band, *MI* myocardial infarction
Adapted from Tunstall-Pedoe et al. [12]

Cardiac Markers

The World Health Organisation (WHO) criteria for the diagnosis of AMI requires at least two of the following three elements: (a) history of typical chest discomfort, (b) electrocardiographic changes consistent with AMI, and (c) rise and fall in serum cardiac markers [12]. The serum cardiac markers that are used in the diagnosis of AMI include creatine kinase (CK), creatine kinase–myocardial band fraction isoenzyme (CK-MB), cardiac-specific troponins, and myoglobin. The American College of Cardiology and the European Society of Cardiology redefined the diagnosis of MI to include any elevation of serum cardiac markers (Table 10.2) [13]. While troponin, especially high sensitive troponin assays, are useful for ruling in most AMII, CK and CK-MB are helpful for diagnosing recurrent myocardial infarction due to the persistent elevation of troponin.

Echocardiography

The portability of echocardiography makes this a valuable clinical tool in the assessment of patients with AMI. This technique can be useful for confirming or excluding the diagnosis of AMI by examining wall motion [14] and to help with risk stratification [15]. The echocardiogram is also very useful in diagnosing the mechanical complications of AMI. However, it is vitally important that rapid initiation of treatment for STEMI is not delayed by reliance on an echocardiogram or any other diagnostic modality if the patient has a high likelihood of STEMI and meets the clinical and electrocardiographic criteria that were described earlier.

Differential Diagnosis

Pericarditis

Pericardial pain is usually aggravated by inspiration and lying supine. It is important to distinguish pericarditis from AMI because inadvertent fibrinolysis in patients with pericarditis may lead to hemopericardium. The ST changes in

pericarditis are diffuse, with a concave upward slope. Other important diagnostic features include PR segment depression and absence of reciprocal ST segment depression.

Myocarditis

Symptoms and signs of myocarditis may closely mimic those of AMI. A thorough history may be helpful if it reveals a more gradual onset of symptoms and prior upper respiratory tract symptoms in a relatively young patient. Serum cardiac markers usually remain elevated rather than peaking and returning to baseline levels.

Aortic Dissection

The pain due to an acute aortic dissection is typically substernal with radiation to the back or shoulders, extremely severe, and often described by the patient as a tearing or ripping sensation. The pain is maximal at onset and persists for many hours. In addition to the history, physical exam finding of differential blood pressures between the arms is worrisome for possible aortic dissection. Chest radiography often shows a widened mediastinum. A transthoracic echocardiogram may show an intimal flap in the proximal aorta. If the echocardiogram is non-diagnostic and dissection is still a clinical possibility, the patient should undergo more definitive testing in the form of computed tomography, magnetic resonance imaging, or transesophageal echocardiography. It is extremely important to diagnose this condition because fibrinolytic therapy usually results in death and if patients are taken to the catheterization lab, not only is definitive treatment delayed but intravascular manipulation with cathethers can result in catastrophic complications.

Hypertrophic Cardiomyopathy

Patients with hypertrophic cardiomyopathy may present with chest discomfort and shortness of breath similar to angina, which is related to increased myocardial oxygen demand. In this case, symptoms have usually been progressive for months or years. Transthoracic echocardiography is a useful test for diagnosing this condition. Use of nitroglycerin or dobutamine may precipitate hypotension and syncope in affected patients. Frequently these patients are treated with beta-blockers and disopyramide.

Pulmonary Embolism

Chest pain associated with severe shortness of breath without clinical or radiographic evidence of pulmonary edema, and a history that is consistent with recent long distance travel or co-morbidities that might suggest a hypercoagulable state should suggest pulmonary embolism. Echocardiography may be useful by demonstrating normal left ventricular wall motion and right ventricular dilatation and strain. Patients with pneumothorax and pleuritis may also present with substernal chest discomfort, but the character of the pain is different, and the pain is often worse with inspiration.

Cholecystitis

Patients with inferior AMI may present with epigastric or right upper quadrant pain that may mimic acute cholecystitis. Conversely, patients with acute cholecystitis may present with symptoms and occasionally ECG findings suggestive of an inferior AMI. The presence of fever, marked leukocytosis, and right upper quadrant tenderness favor the diagnosis of cholecystitis. Esophageal and other upper gastrointestinal symptoms may also mimic ischemic chest discomfort.

Costochondritis

Pain associated with costochondritis is usually associated with localized tenderness over the cartilage connecting the ribs to the sternum. The pain is usually described as sharp, worse with movement or inspiration, and frequently reproducible with palpation. Treatment for costochondritis includes non-steroidal anti-inflammatory medications.

Complications

Mortality after STEMI has steadily decreased over the last 20 years as more frequent use of early treatment with percutaneous coronary angioplasty (PCI) has become mainstream. Sudden cardiac death before hospital admission is the most common cause of mortality in AMI. In-hospital mortality is primarily due to circulatory failure resulting from either severe left ventricular dysfunction or one of the mechanical complications. The complications of AMI may be broadly classified as mechanical, electrical, ischemic, embolic, and pericardial.

Mechanical

Cardiac Rupture

Ventricular septal rupture, papillary muscle rupture, and free wall rupture are serious, life-threatening mechanical complications of AMI. Reperfusion therapy has reduced the overall incidence of cardiac rupture and shifted its occurrence to earlier after AMI.

Ventricular septal rupture occurs in 0.5–2% of patients [16]. The diagnosis should be suspected when a pansystolic murmur develops that was not present initially. Echocardiography with color flow imaging is the test of choice for diagnosing a ventricular septal rupture. Pulmonary artery catheterization with oximetry is also a useful diagnostic aid. This involves measuring oxygen saturations in the superior and inferior venae cavae, right atrium, right ventricle, and pulmonary artery under fluoroscopy. An intraaortic balloon pump (IABP) or temporary circulatory support device should be inserted as early as possible as a bridge to surgery if cardiogenic shock is present, unless there is significant aortic regurgitation. This decreases systemic vascular resistance, decreases shunt fraction, increases coronary perfusion, and maintains blood pressure. After insertion of an IABP or a temporary circulatory support device, vasodilators can be used with close hemodynamic monitoring. Surgical closure is the treatment of choice.

Historically cardiac free wall rupture was reported in 3% of patients after STEMI that were treated medically or with fibrinolytic therapy but the incidence of this has dropped as early reperfusion with PCI has become more common. Advanced age, female gender, hypertension, first AMI, and poor coronary collateral vessels are risk factors for free wall rupture. Free wall rupture constitutes part of the "early hazard" in patients treated with fibrinolytics (the mortality rate among patients who receive fibrinolytics is actually higher for the first 24 h and is attributable partially to cardiac rupture). Emergency thoracotomy with surgical repair is the definitive therapy and may save a few patients who can be taken to surgery immediately. Pseudoaneurysm results from a contained rupture of the left ventricular free wall by the pericardium and mural thrombus. Pseudoaneurysms communicate with the body of the left ventricle through a narrow neck, the diameter of the neck being less than 50% of the diameter of the fundus. Spontaneous rupture can occurs without warning in approximately one third of these patients.

Mitral Regurgitation

Most mitral regurgitation associated with AMI is transient, asymptomatic, and benign. However, severe mitral regurgitation due to papillary muscle rupture is a life-threatening but treatable complication of AMI that contributes to 5% of the cases of mortality after AMI. The overall incidence of papillary muscle rupture is 1%. Papillary muscle rupture is more common with an inferior MI and involves the posteromedial papillary muscle because its blood supply is solely via the posterior descending artery. In contrast, the anterolateral papillary muscle is perfused by both the left anterior descending and the left circumflex arteries. Complete transection of the papillary muscles is rare and usually results in immediate shock and death. Patients with rupture of one or more papillary muscle heads typically present with sudden severe respiratory distress from development of pulmonary edema and may rapidly develop cardiogenic shock. A new pansystolic murmur is audible at the cardiac apex with radiation to the axilla or to the base of the heart. In posterior papillary muscle rupture, the murmur radiates up the left sternal border and may be confused with the murmur of ventricular septal rupture or aortic stenosis. Two-dimensional echocardiography, with Doppler and color flow imaging, is the diagnostic modality of choice. Hemodynamic monitoring with a pulmonary artery catheter may reveal large V waves in the pulmonary capillary wedge pressure (PCWP) tracing. Vasodilator and IABP therapy are very effective therapies in patients with acute severe mitral regurgitation. Surgical therapy should be considered immediately in patients with papillary muscle rupture. The prognosis is very poor in patients treated medically, and even though perioperative mortality (20–25%) is higher than for elective surgery, surgical repair should be considered in every patient.

Left Ventricular Failure and Cardiogenic Shock

The severity of left ventricular dysfunction correlates with the extent of myocardial injury. Patients with a small AMI may have regional wall motion abnormalities but overall normal left ventricular function because of compensatory hyperkinesia of the nonaffected segments. Killip and Kimball [8] classified four subsets of patients on the basis of clinical presentation and physical findings at the onset of AMI (Table 10.3). More recently, in comparison with the 81% mortality in their original paper [8], the 30-day mortality rate was 58% among patients in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) I trial [17] who presented with cardiogenic shock and who were treated with fibrinolytics. An IABP or a temporary circulatory support device should be inserted as soon as possible in a patient with cardiogenic shock.

Prompt revascularization also remains an important consideration in these high-risk patients. In the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? (SHOCK) trial [18], patients with cardiogenic shock were randomly assigned to undergo emergency revascularization (n = 152) or initial medical stabilization (n = 150). The rates of overall mortality at 30 days did not differ significantly between the revascularization and medical therapy groups because of sample size (46.7% vs. 56.0%;

Table 10.3 30-day mortality based on Killip class

Killip class	Physical findings	Mortality (inhospital) (%)
Class I	Clear lungs, no S3 gallop	6
Class II	Basal rales and/or S3 gallop	17
Class III	Pulmonary edema	38
Class IV	Cardiogenic shock	81

Adapted from Killip and Kimball [8]

difference, 9.3%; 95% confidence interval, 20.5–1.9%; $p = 0.11$). However, the 6-month mortality rate was significantly lower among the patients who underwent revascularization than in those receiving medical therapy (50.3% vs. 63.1%; $p = 0.027$). Therefore, emergency revascularization is the standard of care for patients with AMI complicated by cardiogenic shock.

Right Ventricular Failure

Mild right ventricular dysfunction is common after inferior MI, but hemodynamically significant right ventricular impairment is seen in only 10% of patients. Right ventricular involvement depends on the location of the right coronary artery occlusion; significant dysfunction is noted only if occlusion is proximal to a large acute marginal branch. The triad of hypotension, jugular venous distention, and clear lungs is very specific but has poor sensitivity for right ventricular infarction. Patients with severe right ventricular failure have symptoms of low cardiac output. These include diaphoresis, clammy extremities, and altered mental status. Patients are often oliguric and hypotensive. The ECG usually shows an inferior MI. ST elevation in V4R in the setting of suspected right ventricular infarction has a positive predictive value of 80%. Hemodynamic monitoring with a pulmonary artery catheter usually reveals high right atrial (RA) pressures relative to the PCWP. Acute right ventricular failure results in underfilling of the left ventricle and a low cardiac output state. A RA pressure higher than 10 mmHg and a RA/PCWP ratio of 0.8 or higher are strongly suggestive of right ventricular infarction [19]. Treatment of right ventricular infarction involves volume loading, inotropic support with dobutamine, and maintenance of atrioventricular synchrony. Patients who undergo successful reperfusion of the right coronary artery and the right ventricular branches have improved right ventricular function and decreased 30-day mortality rates [20].

Left Ventricular Aneurysm

An acute aneurysm expands in systole, wasting contractile energy generated by the normal myocardium. Chronic true aneurysms develop in 10% of patients after AMI and are more commonly seen after anterior AMI. Chronic aneurysms are defined as those persisting more than 6 weeks after AMI. Patients with acute aneurysms may present with heart failure and even cardiogenic shock. Patients with chronic aneurysms may present with heart failure, ventricular arrhythmias, and systemic embolism, or they may be asymptomatic. Heart failure with acute aneurysms is treated with intravenous vasodilators and IABP. Anticoagulation with warfarin (Coumadin) is indicated for patients with mural thrombus. In patients with refractory heart failure or refractory ventricular arrhythmias, surgical resection of the aneurysm should be considered. Revascularization may be beneficial in patients with a large amount of viable myocardium in the aneurysmal segment.

Early Electrical Complications of Acute Myocardial Infarction

Arrhythmias are the most common complications after AMI, affecting approximately 90% of patients. Conduction abnormalities causing hypotension may necessitate temporary or permanent pacemaker therapy. These are briefly summarized in Table 10.4. An implantable cardioverter defibrillator (ICD) is indicated in patients with sustained ventricular fibrillation (VF) or ventricular tachycardia (VT) more than 2 days after the AMI if recurrent ischemia or transient causes have been ruled-out. The risk of long-term electrical complications after AMI is increased in patients with large infarctions and lower left ventricular ejection fractions, and the management of this issue is addressed below under "Follow-up".

Ischemic Complications of Acute Myocardial Infarction

Infarct extension is a progressive increase in the amount of myocardial necrosis within the same arterial territory as the original AMI. This may manifest as a subendocardial AMI extending to a transmural AMI or as AMI that extends and involves the adjacent myocardium. Recurrent angina within a few hours to 30 days after an acute AMI is defined as postinfarction angina. The incidence is between 23 and 60%. The frequency of postinfarction angina is higher after non–Q wave MI and fibrinolytic therapy than after primary PCI. Patients with postinfarction angina have an increased incidence of sudden death, reinfarction, and acute cardiac events. Either percutaneous or surgical revascularization improves prognosis in these patients. Infarction in a separate territory may be difficult to diagnose in the first 24–48 h after the initial event. It may be very difficult to differentiate ECG changes of reinfarction from the evolving ECG changes of the index MI. Recurrent elevations in CK-MB after normalization or to more than 50% of the prior value are diagnostic for reinfarction. Echocardiography may also be useful by revealing a wall motion abnormality in a new area.

Embolic Complications of Acute Myocardial Infarction

The incidence of clinically evident systemic embolism after AMI is approximately 2%; the incidence is higher in patients with anterior AMI. The overall incidence of mural thrombus after AMI is approximately 20%. Large anterior MIs may be

Table 10.4 Electrical complications of acute myocardial infarction and their management

Category	Arrhythmia	Objective	Treatment
1. Electrical instability	Ventricular premature beats	Correction of electrolyte deficits and increased sympathetic tone	Potassium and magnesium replacement, beta blockers
	Ventricular tachycardia	Prophylaxis against ventricular fibrillation, restoration of hemodynamic stability	Antiarrhythmic agents; cardioversion
	Ventricular fibrillation	Urgent reversion to sinus rhythm	Defibrillation
	Accelerated idioventricular rhythm rhythm	Observation unless hemodynamic function is compromised	Increase sinus rate (atropine, atrial pacing); antiarrhythmic agents
	Nonparoxysmal atrioventricular junctional tachycardia	Search for precipitating causes (e.g., digitalis intoxication); suppress arrhythmia only if hemodynamic function is compromised	Atrial overdrive pacing; antiarrhythmic agents; cardioversion relatively contraindicated if digitalis intoxication present
2. Pump failure/excessive sympathetic stimulation	Sinus tachycardia	Reduce heart rate to diminish myocardial oxygen demands	Antipyretics; analgesics; consider beta blocker unless congestive heart failure present; treat latter with diuretics and afterload reduction
	Atrial fibrillation and/or atrial flutter	Control ventricular rate; restore sinus rhythm	Diltiazem, verapamil, digitalis; anticongestive measures (diuretics, afterload reduction); cardioversion; rapid atrial pacing (for atrial flutter)
	Paroxysmal supraventricular tachycardia	Reduce ventricular rate; restore sinus rhythm	Vagal maneuvers; verapamil, digitalis, beta-adrenergic blockers; cardioversion; rapid atrial pacing
3. Bradyarrhythmias and conduction disturbances	Sinus bradycardia	Acceleration of heart rate only if hemodynamic function is compromised	Atropine; atrial pacing
	Junctional escape rhythm	Acceleration of sinus rate only if loss of atrial "kick" causes hemodynamic compromise	Atropine; atrial pacing
	Atrioventricular block and intraventricular block	–	Ventricular pacing

Adapted from O'Gara et al. [23]

accompanied by associated mural thrombus in 60% of patients. Patients with large anterior MI or mural thrombi should be treated with intravenous heparin for 3–4 days with a target partial thromboplastin time of 50–70 s. Oral therapy with warfarin should be continued for at least 3 months in patients with mural thrombi and in those with large akinetic areas detected by echocardiography.

Pericarditis

The incidence of early pericarditis after AMI is approximately 10%, and it usually develops within 24–96 h [21]. Patients complain of progressive, severe chest pain that lasts for hours. The pain is postural, worse with lying supine, alleviated if the patient sits up and leans forward, usually pleuritic in nature, and worsened with deep inspiration, coughing, and swallowing. Radiation to the trapezius ridge is nearly pathognomonic for acute pericarditis and is not seen in patients with ischemic pain. Postinfarction pericarditis is treated with aspirin in doses of 650 mg every 4–6 h. Nonsteroidal antiinflammatory agents and corticosteroids should not be administered to these patients because they may interfere with myocardial healing and contribute to infarct expansion [22]. Colchicine may be beneficial in patients with recurrent pericarditis. Dressler's syndrome (post-MI syndrome) occurs in 1 and 3% of patients and is seen 1–8 weeks after AMI. Patients present with chest discomfort suggestive of pericarditis, fever, arthralgia, malaise, elevated leukocyte count, and elevated erythrocyte sedimentation rate. Treatment is similar to that for early postinfarction pericarditis.

Therapy

Reperfusion Therapy

One of the most important goals in patients presenting with ST elevation myocardial infarction is to quickly select appropriate patients for reperfusion therapy with percutaneous coronary intervention. A general treatment algorithm [23] is outlined in Fig. 10.1 Initial diagnostic and treatment measures are listed in Table 10.5 Reperfusion therapy, with pri-

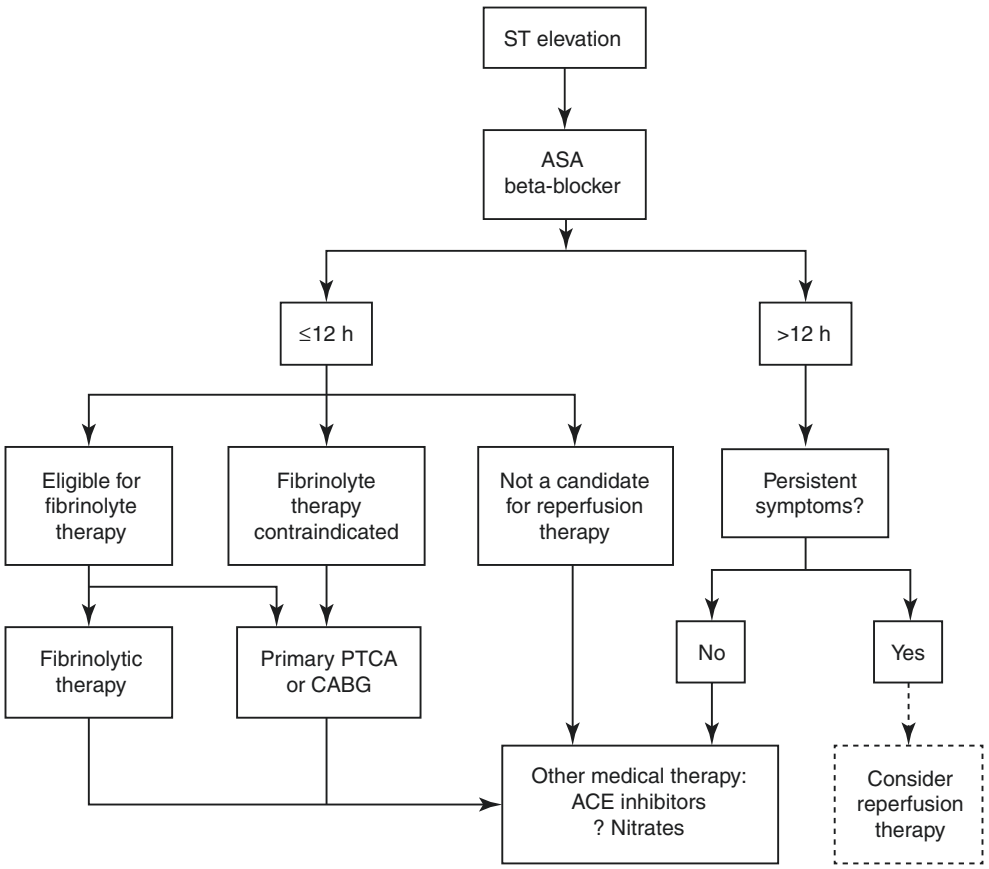

Fig. 10.1 General treatment algorithm. All patients with ST segment elevation on the electrocardiogram should receive aspirin, beta blockers, and heparin (unless receiving streptokinase). Eligible patients evaluated within 12 h should be expeditiously treated with one of the currently available fibrinolytic agents [recombinant tissue plasminogen activator (rt-PA), recombinant plasminogen activator (rPA), tenecteplase–tissue plasminogen activator (TNK-tPA), streptokinase (SK)] or be considered for primary percutaneous coronary intervention (PCI). Primary PCI should also be considered when fibrinolytic therapy is absolutely contraindicated and in patients with cardiogenic shock or delayed presentations. Individuals treated after 12 h should receive medical therapy and, on an individual basis, may be considered for reperfusion therapy or angiotensin-converting enzyme inhibitors (particularly if left ventricular systolic function is impaired)

Table 10.5 Diagnostic and treatment measures in patients with ST segment elevation myocardial infarction

Initial diagnostic measures
Use continuous ECG; automated BP, HR monitoring
Take targeted history (for AMI inclusions, fibrinolysis exclusions); check vital signs, perform focused examination
Start IV administration, draw blood for serum cardiac markers, hematology, chemistry, lipid profile
Obtain 12-lead ECG
Obtain chest radiograph (preferably upright)
General treatment measures
Aspirin, 160–325 mg (chew and swallow)
Nitroglycerin, sublingual: test for Prinzmetal's angina, reversible spasm; antiischemic, antihypertensive effects
Oxygen: sparse data; probably indicated, first 2–3 h in all; continue if low arterial oxygen saturation (<90%)
Specific treatment measures
Reperfusion therapy: goals: door-to-needle time <30 min; door-to-balloon time <90 min
Conjunctive antiplatelets and antithrombotics: clopidogrel, prasugrel, ticagrelor, heparin enoxaparin, bivalirudin
Adjunctive therapies: beta-adrenoceptor blockade if eligible, intravenous nitroglycerin (for antiischemic or antihypertensive effects), ACE inhibitor [especially with large or anterior AMI, heart failure without hypotension (SBP > 100 mmHg), previous MI]

ACE angiotensin converting enzyme, *AMI* acute myocardial infarction, *BP* blood pressure, *ECG* electrocardiogram, *HR* heart rate, *IV* intravenous, *SBP* systolic blood pressure
Adapted from O'Gara et al. [23]

mary PCI as the preferred mode of reperfusion, should be used in all eligible patients presenting with a ST elevation myocardial infarction and symptom onset of less than 12 h or in patients that continue to have angina symptoms or dynamic EKG changes. The target time from first medical contact to percutaneous coronary intervention is less than 90 min. It is important to set up a regional system of care that includes transport by emergency medical services of patients directly to PCI capable hospitals. For patients that arrive at non-PCI capable hospitals, the goal should be immediate transfer to a PCI capable hospital if this can be achieved within 120 min [24–26]. A worksheet documenting the precise timing of these events should be completed and used as part of the continuous quality improvement program to improve efficiency with early data feedback provided to both the catheterization laboratory and emergency department staff.

In cases where there is an anticipated delay of greater than 120 min from first medical contact to device time at a PCI capable hospital, the administration of fibrinolytics should be considered. If a decision is made to use fibrinolytics, this should be administered within 30 min of presentation. The contraindications to fibrinolytic therapy are listed in Table 10.6 [23]. Of the patients given fibrinolytic therapy, 25% have persistent occlusion or early occlusion of the infarct-related artery. Red blood cell transfusion is required in approximately 5% and hemorrhagic stroke occurs in approximately 1% of patients, despite the fact that those at increased risk for bleeding are excluded from treatment.

Table 10.6 Absolute and relative contraindications for fibrinolytic therapy in acute myocardial infarction

Contraindications
Previous hemorrhagic stroke at any time; other strokes or cerebrovascular events within 1 year
Known intracranial neoplasm
Active internal bleeding (does not include menses)
Suspected aortic dissection
Cautions/relative contraindications
Severe uncontrolled hypertension on presentation (blood pressure >180/110 mmHg)
History of prior cerebrovascular accident or known intracerebral pathology not covered in contraindications
Current use of anticoagulants in therapeutic doses (INR, 2.0–3.0); known bleeding diathesis
Recent trauma (within 2–4 weeks), including head trauma or traumatic or prolonged (>10 min) CPR or major surgery (<weeks)
Noncompressible vascular punctures
Recent (within 2–4 weeks) internal bleeding
For streptokinase/anistreplase: prior exposure (especially within 5 days–2 years) or prior allergic reaction
Pregnancy
Active peptic ulcer
History of chronic severe hypertension

CPR cardiopulmonary resuscitation, *INR* International Normalized Ratio
Adapted from O'Gara et al. [23]

Primary percutaneous coronary intervention (PCI), with patency rates of more than 90% and few contraindications has become the preferred mode of reperfusion. Keeley et al. [27] analyzed 23 trials, including data from 7739 patients, comparing primary PCI with fibrinolytic therapy. PCI was associated with a significant reduction in short-term mortality, reinfarction, and hemorrhagic stroke. Primary PCI is the preferred reperfusion strategy when performed in a timely manner (balloon inflation in less than 90 min), by individuals skilled in the procedure (performing more than 75 PCI procedures per year), and supported by experienced personnel in high-volume centers (more than 200 PCI procedures per year) [23, 28]. Patients with persistent ischemia refractory to medical therapy who are not candidates for primary PCI and patients in whom PCI fails should be considered for coronary bypass surgery. Coronary bypass surgery is also indicated in patients at the time of surgical repair of mechanical complications of AMI.

Adjunctive Pharmacotherapy

Several interventions should quickly be undertaken while patients are being evaluated for reperfusion therapy (Tables 10.5 and 10.10) [23]. Pharmacotherapy for STEMI patients can be broadly divided into antiplatelets, anticoagulants, and pharmacotherapy aimed at combating the effects of poor cardiac function such as beta blockers, diuretics, nitrates, etc.

Antiplatelet

All patients should be given 162–325 mg of aspirin on presentation and continued indefinitely [29]. Dual anti-platelet therapy with a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, ticagrelor) should also be administered as early as possible in patients with suspected ST elevation myocardial infarction as these medications have been shown to reduce a combined endpoint of death, re-infarction, and stroke across various patient populations including those who receive reperfusion therapy [30–35]. While there are small differences in major cardiovascular end points with the different novel antiplatelet agents, two of the biggest discriminators that determine which agent is best for the individual patient are onset of action from taking the medication and how the drug metabolites are eliminated (Table 10.7).

Anticoagulation

The anticoagulants used during a STEMI fall into three broad categories: direct thrombin inhibitors (bivalirudin), in-direct thrombin inhibitors (unfractionated heparin and low molecular weight heparins such as enoxaparin) and GP 2b/3a inhibitors (Abciximab, tirofiban, and eptifibatide). While heparin therapy is the standard of care, there

is limited large scale randomized trial data to support this recommendation and even the most recent ACC/AHA guidelines give heparin monotherapy during a STEMI a level of evidence C indicating that this recommendation is based on expert consensus and limited trial data. Despite this, heparin treatment is a cornerstone for the treatment of STEMI. The recommended heparin regimen is a bolus of 60 U per kilogram (maximum, 4000 U) and a maintenance of 12 U per kilogram per hour (maximum, 1000 U per hour) to maintain an activated partial thromboplastin time 1.5–2.0 times that of control times (i.e., 50–70 s). The addition of intravenous glycoprotein GP IIb/IIIa receptor antagonists (abciximab, tirofiban, eptifibatide) to heparin can be considered, especially if there is evidence of large thrombus burden, however, due to the increased bleeding risk with concomitant Gp 2b/3a inhibition, the current ACC/AHA STEMI guidelines advocate the use of dual anticoagulation only in high risk patients with large thrombus burden.

The role of Bivalirudin in STEMI care is evolving rapidly based on recently presented trial results (Table 10.8). The strongest data for Bivalirudin vs Heparin + GP 2b/3a inhibition is based on the large multi-center HORIZONS AMI trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction). HORIZONS AMI randomized 3602 STEMI patients to either Bivalirudin or Heparin + GP IIb/IIIa inhibition and showed a slight all cause mortality benefit (2.1% vs 3.1%, p = 0.047) and a decrease in 30 day major bleeding (4.9% vs 8.3%, p < 0.01) with the use of Bivalirdin [36]. The biggest complication in the bivalirudin arm was a greater risk for stent thrombosis in the first 24 h (1.3% vs 0.3%, p < 0.001). Like, HORIZONS AMI, the EUROMAX trial (European Ambulance Acute Coronary Syndrome Angiography) also revealed a lower rate of major bleeding (2.6% vs 6.0%, p < 0.001) when compared to standard therapy (heparin and in most cases concomitant use of GP IIa/IIIb inhibition) but did not find a significant mortality advantage with the use of bivalirudin. Unlike HORIZONS AMI, a large number of patients in the ERUOMAX trial underwent radial interventions, perhaps explaining the lower rates of major bleeding and the lack of mortality difference seen between the two groups [37]. Similar to HORIZONS AMI, there was an increased risk of stent thrombosis with the use of Bivalirudin in EUROMAX (1.1% vs 0/2%, p = 0.007).

In addition to the greater risk for stent thrombosis with the use of Bivalirudin, another concern that has been raised with both of the aforementioned trials is that they are not actual comparisons between heparin and Bivalirudin as the use of GP IIa/IIIb inhibition and its associated bleeding risk is a very important confounder. Based on these concerns, recent single center studies have examined the role of Bivalirudin versus Heparin monotherapy. HEAT PPCI was a single center European study that examined the role of Bivalirudin vs Heparin in 1917 STEMI patients and revealed no significant difference in bleeding risk with heparin monotherapy versus bivalirudin (3.1% vs 3.5%, p = 0.59) [38]. Driven largely by increased stent thrombosis (3.4% vs 0.9%, p = 0.001) and re-infarction, the major adverse cardiovascular event (MACE) rate with bivalirudin therapy was significantly higher than the MACE rate with heparin therapy (8.7% vs 5.7% p = 0.01). Like EUROMAX, a large percentage of procedures (~80%) in HEAT PPCI were performed via radial access. Also, as opposed to both EUROMAX and HORIZONS AMI where Plavix was the preferred P2Y12 inhibitor of choice, in HEAT PPCI, 89% of patients received one of the newer P2Y12 agents (Prasugrel and Ticagrelor). Due to the fact that HEAT PPCI was a single center trial and the results differed greatly from prior studies done with Bivalirudin, more work needs to be done to identify the optimal anticoagulation regimen.

Table 10.7 P2Y12 Inhibitors

	Onset	Metabolism/elimination
Clopidogrel	2 h	Renal
Prasugrel	30 min	Renal
Ticagrelor	2–3 h	Hepatic

Table 10.8 Anticoagulants

	HORIZONS AMI (3602 patients)			EUROMAX (2218 patients)			HEAT PPCI (1829 patients)		
	All patients received Plavix			*Bivalirudin given in Ambulance*			*80% Radial, Bailout GP Iia/IIIb use (~15% of cases)*		
				Frequent GP Iia/IIIb use, Frequent radial use			*Frequent use of novel P2Y12 agent (89% of cases)*		
	Heparin (%)	Bivalirudin (%)	p-value	Heparin (%)	Bivalirudin (%)	p-value	Heparin (%)	Bivalirudin (%)	p-value
All cause mortality	3.1	2.1	p = 0.047	3.1	2.9	0.86	4.3	5.1	
MACE	2.9	1.8	p = 0.03	5.5	6.0	0.64	5.7	8.7	0.01
Major bleeding	8.3	4.9	<0.01	6.0	2.6	p < 0.001	3.1	3.5	0.59
Stent thrombosis	0.3	1.3	p < 0.001	0.2	1.1	p = 0.07	0.9	3.4	0.001

Other Pharmacotherapy

Routine use of early intravenous beta blockers does not appear to have significant benefit and should be reserved for those with hypertension or tachycardia [39]. If used, beta blockers should be given orally and started after hemodynamic conditions stabilize. Intravenous nitroglycerin should be given for the first 24–48 h in patients with congestive heart failure, large anterior infarction, persistent ischemia, or hypertension. It should be continued beyond 48 h in patients with recurrent angina or persistent pulmonary congestion. Patients should be asked about recent use of sildenafil (Viagra) because administration of nitroglycerin within 24 h of sildenafil ingestion may cause severe hypotension. Finally, angiotensin-converting enzyme (ACE) inhibitor therapy and long-term aldosterone blockade is recommended in patients with ST segment elevation in two or more anterior leads, with clinical heart failure in the absence of hypotension or known contraindications, and with left ventricular ejection fraction less than 40%. Contraindications to long-term aldosterone blockade include renal insufficiency (serum creatinine >2.0 mg/dL) or hyperkalemia (potassium >5.0 mg/dL) and should only be pursued in those who are already receiving adequate doses of an ACE inhibitor. Other medications may be necessary to treat electrical complications or left ventricular failure (Table 10.9).

Table 10.9 Dosages of drugs commonly used in the management of complicated acute myocardial infarction

Drug	Dose	Side effects
Bradycardia, atrioventricular block		
Atropine	0.5 mg IV q5min to maximum of 2.0 mg	Hallucinations, fever, VT/VF, urinary retention, acute angle glaucoma
Isoproterenol (Isuprel)	2–10 μg/min IV titrated to HR	Tachycardia, hypotension, increased O_2 demand
Aminophylline	300–400 mg IV over 15–30 min	Tachycardia, atrial arrhythmia, CNS toxicity
Supraventricular arrhythmias		
Esmolol (Brevibloc)	500 μg/kg IV over 1 min, repeated before each upward titration	CHF, bronchospasm, hypotension, bradycardia, AV block
	50 μg/kg min infusion, increased by 50 μg/kg every 5 min up to 200 μg/kg/min	
Propranolol (Inderal)	1 mg/min IV up to 0.1 mg/kg	Same as for esmolol
Metoprolol (Lopressor)	5 mg IV over 2 min; repeated q5min twice	Same as for esmolol
Atenolol (Tenormin)	5 mg IV over 2 min; repeated in 10 min	Same as for esmolol
Verapamil (Calan, Isoptin)	5 mg IV over 2 min; then 1–2 mg q2min up to 20 mg	CHF, hypotension, heart block, bradycardia
Diltiazem (Cardizem)	0.25 mg/kg IV over 2 min, then 5–15 mg/h	Same as for verapamil
Digoxin (Lanoxin)	0.5 mg IV over 5 min, then 0.25 mg IV q4h to 1 mg	Ventricular dysrhythmias, heart block, increased infarction size
Procainamide (Pronestyl)	20–30 mg/min IV to 12–17 mg/kg, then 1–4 mg/min	Hypotension
Adenosine (Adenocard)	6 mg IV, then 12 mg IV if not effective	Flushing, chest pain, dyspnea, sinus pauses
Ventricular arrhythmias		
Lidocaine (Xylocaine)	1 mg/kg IV, 0.5 mg/kg IV q10min one to four times, followed by 2–4 mg/min infusion	Nausea, numbness, confusion, slurred speech, respiratory depression, tremors, seizures, sinus arrest
Amiodarone (Cordarone)	150 mg over 10 min, 1 mg/min × 6 h, then 0.5 mg/min	Hypotension, myocardial depression, bradycardia, conduction block
Magnesium sulfate	2 g over 5 min, 8 g over 24 h	Flushing, bradycardia
Heart failure, shock		
Nitroglycerin	50–200 μg/min as IV infusion	Hypotension
Nitroprusside (Nipride)	0.25–10 μg/kg/min IV infusion	Hypotension, thiocyanate toxicity
Enalaprilat (Vasotec)	0.625–1.25 mg IV q6h	Hypotension, azotemia
Labetalol (Normodyne)	20–80 mg IV q10min, then 2 mg/min IV infusion	Hypotension, bradycardia
Furosemide (Lasix)	20–160 mg IV	Hypokalemia, hypomagnesemia
Bumetanide (Bumex)	1–3 mg IV	Nausea, cramps
Dobutamine (Dobutrex)	5–20 μg/kg/min IV	Tolerance
Dopamine (Inotropin)	2–20 μg/kg/min IV	Increased oxygen demand
Norepinephrine (Levophed)	2–16 μg/min IV	Peripheral and visceral vasoconstriction
Milrinone (Primacor)	50 μg/kg over 10 min IV, then 0.375–0.75 μg/kg/min	Ventricular dysrhythmias

AV indicates atrioventricular, *CHF* congestive heart failure, *CNS* central nervous system, *HR* heart rate, *IV* intravenous, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Table 10.10 Adjunctive pharmacologic management for acute myocardial infarction with doses

Oxygen	2–4 L/min by nasal cannula
Sublingual nitroglycerin	0.4 mg every 2–5 min three times
Aspirin	160–325 mg every day
Clopidogrel	600 mg initially and 75 mg every day maintenance
Prasugrel	60 mg initially and 10 mg every day maintenance
Ticagrelor	180 mg initially and 90 mg every day maintenance
Morphine	2–5 mg every 5–30 min
Heparin	60 U/kg (max, 4000 U), 12 U/kg/h (max, 1000/h) adjusted to keep aPTT 50–70 s × 48 h
Beta blockers	
Metoprolol (Lopressor)	5 mg IV three times over 15 min; 50 mg orally 10 min later; then 100 mg orally twice daily
Atenolol (Tenormin)	5 mg IV twice over 10 min; 50 mg orally 10 min later; then 100 mg orally every day
Intravenous nitroglycerin	10–200 μg/min infusion
ACE inhibitors	
Captopril (Capoten)	6.25–50 mg orally t.i.d.
Enalapril (Vasotec)	2.5–20 mg orally b.i.d.
Lisinopril (Prinivil, Zestril)	2.5–20 mg orally daily
Ramipril (Altace)	2.5–20 mg orally daily
Warfarin (Coumadin)	2–10 mg orally adjusted to INR

ACE angiotensin-converting enzyme, *INR* International Normalized Ratio

Evolving Therapy

There are several ways in which reperfusion rates and patient outcomes might be improved. Potential options include improving prompt access to reperfusion, different dosing regimens of established agents; improved adjunctive therapy (Table 10.10); the development of novel antiplatelet and anticoagulant agents; and the use of temporary circulatory assist devices. While outside the scope of this discussion, additional work is also being done on culprit vs multi-vessel PCI in patients presenting with multiple coronary lesions, the use of aspirations devices for thrombectomy, and the role for left ventricular decompression with cardiac support devices.

Prognosis

The Thrombolysis in Myocardial Infarction (TIMI) risk score for ST segment elevation AMI is a simple tool for bedside risk assessment [40, 41]. This score has been validated in multiple clinical trials. The elements of the TIMI score are shown in Fig. 10.2 and include history, physical examination, and electrocardiographic findings on presentation. The actual score is a summed weighted integer score based on eight characteristics. Application of the TIMI risk score has revealed a significant, nearly linear, 30-fold graded increase in risk between patients with a score of 0 and those with a score of 8 or higher. Figure 10.2 shows the prediction of in-hospital mortality with TIMI risk score for ST segment elevation MI.

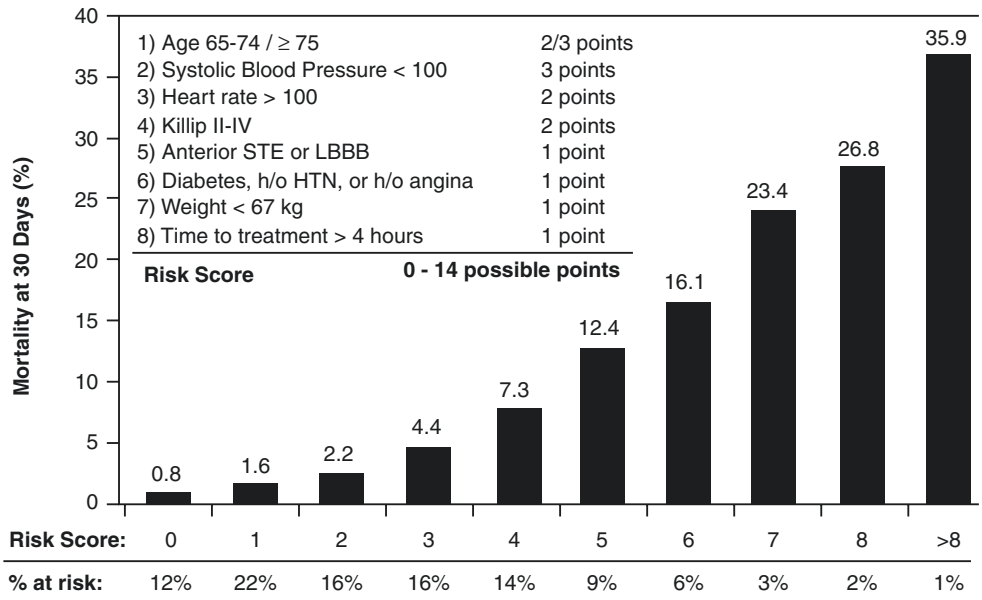

Fig. 10.2 Prediction of inhospital mortality with Thrombolysis In Myocardial Infarction (TIMI) risk score for ST-segment elevation myocardial infarction stratified by reperfusion therapy

Follow-Up

Secondary prevention is extremely important and reflects medical therapy and risk factor modification related to atherosclerotic disease (see Chap. 7). All patients should be considered for a cardiac rehabilitation program and should follow diet and exercise prescriptions [42]. All patients should be considered for long-term therapy with aspirin [43], beta blockers [44], statins [45], and ACE inhibitors [46]. Long-term anticoagulation is indicated for patients with persistent atrial fibrillation, for patients with left ventricular thrombus, and for secondary prevention in patients unable to take aspirin or clopidogrel. For statins, high-dose therapy is recommended given evidence of potential benefit with this strategy following acute coronary syndromes [47]. Smoking cessation and control of hypertension, dyslipidemia, diabetes, and weight to target values should be vigorously pursued.

Practical Points

- Age, blood pressure, heart rate, congestive heart failure, and ECG findings allow early risk stratification in the emergency department.
- Echocardiography should be performed in hemodynamically unstable patients to exclude mechanical complications.
- All patients should be given 162–325 mg of aspirin. Clopidogrel should be considered for dual antiplatelet therapy and is an alternative if the patient has a true allergy to aspirin. Other new antiplatelet drugs should also be considered.
- Patients should receive heparin (or other anticoagulation) unless they are treated with streptokinase.
- Patients should receive beta blockers unless beta blockers are contraindicated.
- Expeditious reperfusion therapy should be the goal in all patients with AMI.
- Primary PCI is superior to fibrinolytic therapy if performed in a timely manner (less than 90 min) in an experienced interventional laboratory.
- ACE inhibitors and aldosterone blockade are indicated in patients with large anterior AMI or left ventricular systolic dysfunction.
- Risk stratification should be performed to select high-risk patients for elective coronary artery revascularization and ICD therapy.
- Aspirin, beta blockers, statins, and ACE inhibitors have each been shown to reduce long-term mortality.
- American Heart Association Step II diet, exercise, and complete smoking cessation are indicated. Control of hypertension, hyperlipidemia, diabetes, and weight to target values should be aggressively pursued.

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Primary Hypertension

11

Kenneth A. Jamerson

Definition/Differential Diagnosis

Hypertension is a leading cause of mortality worldwide. While the association between blood pressure and cardiovascular (CV) risk exists at every level of systolic and diastolic blood pressure, the definition of hypertension is established by exceeding a blood pressure threshold of 140/90 mmHg on two occasions [1]. Repeat measures of blood pressure will determine whether initial elevations persist and require immediate attention or return to normal values requiring only surveillance. The 140/90 mmHg cut point correlates to acceleration in CV risk that has been established from natural history studies (the Framingham Heart study) [2]. However, the amount of CV risk that is acceptable in a population may vary from country to country. For example, Canada and Europe accept higher blood pressure cut points to confirm the diagnosis of hypertension [3]. Over the decades the United States has modified the threshold of elevated blood pressure that confers the diagnosis of hypertension from 160/95 mmHg to the present value of 140/90 mmHg thereby increasing the prevalence of hypertension from approximately 14.5% of the population to 23% (Table 11.1) [4]. In a recent systematic review on the topic of determining the threshold on which to treat hypertension, strong support was found for initiating treatment at a threshold of 150/90 mmHg in subject greater than age 60, while little evidence could be found for the current target of <140/90 mmHg for subjects less than age 60 [5].

The classification of blood pressure in the adult population is presented in Table 11.2. It is assumed that the blood pressure represent subjects who are not taking antihypertensive drugs and are not acutely ill. When systolic and diastolic blood pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For example, 180/90 mmHg should be classified as stage 2 hypertension, as would 140/110 mmHg. Isolated systolic hypertension is defined as systolic blood pressure (SBP) of 140 mmHg or greater and diastolic blood pressure (DBP) below 90 mmHg and staged appropriately (e.g., 170/85 mmHg is defined as stage 2 isolated systolic hypertension). In addition to clas-

Table 11.1 Age-adjusted and age-specific prevalence of hypertension[a]

Population group	NHANES III: prevalence of hypertension (%)
Overall	29.1
Men	29.7
Women	28.5
Age 18–39 years	7.3
Age 40–59 years	32.4
Age 60 years and over	65.0
Black	42.1
White	28.0
Hispanic	26.0
Asian	24.7

U.S. population aged 18 and over, 2011–2012
Adapted from Nwankwo et al. [57]
[a]Hypertension is defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg and/or taking antihypertensive medication or as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or currently taking antihypertensive medication. Values are percentages

Table 11.2 Categories of BP in Adults*

BP Category	SBP	DBP
Normal	<120 mm Hg	<80 mm Hg
Elevated	120–129 mm Hg	80–84 mm Hg
Hypertension		
Stage 1	130–139 mm Hg	85–89 mm Hg
Stage 2	140–159 mm Hg	90–99 mm Hg

*Individuals with SBP and DBP in 2 categories should be considered in the higher category
BP indicates blood pressure; DBP diastolic blood pressure; and SBP systolic blood pressure

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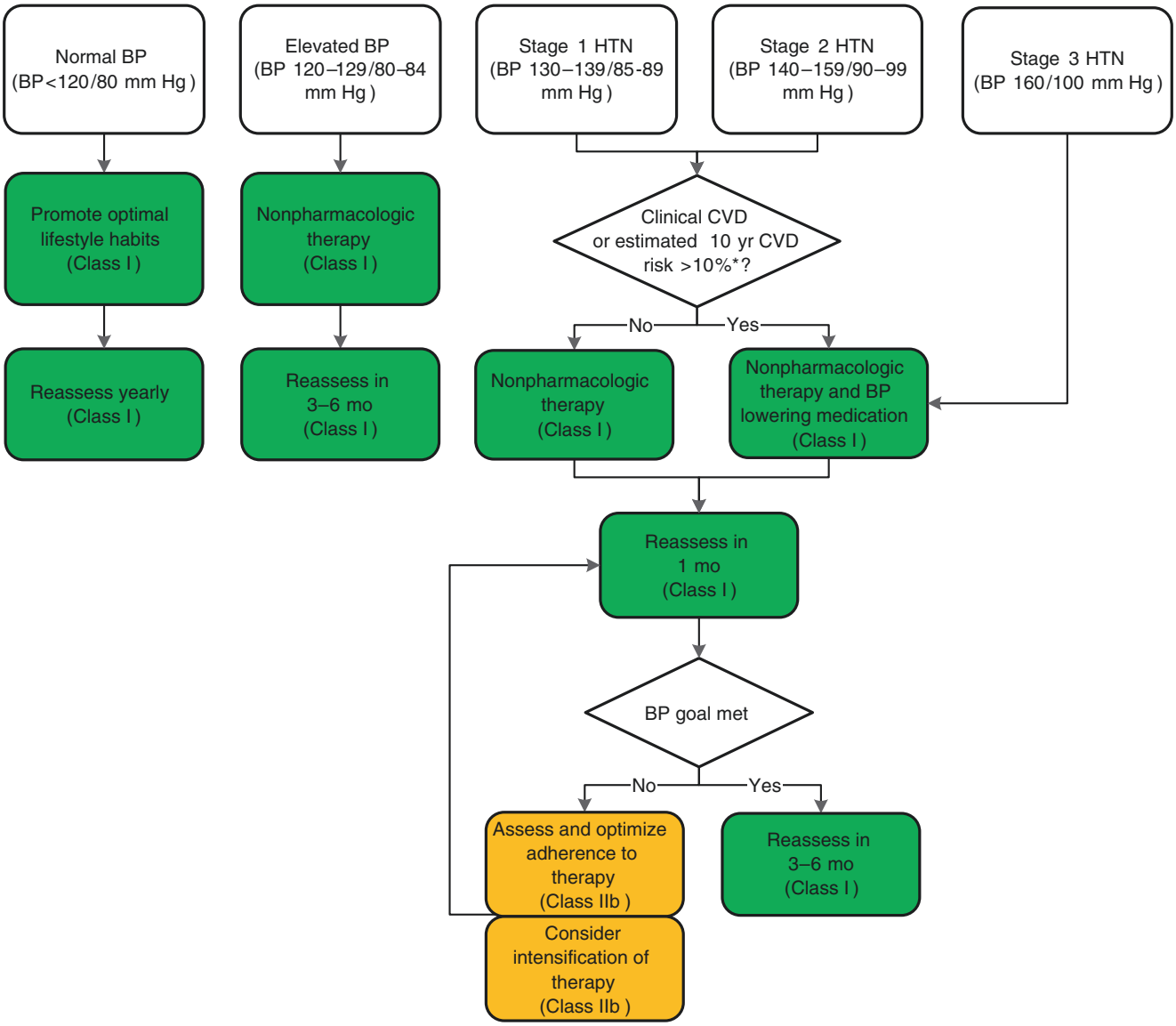

Fig. 11.1 Risk stratification and treatment

sifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify presence or absence of target organ disease and additional risk factors. This specificity is important for risk classification and treatment (see Fig 11.1). For example, a patient with diabetes and a blood pressure of 142/94 mmHg should be classified as having stage 1 hypertension with another major risk factor (diabetes). The identification of co-morbid conditions is important for assessing an individual's overall cardiovascular risk and may have some bearing on treatment (hypertension and chronic kidney disease is an indication for initiating therapy with a blocker of the renin-angiotensin system) [5].

Previous guidelines advocated for even lower levels of blood pressure in some sub-population of hypertension at higher risk for cardiovascular disease (CVD) (diabetes and renal insufficiency) to targets below 130/85 mmHg [6, 7]. However, the recommendations for aggressive targets for blood pressure control stem from epidemiology studies and retrospective analyses of clinical trials. The studies are able to show an association between lower levels of blood pressure with lower CVD risk, but do not prove that the intervention with lowering blood pressure to targets below 130/85 mmHg is of any greater benefit than that seen with achieving more conventional targets of 140/90 mmHg. Clinical trials were needed to provide the evidence on which clinicians could make changes in patient management for more aggressive blood pressure targets. Recently completed clinical trials on aggressive blood pressure control are reviewed in this chapter (man-

agement of hypertension). There is a paucity of data demonstrating any clinical benefit of targeting a SBP much below 140 mmHg.

Natural history surveys indicate that both SPB and DBP confer risk for CVD, however, national guidelines prior to 1997 placed emphasis on the DBP for the purpose defining hypertension [8]. Current blood pressure guidelines define hypertension based on either systolic or diastolic blood pressure levels. Moreover, SBP level may better predict CV risk than diastolic [9]. There is considerable evidence that pulse pressure (the difference between systolic-diastolic) may provide even greater prognostic information on CV risk than either systolic or diastolic. In Framingham, middle-aged and elderly persons had increased CVD risk with lower DBP at any level of SBP ≥120 mmHg, suggesting that higher pulse pressure (PP) is an important component of risk. Ultimately, one can only reduce or control PP by targeting SBP [10]. Thus while all parameters of blood pressure are important to estimating CV risk, it is clinically prudent to focus special attention on lowering SBP for reducing CV risk.

Gender and ethnicity have a significant effect of the prevalence of hypertension in the United States. The estimated prevalence rate of hypertension is approximately 21% in the general population but as high as 41% in African Africans (Table 11.1). The epidemiology of hypertension may also help distinguish primary from secondary hypertension. Primary hypertension occurs most frequently in the fifth and sixth decades of life. African Americans have higher incident rates of hypertension occurring at earlier ages [11]. Thus, the onset of hypertension in very young Caucasian women and in adults in during the seventh decade of life and beyond may infer secondary hypertension more frequently than primary as etiology of elevated blood pressure.

Usual Causes of Hypertension

Subjects with hypertension can be sub-categorized into two groups: those where the rise in blood pressure is secondary to another medical problem or ingestion of exogenous materials, secondary hypertension; and those where the primary pathophysiologic process is elevated blood pressure, or primary (essential) hypertension. This chapter will focus only on essential or primary hypertension. In essential hypertension, both hereditary and environmental factors contribute to elevated blood pressure.

Heredity

From epidemiology surveys it has been estimated that approximately 30% of the population variation in systolic blood pressure can be accounted for by heritability or polygenetic factors [12]. Evidence from twin studies and family cohorts provide estimates as high as 70%. The differences in heritability estimates reflect the diversity of the population under study and the influence of obesity and other environmental factors that interact with genes in producing hypertension [13]. While the familial distribution of blood pressure is a plausible explanation for the aggregation of blood pressure in families, few studies have unequivocally confirmed that genetic relationships are more important than environmental components of family life [14]. Advances in cellular and molecular biology have identified candidate gene with altered in ion channels and ion channel regulation, aldosterone signaling, vasoconstriction and inflammation while genome-wide association studies have detected more than 50 blood pressure loci, and mapping by admixture linkage disequilibrium identified the role of the apolipoprotein L1 (APOL1) in hypertension-attributed kidney disease in African Americans [15].

Environmental Factors

There are many environmental factors that might affect level of blood pressure. The following section briefly discusses the mutable factors that have a significant impact on the treatment of hypertension identified by a consensus of experts [1].

Obesity

Obesity is common in middle aged Americans especially in those that develop hypertension. In one follow-up study of First National Health and Nutrition Examination Survey (NHANES I), adiposity as measured by body mass index (BMI) was a strong predictor of hypertension and conversely weight loss was associated with a decrease in blood pressure [16]. In Framingham, nearly 70% of newly acquired hypertension was attributable to prior obesity [17]. It is alleged that obesity is more deleterious to the CV system than is generalized obesity [18]. The mechanism whereby obesity is related to blood pressure is not well understood but it includes adipokines, inflammation, and oxidative stress. For subjects with BMI > 40, bariatric surgery may be a more potent intervention [19]. Importantly, the risk of adiposity can be improved with weight loss of only a few kilograms [20].

Salt

There is significant data to suggest that salt is linked to hypertension. In a small series of studies it has been estimated that SBP raises 1.2 mmHg per every 10 mmol increase in dietary sodium [21–23]. Considerable evidence can be mounted to contest the relationship between sodium intake and blood pressure within populations [23–27]. Although there exists controversy in regard to a causal role for sodium in the genesis of hypertension, the impact of sodium restric-

tion on lowering blood pressure has been clearly demonstrated. The Dietary Approach to Stop Hypertension (DASH) diet described a dose related reduction in blood pressure in response to dietary sodium restriction. The reduction in sodium intake to levels below current recommendations of 100 mmol per day and the DASH diet led to a 7.1 mmHg reduction in blood pressure in normotensive participants and 11.5 mmHg in hypertensive subjects [28].

Stress

Although both perceived and experienced stresses are associated with hypertension, there are few ways to quantify their impact on individuals. This limitation has led to maneuvers such as mental arithmetic and immersion of the arm into cold water as standard measure of stress. Although it is difficult to quantitate stress, it is becoming increasingly clear that stress reduction has important benefits for health [29, 30]. Transcendental meditation has resulted in significant reduction in blood pressure and regression in left ventricle hypertrophy. The effect of meditation in African Americans has led to blood pressure reductions (on average 10.7 mmHg) that exceed the response from most single drug therapies [31].

Alcohol

A true direct relationship between regular alcohol use and hypertension remains unproven. Several series of comparing periods of alcohol withdrawal (during hospitalization) find a reduction in blood pressure during abstinence [32]. The results of short-term intervention studies suggest a short-term presser effect of drinking 3–8 drinks per day [33]. While a cause and effect relationship has yet to be established, it remains prudent to resurrect alcohol intake to 1–2 ounces per day as suggested by the American Heart Association.

Helpful Tests/Presenting Symptoms and Signs

When a patient's blood pressure has been documented at greater than 140/90 mmHg on more than two occasions the diagnosis of hypertension is confirmed. The initial evaluation includes three components that all converge to estimate the amount of target organ damage that currently exists and to estimate the risk.

The first component is a patient interview that includes a family history, a review of organ systems with particular attention given to the cardiovascular system and the identification of lifestyle factors that impart excess CV risk.

The second component includes a physical exam that with careful attention to eye grounds, the neck, heart, lungs, abdomen and the peripheral vasculature. Abbreviated exams of other organ system may be appropriate for the initial examination. Hemorrhages and exudates on fundoscopic exam, specific valvular murmurs, abdominal bruits, and polycystic kidneys are key findings that describe either severity of hypertension or indicates the etiology of elevated blood pressure.

Table 11.3 Initial laboratory evaluation

Test	Implications
Urine examination	Helpful in ruling out renal disease
Urea nitrogen or serum creatinine determination	Can rule out kidney failure; provides an index of baseline kidney function
Serum potassium;	Hypokalemia (<3.5 mEq/L) in patients not taking medication suggests a search for primary hyperaldosteronism
Serum glucose elevation[a]	Assists in diagnosis of diabetes mellitus
Uric acid measurements[a]	Provides baseline; may be predictor of future gout
Serum cholesterol with HDL, LDL, and triglycerides if indicated[a]	Provides information about another risk factor for heart disease
Calcium level[a]	Excludes hypercalcemia as a primary cause of hypertension
ECG	Helpful in determining the presence of LVH, ischemia, heart block, etc.

HDL high-density lipoprotein, *LDL* Low-density lipoprotein, *LVH* left ventricular hypertrophy

[a]An automated blood chemistry may be less expensive than individual determinations

The third component includes laboratory assessment. The initial lab panel is a basic screening chemistry profile to measure electrolytes (Table 11.3). Electrolytes provide screening information of renal function while serum potassium is the recommended screening test for primary hyperaldosterone. A urinalysis provides addition information on renal function and possible renal causes for hypertension. Electrocardiography (EKG) is the recommended screening test for hypertension induced changes in the heart. The recommendation for a CBC and uric acid level provides less information on target organ damage but does uncover the frequent association of gout and low hematocrit as risk factors for arteriosclerosis. A fasting glucose and lipid profile will similarly uncover increased CV risk from diabetes mellitus and dyslipidemia.

Clinical Management

There are a few fundamental questions that guide hypertension management: (a) when to initiate therapy?, (b) will specific antihypertensive medications provide CV benefits beyond lowering blood pressure alone?, and (c) what the optimal blood pressure target that confers maximal CV protection?

At What Threshold Should Drug Therapy Be Initiated?

The Veterans Administration Cooperative study was one the first randomized trial to show reduction in morbidity and mortality with the treatment of hypertension. The initial report focused on subjects with diastolic pressures between 115–129 mmHg [34]. But of greater public health interest was the second report on subjects with DBP 90–114 mmHg proving that hypertensive morbidity and progression of hypertension were obviated by treatment [35]. In a systematic review on when to initiate therapy, the resulting recommendation is to initiate treatment at the threshold of SBP of 150 mmHg in subjects greater than age 60 [5]. While the evidence for treating hypertension in younger subjects were not as compelling, the early lesson learned from the VA study prevails and the threshold for initiating therapy is 140/90 mmHg.

Will Specific Antihypertensive Medications Provide CV Benefits Beyond Lowering Blood Pressure Alone?

In November 1997, when the Sixth Joint National Committee on Prevention, Reduction, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) issued its recommendations, there was a paucity of data suggesting that antihypertensive agents other than diuretics and ß-blockers could provide such benefits [1]. However, clinical trials involving hundreds of thousands of subjects have been conducted yet they yield very little new data.

The completion of several large clinical trials: the Captopril Prevention Project (CAPPP) [36], the Intervention as a Goal in Hypertension Treatment (INSIGHT) [37], the Nordic Diltiazem (NORDIL) study [38], the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) [39], the United Kingdom Prospective Diabetes Study (UKPDS) [40], the Reduction of Endpoints in NIDDM with the AII Antagonist Losartan (RENAAL) [41], the Ibesartan Diabetic Nephropathy Trial (IDNT) [42] and the African American Study of Kidney Disease and Hypertension (AASK) [43] has provided important information on the selection of specific antihypertensive drug classes. The most robust of the prospective trials for assessing the cardio-protective benefits of specific drug classes is the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The ALLHAT study evaluated 40,389 high-risk patients with hypertension, aged 55 years or older. The study compared chlorthalidone, a diuretic; amlodipine, a calcium channel blocker (CCB); lisinopril, an ACEI; and doxazosin, an α-adrenergic blocker. The primary outcome is a composite of fatal coronary heart disease (CHD) and nonfatal MI. The doxazosin arm was discontinued early when patients demonstrated a 25% increase in CV events driven primarily by a twofold greater hospitalization rate for heart failure when compared to the participants in the diuretic arm [44, 45]. In the final report on the primary outcomes, there was no advantage of lisinopril, or amlodipine, for preventing fatal and non-fatal MI when compared to chlorthalidone [45].

Subjects with stage 2 hypertension in general will not achieve of a reduction to <140/90 mmHg with a single agent and may be candidates for combination therapy. Thiazide-like diuretics were considered an essential component of any drug combination [46]. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPISH) trial, investigators compared initial combination therapy with benazepril and HCTZ to benazepril with amlodipine in 10,567 patients with hypertension and high risk for CAD. The trial was termination early for efficacy in favor of amlodipine and benazepril. Both therapies achieved blood pressure control in more than half the participants with only a single tablet but amlodipine and benazepril conferred a 20% advantage for the primary endpoint of stroke, MI, coronary revascularization, and cardiovascular death. Initial combination therapy is effective and safe [47]. The ASCOT investigators reported similar observations when they compared a strategy of sequential monotherapy with either amlodipine ± perindopril or atenolol ± thiazide diuretic finding a 32% survival free rate for composite CV endpoint of stroke MI and CVD death in favor of amlo ± perindopril. The trial was terminated early before the primary end point of fatal + non-fatal MI could be adequately addressed [48].

No specific drug class has demonstrated superiority in modifying CV outcomes. However, blocking the renin-angiotensin system has proven superiority for retarding progression to dialysis in subjects with impaired renal function. Beta blocker therapy has been relegated to second line therapy for hypertension after retrospective analyses find little effect on reducing strokes in hypertensive subjects [49]. A modified treatment algorithm is provided in Fig. 11.2.

Trials That Assess the Impact of Aggressive Blood Pressure Control

The comparable effectiveness of more than one blood pressure target has been addressed by a few studies. Five clinical trials have assessed the impact of aggressive blood pressure control (when compared to traditional levels) on cardiovas-

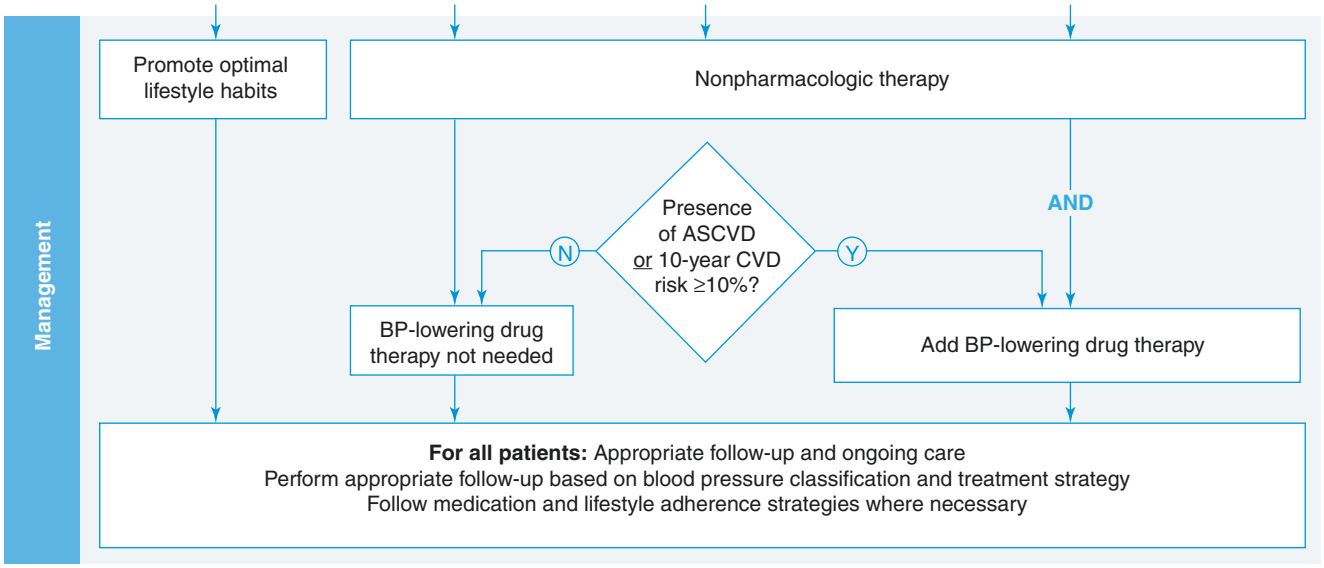

Fig. 11.2 Modified algorithm for the treatment of essential hypertension. (Adapted from Joint National Committee on Prevention, Disease, Detection, Evaluation and Treatment of High Blood Pressure [1])

cular risk in various patient populations. The Hypertension Optimal Treatment (HOT) study [48] in a general hypertensive population, the United Kingdom Prospective Diabetes Study (UKPDS) [50] in hypertensive diabetic patients, the Appropriate Blood Pressure Control in Diabetes trial (ABCD) [51–54] in normotensive and hypertensive diabetics, the African American Study of Kidney Disease and Hypertension (AASK) [43] in hypertensive African American patients with renal insufficiency and the Action to Control Cardiovascular Risk in Diabetes (ACCORD study) conducted in participants with type diabetes mellitus [55].

The investigators in the HOT study sought to determine the optimal DBP target in a cohort of 18,790 hypertensive patients, by measuring the incidence of CV events that occurred when DBP was lowered to each of three target levels: <90, <85, and <80 mmHg. The study participants were aged 50–80 years (mean age, 61.5 years) with DBP between 100 and 115 mmHg. Within this population, 8.0% had diabetes, 6.0% had coronary heart disease (CHD), and 1.2% had suffered a stroke. Felodipine was given to all patients, with additional therapy and dosage increases permitted to achieve target DBP. After almost 46 months of follow-up, the incidence of CV events was similar among the three target-level groups. However, the incidence of CV events among the diabetic sub-population was twice as low in the <80 mmHg group as in the <90 mmHg group (22 vs. 45; p for trend = 0.005). These results suggest a benefit of aggressive blood pressure control in diabetics but only in a secondary analysis [48].

The UKPDS study examined whether the relatively more tight control of blood pressure would prevent microvascular and microvascular sequela in 1148 hypertensive patients with type 2 diabetes. The participants in this study, aged 25–65 years (mean age, 56.4 years), had a mean blood pressure of 160/94 mmHg. Participants were randomized to undergo tight control (<150/85 mmHg) or less tight control (<180/105 mmHg). The data demonstrated a prominent reduction in CV risk, death, and complications due to diabetes among the patients who underwent tight control [50]. Blood pressure control was more important than glycemic control in this cohort. The study was not, however, able to recommend aggressive blood pressure targets below 140/90 mmHg.

The ABCD trial compared the effects of intensive blood pressure control (goal DBP of 75 mmHg) with those of moderate control (goal DBP of 80–89 mmHg) in 480 normotensive patients and 470 hypertensive patients with type 2 diabetes. The patients in this study were aged 40–74 years. Among patients without gross albuminuria, there was no difference between the intensive and moderate control in the progression of microvascular disease [51, 52]. The incidence of all-cause mortality was lower in patients who received intensive blood pressure control than in those who received moderate control.

The AASK study examined the effect of aggressive blood pressure control on progression to renal failure in 1094 African Americans aged 18–70 years with hypertension and renal impairment (glomerular filtration rate of 25–65 mL/min per 1.73 m^2 at baseline). The investigators compared a mean arterial blood pressure (MAP) of less than 92 mmHg (SBP 128 and DBP 79 mmHg) to a MAP of 102–107 (or SBP 140 and DBP 90 mmHg). In this trial there was no

advantage to achieving the more aggressive blood pressure target [Abstract presented at the American Heart Association 201 Scientific Sessions] [56].

The ACCORD study sought to determine if aggressive blood pressure control target (to a SBP target <120 mmHg) would decrees the combined rates of fatal and non-fatal stroke and MI, a major cardiovascular event, or cardiovascular death when compared to a usual blood pressure target of <140 mmHg [53]. The investigators were able to achieve a greater than 17 mmHg difference in SBP between the two treatment groups, but failed to show any significant difference in the primary composite endpoint. The pre-specified secondary analyses provide little insight on the overall strategy of aggressive blood pressure control. There was a trend toward reduction in total stroke, MI and cardiovascular death (hazard ratio of 0.90 95% CI 0.78–1.04) this finding was driven by a significant reduction in total stroke in the intensive group. The intensive group (intensive glycemic and blood pressure control) had a slightly higher mortality rate (hazard ratio 1.22 95% CI 1.01–1.46). Thus with no benefit on the primary end point, a lower stoke rate but higher mortality, there is no evidence supporting the target a SBP of <120 mmHg in type II diabetic subjects.

Summary

As is evident from the completed clinical trials mentioned here, investigators have committed significant effort to determine whether there are distinctions among anti-hypertensive drug classes or combination or drugs that confer CV protection. The key findings from these trials indicate that most drug classes are effective, combination therapy with calcium channel blocker and Ace inhibitor have advantages, and beta blocker therapy should be deferred to second line or add on therapy.

Many of the large-scale trials show that blood pressure control is critical for the general hypertensive population. This is particularly true for subjects with hypertension and higher risk for CV complications like concomitant diabetes or renal insufficiency. However, it appears that control of SBP to >140 mmHg is as effective in preventing CV events, as is achieving the more aggressive targets of SBP of 130 mmHg or less. These observations in prospective trials are in contrast to the recommendations of consensus panels that used retrospective studies to arrive at the recommendation for aggressive blood pressure control for diabetics and patients with renal insufficiency. In a systematic review on blood pressure targets, strong evidence is found for the target SBP < 140/90 mmHg even those with diabetes and or renal disease [5].

At this time, there appears to be no reason to recommend specific drug class in the management of hypertension in a general population. An exception is blocking the renin-angiotensin system in hypertensive patients with diabetic nephropathy. The ALLHAT study continues, but its investigators have already determined that alpha-blockers do not decrease CV risk as well as diuretics and, accordingly, are relegated to second-line or add-on therapy.

As the inquiry into the "best" antihypertensive drug class continues, it appears that diuretics, ACEI's, beta blockers, angiotensin receptor blockers, and calcium channel blockers (excluding their use in patients with impaired renal function) are still contenders. It is likely that multiple drugs will be necessary to control blood pressure to a target of SBP less than 140 mmHg.

Practical Points

- Stage 1 hypertension is diagnosed based on persistent elevation in blood pressure above 130–139/80–89 mmHg.
- Hypertension therapy can be initiated with a calcium channel blocker, diuretic, ACE-inhibitor, ARB, or combination therapy. Ace-inhibitors and ARB's are indicated for renal disease.
- The target blood pressure level for treatment is <130/80 mmHg even in those with diabetes and renal disease hypertensive diagnosed based on persistent elevation in blood pressure above 130/80 mmHg.
- The treatment target for blood pressure control is to less than 130/80 mmHg (~138/85).
- Diuretics, Calcium Channel Blockers, and Ace inhibitors are recommended selections for initial drug therapy.
- Combinations of classes may be necessary to achieve optimal control of blood pressure.

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Approach to Secondary Hypertension

12

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An imperfect, but widely-accepted distinction has been drawn between primary and secondary hypertension. As a description, "primary" is no more informative than the term it replaced, "essential." Moreover, authorities variably describe obesity—common in hypertensive patients—as a primary or secondary factor in hypertension. This inconsistent classification of such an important factor suggests that the dichotomy between primary and secondary forms of hypertension is false, or at least poorly-defined. Nonetheless, classification of hypertension as primary or secondary yields a clinically-useful heuristic, and the focus of this chapter will be putting the concept of secondary hypertension to use in helping patients.

It has been estimated that roughly 90–95% of people with hypertension have primary hypertension. Primary hypertension is multifactorial in origin and probably represents a complex interaction of multiple genetic traits with environmentally-influenced factors such as weight, sodium intake and excretion, and stress. In contrast, patients with secondary hypertension have a clearly identifiable cause of or contributor to their blood pressure elevation and may benefit from correction of the underlying problem. It is important to note that the likelihood that a patient's hypertension is secondary, rather than primary, depends heavily upon the clinical setting. The approximate prevalence of 5% in the general population increases to as high as 10–26% among refractory hypertensive patients seen at referral centers. This chapter describes the most common causes of secondary hypertension, with particular focus on issues relevant to patient management. It is important to remember that many people have secondary hypertension *in addition* to primary hypertension and that addressing the secondary issues can lead to reduction, but not necessarily elimination, of a patient's need for blood pressure–lowering therapy.

The best up-to-date estimate from the National Health and Nutrition Examination Survey suggests that 8.9% of patients with hypertension are "resistant" to triple-drug therapy [1]. An excellent statement regarding the diagnosis, evaluation, and treatment of resistant hypertension has been published by the American Heart Association [2]. The 8th Joint National Committee (JNC) panel members did not address secondary hypertension in their report [3]. The report instead focused largely on a review of clinical trial evidence, which led the panel members to recommend a more liberal threshold for treatment and treatment goal (150/90 mmHg) in most hypertensive patients over the age of 60. However, JNC's earlier Seventh Report recommends considering secondary causes of hypertension under several circumstances: "(1) age, history, physical examination, severity of hypertension, or initial laboratory findings suggest such causes; (2) BP responds poorly to drug therapy; (3) BP begins to increase for uncertain reason after being well controlled; and (4) onset of hypertension is sudden" [4]. To expand upon the first, rather vague element of this JNC-7 advice, the following features are suggestive of secondary forms of hypertension:

- New hypertension or changing blood pressure control among relatively young or old patients (e.g. individuals <30–35 or >75–80 years old),
- A paucity of primary hypertension risk factors, such as obesity and family history,
- Symptoms (e.g. spells) or clinical findings (hypokalemia) suggestive of a specific secondary etiology,
- A history of hypertensive emergencies, repeated severe hypertensive urgencies, or repeated episodes of flash pulmonary edema,

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- Severe or progressive target organ damage (e.g. worsening renal function),
- True refractory hypertension (i.e. as opposed to pseudohypertension, discussed below).

The recent Systolic Blood Pressure Intervention Trial (SPRINT) studied intensive (<120 mmHg) or standard (<140 mmHg) blood pressure goals in participants 50 years of age or older without diabetes mellitus or prior stroke but with increased cardiovascular risk [5]. SPRINT used automated unattended office blood pressures, which are lower compared to usual clinic blood pressures. Thus, although intensive blood pressure lowering led to better outcomes in SPRINT, experts have debated whether the achieved blood pressures were much lower than usual practice prior to the trial. It remains to be seen whether future guidelines will comment on specific blood pressure goals for patients with resistant hypertension.

General Clinical Approach

A suggested overall approach to evaluating the patient with difficult-to-control hypertension and with a possible secondary etiology is given in Table 12.1.

Verify Accuracy of Measurements

Before instituting an extensive evaluation for secondary causes of hypertension, the clinician must be certain that the blood pressure data prompting such an evaluation reflect the patient's "true" blood pressure during the majority of the day. It is of foremost importance to first establish that the blood pressure measurement methods are valid and accurate per established guidelines [6]. Lack of attention to proper measurement techniques, a problem reported to occur among trained medical staff and cardiologists, can lead to a false diagnosis of resistant hypertension. To prevent some of the common errors, careful attention should be given to using an appropriate arm cuff size (particularly in obese patients), keeping the upper arm at heart level (i.e. at the mid-sternum), and allowing for a full 5 min of rest in a seated position prior to obtaining duplicate or triplicate readings. Physicians must confirm non-emergent hypertension by corroborating readings on several occasions and should not be overly concerned by asymptomatic high values which occur only once or on a few occasions, as long as there is no evidence of target organ damage. Several devices are available for the automated oscillometric measurement of blood pressure in the clinic while health care providers are absent from the exam room. These devices can be programmed to measure and average multiple readings and have shown to provide clinic readings that more accurately reflect ambulatory blood pressure levels than readings obtained using standard techniques.

Table 12.1 Overall approach to secondary hypertension

Possible cause of secondary hypertension	Screening diagnostic approach ∗Follow-up diagnostic measures
First: evaluate for common reversible etiologies of severe hypertension	
White-coat hypertension or resistance	Home blood pressure measurements ∗24-h ambulatory monitoring in some patients
Medical nonadherence	Focused history, including drug cost and adverse effects and patient's knowledge of regimen ∗Possible admission to the hospital for observed medical therapy in rare cases
Pseudohypertension	Assure accuracy in blood pressure measurement ∗Wrist, finger, or intra-arterial measurement ∗History for paroxysmal hypertension syndrome ∗Consider aortic blood pressure measurement in rare situations
Exogenous drug use	Focused history, including over-the-counter drugs ∗Blood/urine drug screening tests ∗Hospital admission
After above situations are appropriately addressed, the next step includes evaluations for true secondary etiologies	
Renal parenchymal disease	General blood chemistry, urinalysis, urine for microalbumin and protein ∗More detailed work-up as required on follow-up
Renal artery stenosis	Non-invasive renal artery imaging, including MRA, CTA, duplex ultrasonography ∗Angiography for confirmation and percutaneous treatment in very carefully selected cases
Primary aldosteronism	Screening test with serum potassium, ratio of serum aldosterone/plasma renin activity ∗Confirmatory testing (saline suppression) as required on follow-up. CT for patients with confirmed primary aldosteronism
Pheochromocytoma	Plasma free normetanephrines and metanephrines Confirmatory testing (clonidine suppression) and imaging (CT, MRI) as required on follow-up
Cushing's syndrome	24-h urine for free cortisol ∗Confirmatory testing and imaging as required on follow-up
Thyroid disease	TSH or free thyroxine
Parathyroid disease	Serum calcium ∗Ionized calcium level, PTH as required
Obstructive sleep apnea	Sleep study ∗CPAP trial
Aortic coarctation	CT, surface echocardiogram with appropriate window views, transesophageal echocardiogram
Pregnancy-related	Gestational hypertension, pre-eclampsia evaluation

Table 12.1 (continued)

Other rare conditions to consider:	
Monogenic hypertension: (e.g. Liddle's syndrome, congenital adrenal hyperplasia)	Work-up as indicated for the condition Clues: early onset hypertension or family history
Renal: Infarct, compression, polycystic disease, arterial aneurysm	Clues: sudden onset hypertension, hematuria
Autonomic failure and baro-reflex failure syndromes	Clues: Highly labile blood pressure
Geller's syndrome	Clues: Hypertension in pregnancy due to aldosterone receptor activity alteration
Juxtaglomerular apparatus tumor	Severe hypertension, polyuria, several-fold elevation of renin
Environmental factors	Noise, air pollution, cold weather, lack of sleep

CT computed tomography, *MRI* magnetic resonance angiography, *CTA* computed tomography angiography, *TSH* thyroid-stimulating hormone, *PTH* serum parathyroid hormone, *CPAP* continuous positive airway pressure
The distinction indicated by *

Determine Whether Seeming Resistant Hypertension Is Attributable to the "White Coat" Effect

Although office blood pressures are most commonly used for clinical decision-making, many patients have significant hypertension only in the physician's office ("white-coat" hypertension). Although its clinical significance is the subject of ongoing debate, white-coat hypertension (in which home daytime blood pressures are less than 135/85 mmHg) is generally considered a comparatively benign condition and does not usually require (more) treatment [7]. Patients on multi-drug treatment with elevated office readings, but controlled 24-h ambulatory blood pressures, are at markedly lower cardiovascular risk than those with sustained hypertension out of the medical office setting. On the contrary, true labile hypertension and "borderline" hypertension carry an increased risk of cardiovascular events and generally warrant treatment. Home blood pressure readings or 24-h ambulatory monitoring can help distinguish a patient with true severe hypertension from one whose usually-controlled blood pressure is only uncontrolled in anxiety-provoking medical environments (i.e. "pseudoresistance"). A workup for secondary causes in a patient with near-normal home blood pressure readings is likely to be unrevealing, and the cost of home blood pressure monitoring is low in comparison with most secondary hypertension evaluations. Moreover, home blood pressure readings can prevent overtreatment in patients with labile blood pressure, decrease drug side effects and increase the patient's ability to adhere to prescribed medical regimens. Basing treatment decisions upon home blood pressure values leads to adequate blood pressure control without compromising clinical outcomes. Therefore, all patients with refractory office hypertension should have the diagnosis corroborated by ruling out "white-coat resistant hypertension" with either proper home blood pressure and/or 24-h ambulatory monitoring.

Evaluate for Pseudohypertension

The confounding presence of pseudohypertension is also important to consider prior to undertaking a secondary hypertension evaluation. In elderly patients and those with renal insufficiency, conventional arm blood pressure measurement in a calcified and noncompressible brachial artery can lead to falsely elevated systolic cuff readings and to subsequent overtreatment. In these patients, alternative blood pressure–measuring devices such as wrist and finger monitors, or even arterial lines, can be useful to establish the actual intra-arterial blood pressure. In addition, a number of patients with labile refractory hypertension actually have "pseudopheochromocytoma" (alternatively termed "paroxysmal hypertension syndrome"). In patients with this syndrome, blood pressure levels and variability are normal at most times. However, there are frequent, seemingly unprovoked paroxysms involving large blood pressure elevations, most often associated with somatic symptoms (e.g. headache, panic, skin flushing). Patients often conclude that the blood pressure increase causes their symptoms. In actuality, the reverse relationship is at least as likely. Patients with this syndrome may also manifest significant white-coat hypertension as well. An association has been reported between this increasingly recognized phenomenon and previous severe traumatic life events. The underlying biology is poorly understood. However, in 11 patients with pseudopheochromocytoma, investigators found increased epinephrine release from the adrenal glands, as well as increased circulatory responses to catecholamines [8]. Most patients with this condition are not able to identify an obvious precipitant of the frequent, often very severe intermittent hypertensive episodes. These patients often undergo repeated negative evaluations for pheochromocytoma. Ambulatory blood pressure monitoring, calming non-judgmental reassurance, focused testing to rule out worrisome diseases, and treatment of the underlying disorder (e.g. with anti-depressants, anxiolytics) might be effective in improving blood pressure control, decreasing the frequency of paroxysms, and reducing associated symptoms. Finally, "pseudohypertension of youth," should be considered in young patients who otherwise have no apparent cause for their hypertension. Individuals with pseudohypertension of youth are typically tall, athletic young men between 15 and 30 years old with isolated systolic hypertension. In a study of a small number of such

individuals, central aortic blood pressures were normal despite an elevated brachial systolic pressure, possibly due to enhanced peripheral pulse pressure amplification [9]. However, more recent studies have reported elevated central aortic pressure in such patients, calling into question the label "pseudohypertension" [10, 11]. The precise etiology, prevalence, and prognosis associated with this syndrome remain to be determined.

Assure Medical Adherence

Because patients often discontinue their antihypertensive medications [12–14], the health care provider must assess a patient's adherence with prescribed treatment plans before embarking on an extensive workup for secondary causes of hypertension. Unsurprisingly, poor antihypertensive medication adherence is associated with worse cardiovascular outcomes [15]. Estimating adherence can often be a difficult task. For example, self-report and pill counts may overestimate the degree of patients' adherence. In very rare circumstances, an admission to the hospital for observed therapy is even required to evaluate adherence. Often, though, a detailed history with a non-judgmental questioning style and an assessment of the patient's knowledge of their medical regimen can provide insight into his or her level of adherence. Clinicians should not assume that patients with poor adherence are uninterested in following the prescribed medical regimen. Rather, it is essential that the clinician inquire about adverse effects, patients' misgivings (often informed by warnings on medication labels or information from friends), and other barriers to complete adherence and remedy them if possible. When assessing factors contributing to non-adherence, clinicians should consider medication adverse effect profiles and ease of adherence, both in terms of the number of tablets and the dosing schedule. Moderate-to-severe hypertension is often treated with multiple drugs, which may be expensive and may produce difficult-to-tolerate adverse effects in some patients. Because of their potency in lowering blood pressure, drugs such as clonidine, hydralazine, and minoxidil are often prescribed without regard for the patient's ability to tolerate their adverse effects, some of which may be exacerbated by interactions with other drugs. In short, patients should not be expected to eagerly spend money each month on medication that makes them feel unwell to treat a condition that does not. For an asymptomatic condition such as hypertension, the assessment of medication adherence is an absolutely essential element of successful treatment.

Finally, discrepancies between blood pressure data and physical examination findings in a patient may provide an additional means of judging the value of a secondary hypertension workup. A patient with years of extremely elevated office blood pressures but no evidence of any target organ damage (microalbuminuria, left ventricular hypertrophy, retinal abnormalities) is unlikely to have sustained levels of blood pressure elevation out of the physician's office and would be a poor candidate for a secondary hypertension workup. By a related rationale, stronger consideration should be given to a secondary hypertension evaluation in patients with modestly elevated readings in the physician's office but evidence of target organ damage. This may be a sign of "masked" hypertension (elevated ambulatory blood pressures significantly higher than office readings), which carries a poor prognosis [16].

Once the accuracy of the blood pressure measurements and pattern is confirmed and the patient's adherence to the medical regimen is reasonably documented, an evaluation for secondary causes of hypertension can proceed. Many rare causes of secondary hypertension have now been identified. However, this chapter will focus on the evaluation and treatment of several of the more common secondary causes of hypertension that may be encountered in a general medical or cardiology outpatient practice (Table 12.1). Clinicians should be aware that the credentialed discipline of "Hypertension Specialist" now exists and should not delay in referring patients to such expert care if needed for adequate evaluation or treatment.

Exogenous Drug Use

An appraisal for exogenous drug use is an important step in the evaluation of secondary (potentially reversible) causes of hypertension [17]. Some of the more commonly prescribed drugs which can cause or exacerbate hypertension include oral contraceptives and other estrogen-containing compounds, sympathomimetic drugs for weight loss and sinus congestion, stimulant drugs (e.g. amphetamines, cocaine), excessive alcohol, immunosuppressive drugs (e.g. cyclosporine), migraine medications (e.g. ergotamines and "triptans"), anabolic steroids, and nonsteroidal anti-inflammatory drugs. In addition, some less commonly used medications for depression (venlafaxine, bupropion, and monoamine oxidase inhibitors) have been associated with significant blood pressure elevations. It has also been recognized that some anti-hormonal prostate cancer treatments (e.g. abiraterone) and the anti-vascular endothelial growth factor cancer drugs (e.g. bevacizumab) are capable of causing severe hypertension. Sunitinib, a tyrosine kinase inhibitor used to treat a variety of cancers, has also been shown to increase blood pressure. Finally, herbal remedies (e.g. Ephedra, Yohimbine) and some types of confectionery licorice [18] may alter blood pressure. A full history of all non-prescription drugs

should be specifically addressed, as many patients fail to mention over-the-counter pills during routine histories.

A relatively large proportion of young women use oral contraceptive medications. Although these medications produce only small increases of blood pressure in most patients, a subset of patients experience significant increases in systolic blood pressure, sometimes exceeding 20 mmHg [19]. Indeed, large reductions in blood pressure >20 mmHg systolic have been demonstrated among hypertensive young women after stopping oral contraceptives [20]. Because the population of women at highest risk for renal artery fibromuscular dysplasia overlaps significantly with the population of oral contraceptive users, it may be worthwhile to consider a trial of discontinuation of oral contraceptives before embarking on an extensive evaluation (discussed later) for renal artery fibromuscular dysplasia. Estrogen replacement therapy does not appear to have a similar hypertensive effect.

Numerous sympathomimetic drugs can be purchased over-the-counter and at health food stores for the treatment of sinus congestion (pseudoephedrine and phenylephrine) or obesity (phenylpropanolamine and others). Though the FDA asked manufacturers of phenylpropanolamine-containing products to withdraw them from the market over a decade ago, the voluntary nature of this request leaves open to possibility that patients may be exposed to this drug. Sympathomimetic drugs can increase blood pressure significantly, and hypertensive patients are generally advised to avoid these drugs. Certainly, a newly hypertensive patient exposed to one of these drugs should be advised to discontinue its use to identify whether the drug is responsible for the elevation in blood pressure. Because of the FDA's concerns about an association between phenylpropanolamine (PPA) and hemorrhagic stroke, most over-the-counter drugs containing PPA were voluntarily withdrawn from the market years ago. Patients taking PPA-containing products should discontinue them. Cold remedies without sympathomimetic medications (e.g. Coricidin HBP) have been marketed, and in principle, should constitute a safer alternative. Over-the-counter and prescription drugs for weight loss (i.e. phentermine) have also been associated with modest increases in blood pressure. These drugs can occasionally produce profound increases in blood pressure through peripheral vasoconstriction and tachycardia. Because many hypertensive patients are also overweight, it is useful to ask patients specifically whether they use over-the-counter weight-loss drugs during evaluation for secondary causes of hypertension. Inquiry should also be made about food supplements because sympathomimetics may be included and because some products from overseas may not be labeled in English.

Cocaine can cause transient severe episodes of elevated blood pressure [21] but results in no chronic elevation of blood pressure [22]. These transient episodes can also to significant myocardial ischemia and coronary spasm. Alcohol intake of more than two standard drinks (i.e. 20 g of ethanol) per day and binge drinking can be associated with hypertension resistant to medical therapy, and patients whose condition appears refractory to the effects of medical therapy should be questioned about alcohol intake. A reduction in alcohol intake, particularly among heavy drinkers, can results in substantial reductions in blood pressure [23]. In such patients, clinicians should definitively evaluate the issue of medication adherence prior to initiating an extensive workup for other secondary causes of hypertension. On the other hand, although short-term caffeine ingestion does raise blood pressure via vasoconstriction, there is little evidence that long-term intake increases the risk of developing chronic hypertension [24].

More patients are receiving solid organ transplants each year, and a greater proportion of these patients are surviving longer. The immunosuppressive medications cyclosporine and tacrolimus contribute to nephrotoxicity and hypertension in many patients. The mechanism of the hypertension caused by cyclosporine and tacrolimus is not completely understood, though recent animal and human data suggest that activation of the renal sodium chloride cotransporter is involved [25]. Because cyclosporine or tacrolimus may play a central role in survival of the transplanted organ and/or the patient, blood pressure must often simply be treated with the usual armamentarium of antihypertensive drugs. Isradipine is frequently the favored calcium channel blocker because of its lack of effect on cyclosporine metabolism.

Exogenous intake of anabolic steroid medications, primarily for bodybuilding, can lead to mild increases in blood pressure as a result of sodium retention. It is important to counsel hypertensive patients who engage in bodybuilding to avoid exogenous steroid usage and also to inform them that bodybuilding itself can exacerbate hypertension. Rarely, even physiologic topical testosterone therapy has been associated with significant hypertension, particularly among older individuals.

Finally, the increasing use of nonsteroidal anti-inflammatory drugs can cause hypertension both acutely and chronically by causing an analgesic nephropathy [26, 27]. In most patients, this class of drugs produces a small elevation in blood pressure, if any elevation at all, but certain patients have a marked increase in blood pressure. It is important to consider nonsteroidal drugs as a cause of increased blood pressure, particularly in elderly patients, who often use these drugs at high doses. Simply withholding these medications for a few weeks may result in normalization of blood pressure and eliminate the need to pursue a workup for other secondary causes of high blood pressure.

Renal Parenchymal Disease

Disease of the renal parenchyma can be responsible for acute and chronic hypertension. When a patient presents with a hypertensive crisis, it is mandatory to evaluate renal function through a general chemistry profile and a complete urinalysis. A large number of additional tests (e.g. serum protein electrophoresis) may be appropriate depending upon the clinical scenario. Although abnormalities may be the result of the hypertension itself, evaluation for acute renal processes such as glomerulonephritis, renal artery embolism, worsening of ischemic nephropathy, microangiopathic disease, and bilateral ureteral obstruction should be considered. Other processes such as vasculitis and high-dose nonsteroidal drug ingestion can also lead to acute renal failure and hypertension, and prompt consultation with a nephrologist or, if indicated, a vascular surgeon or urologist should be made in these cases.

More commonly, chronic hypertension can be caused by chronic renal insufficiency (and vice versa). Prompt evaluation of renal function (serum creatinine) and the degree of proteinuria are essential in all patients with difficult-to-control or worsening hypertension. Many diseases can reduce renal function and thereby cause or exacerbate hypertension. Most commonly, long-standing diabetic and/or hypertensive nephropathy can result in decreases in glomerular filtration rate and sodium retention. Specifically among young patients, reflux nephropathy is a particularly common etiology of secondary hypertension. Elevation of serum creatinine may be minimal or absent in reflux nephropathy. Urologic evaluation for this clinical entity is very important, particularly among young women and patients with a history of urinary tract infections. Clinicians should undertake additional evaluation for a specific etiology of the renal dysfunction and refer for formal nephrology assessment as appropriate on a case-by-case basis.

From a treatment standpoint, much evidence suggests that angiotensin-converting enzyme inhibition or angiotensin receptor blockade can result in decreased blood pressure as well as preservation of renal function [28]. Whether the renal protection conferred by these medications exceeds the expected benefits of reduced blood pressure is the subject of ongoing debate. Nevertheless, use of these drugs is appropriate for most patients with renal disease. The most important aspect of anti-hypertensive therapy among patients with impaired renal function is that most will require three or more medications to achieve adequate blood pressure control (<130/80 mmHg). Meticulous control of intravascular volume status is also critical. A common cause of refractory hypertension among patients with secondary hypertension due to renal disease is under-treatment with diuretics and poor control of intravascular volume status. Appropriate doses of loop diuretics (often requiring twice daily usage for short-acting agents such as furosemide for adequate volume control), even in combination with a thiazide, is often required once glomerular filtration rate is significantly reduced (<40–50% normal). Patients who are likely to proceed to dialysis or renal transplantation should receive prompt referral to a nephrologist. Aggressive cardiovascular risk modification is also warranted in patients with end-stage renal disease, in whom the primary cause of death is cardiovascular in origin.

Renal Artery Stenosis

Renal artery stenosis most often results from either of two entirely separate entities: atherosclerotic renal artery stenosis and renal artery fibromuscular dysplasia (Fig. 12.1). Other rare causes are external compression (cysts, mass lesions), long tortuous polar arteries, proximal aortic lesions (e.g. mid-aortic syndrome), and stenoses associated with specific medical conditions (e.g. neurofibromatosis). However, clinicians must bear in mind that atherosclerotic renal artery stenosis is prevalent and can exist in many patients without contributing significantly to elevations in blood pressure. The differentiation between incidentally-identified renal artery atherosclerosis and true reno-vascular hypertension is a difficult task. Despite technical improvements in percutaneous renal artery stent placement, leading to a very high technical success rate in the modern era, the significant challenge of proper selection of patients most likely to benefit from these procedures persists.

Atherosclerotic renal artery stenosis is primarily a disease of the renal artery ostium and the proximal one-third of the renal artery. Because atherosclerosis is a systemic disease, renal artery stenosis occurs in patients with other cardiovascular risk factors, and a high proportion of patients with atherosclerotic renal artery disease also have coronary artery disease, an important consideration when renal revascularization is contemplated. Noninvasive imaging with renal magnetic resonance angiography (MRA), Doppler ultrasonography, or computed tomography (CT) can be helpful in identifying patients in whom invasive angiography and revascularization would be useful. There is wide variability in the sensitivity, specificity, and availability of these modalities among institutions, and it is most important for the clinician to explore a particular institution's area of expertise when ordering renal artery imaging. An assessment of the overall accuracies of imaging modalities at multiple centers showed that CT angiography and MRA are not particularly sensitive (62–64%). Both imaging modalities were found to be more specific (84–92%) than Doppler. These findings suggest that non-invasive studies are not sensitive enough to rule out disease in patients with a normal test and a high pre-test probability, but that an abnormal test is usually associated with a true stenosis of the renal artery. Therefore,

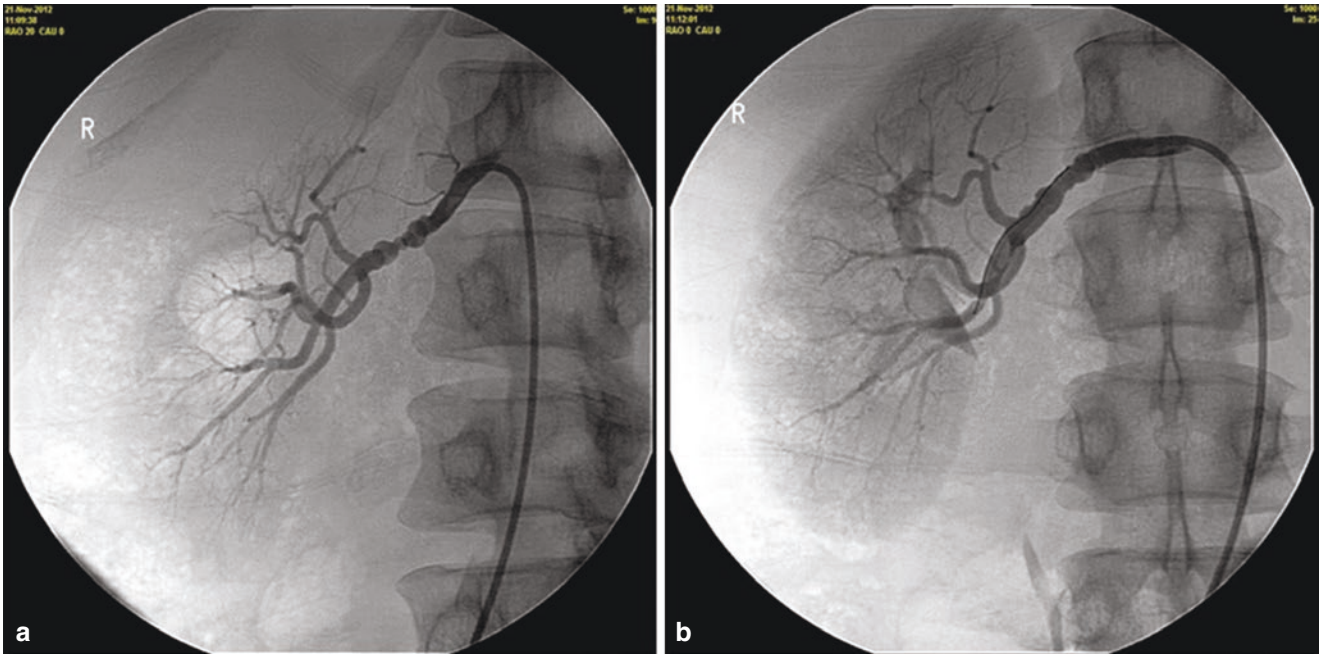

Fig. 12.1 Renovascular hypertension during pregnancy. (**a**, **b**) Right renal artery, before and after angioplasty, respectively. A 36-year-old woman presented at 14 weeks in her first pregnancy for management of hypertension. She was started on Labetalol 100 mg twice a day. Her follow-up blood pressure (BP) was 184/114 mmHg and evaluation for secondary causes of hypertension was initiated. A Doppler study of the renal arteries showed markedly elevated velocities in the mid-distal right renal artery; peak systolic velocity (PSV) of 533 cm/s, consistent with fibromuscular dysplasia (FMD) causing a high-grade right renal artery stenosis, and borderline elevated velocities in the left renal artery (PSV 199 cm/s), suggesting probable moderate stenosis caused by FMD of the left renal artery. The decision was made to optimize her medical management, with intervention to be considered only if she were to fail pharmacotherapy. The dose of labetalol was gradually increased to 200 mg 4 times a day and, ultimately, nifedipine XL 90 mg was added. On that regimen, her systolic BP averaged 122–144 mmHg, diastolic 78–92 mmHg for the remainder of her pregnancy. At 38 weeks of gestation (BP of 146/94 mmHg), she delivered, by Caesarean section, a healthy 2.8 kg baby boy with Apgar score of 8 and 9 at 1 and 5 min, respectively. Six-months postpartum, she underwent a renal angiogram with successful bilateral angioplasty. She is currently normotensive and off all BP medications. (From Scantlebury et al. [39]; with permission)

the pre-test probability of disease, level of clinical suspicion, patient characteristics, severity of blood pressure elevation or recent changes, kidney function, and local availability of study methods usually inform the initial choice of testing. Invasive arteriography remains the gold standard for determining the degree of stenosis and also enables the operator to measure the pressure gradient across the stenosis to evaluate the hemodynamic significance of a lesion. Other invasive tests such as intra-vascular ultrasound, fractional flow reserve or peak flow reserve and selective renal vein renin values, as well as non-invasive measures such as captopril renograms, duplex-guided renal resistance indices, brain natriuretic peptide and advanced MRI blood oxygenation measures can sometimes help further clarify whether to perform revascularization. Over the past decade, there have been many additional efforts—including the development of clinical criteria, guidelines, and specific tests—to help discern patients most likely to benefit from procedures. However, their validity in standard clinical practice remains to be fully evaluated. Clinically, there exist some hints that renovascular hypertension is present, including: the relatively sudden onset of severe hypertension, rapid deterioration of hypertension control (or kidney function), or change in kidney size by imaging, particularly in the setting of other atherogenic risk factors. Selection of patients most likely to benefit from renal artery revascularization remains an area of controversy. Present-day guidelines remain fairly conservative given the lack of clear evidence of clinical benefit following repair of renal artery disease. Indeed three randomized outcome trials (i.e. STAR, ASTRAL, and CORAL) have failed to show that the benefits of percutaneous revascularization (e.g. blood pressure reduction, kidney protection) outweigh the associated risks or side effects.

In light of these clinical trial data, the benefits of revascularization have been cast into serious doubt. However, it is difficult to rule out the possibility that the procedure offers benefit greater than risk in carefully-selected patients. Several features that may be associated with a more favorable risk-to-benefit ratio for revascularization include:

- Bilateral severe stenoses >70% (particularly with worsening kidney function),
- Patients with recurrent pulmonary edema due to underlying renal atherosclerosis,

- Completely refractory hypertension despite multiple appropriate drugs,
- Inability to tolerate an indicated angiotensin converting inhibitor for another disease (e.g. heart failure) due to drug-provoked azotemia or hyperkalemia.

Renal artery fibromuscular dysplasia differs in important ways from atherosclerotic disease of the renal arteries. Patients with renal artery fibromuscular dysplasia generally have abnormalities in the arterial media, leading to weblike stenoses in the distal two thirds of the renal artery. The disease occurs in both sexes and at all ages, but young women are the most frequently affected by this disease. Many patients present with non-specific symptoms, delaying diagnosis of the condition [29]. Most noninvasive imaging studies do not provide an adequate assessment of the distal two thirds of the renal arteries; it is often necessary to perform arteriography in patients in whom medial fibromuscular dysplasia is suspected. This disease is worth finding in afflicted patients because a significant improvement in hypertension can be accomplished in 60–70% of patients, with simple balloon angioplasty, without stent placement. Note that this treatment contrasts with the stenting typically employed in treatment of atherosclerotic renal artery stenosis. In rare situations, fibromuscular disease of the intima or adventitia, failed angioplasty, or concomitant arterial aneurysms may require patients to have surgical revascularization.

Adrenal Disease

Adrenal hormonal excesses are responsible for a variety of causes of secondary hypertension. This section describes the evaluation and treatment of the three most common causes.

Primary Aldosteronism

Primary aldosteronism (Conn's Syndrome), or oversecretion of aldosterone unregulated by angiotensin II, is classically thought to manifest with low serum potassium or an exaggerated potassium loss with small doses of diuretic. Once thought to be uncommon, primary aldosteronism is now recognized as one of the most common causes of secondary and/or refractory hypertension (5–15% of cases). Primary aldosteronism typically occurs in the setting of either bilateral adrenal hyperplasia or aldosterone-producing adenoma. The etiology of bilateral adrenal hyperplasia is not clear, but somatic and germline mutations have been identified recently in some cases of aldosterone-producing adenoma [30, 31]. In most patients with difficult-to-control blood pressure, an evaluation for primary aldosteronism should be strongly considered, even among those with normal electrolytes.

For the purposes of a screening evaluation, venous blood can be drawn in ambulatory patients who have been seated for 15 min during morning hours. Although altered by a variety of medications, the ratio of serum aldosterone to plasma renin activity (serum aldosterone/plasma renin activity) can be interpreted a valid fashion even while patients are taking most blood pressure pills, although a valid interpretation requires knowledge of the effects of these drugs on the renin and aldosterone [32]. Many situations (e.g. time of day, volume status) and pills alter these hormones (e.g. plasma renin activity reduced by beta blockers and direct renin inhibitors and increased by ACEI or diuretics) and their effect on the ratio must be considered in order to make such a valid interpretation. The risk of discontinuing anti-hypertensive agents in these patients, who often require multi-drug therapy, is not usually warranted in order to adequately screen for this disorder. The absolute hormone levels and the ratios that are abnormal are vigorously debated. However, a serum aldosterone (ng/dL)/plasma renin activity (ng/mL/h) ratio of greater than 20–30 is a fairly sensitive threshold for identifying primary aldosteronism. An important consideration is that the units of both measurements, and thus the ratio, may vary by lab. In addition, the ratio is very sensitive to low renin levels such that the calculated ratio may vary considerably depending upon the lowest renin value reported by a specific laboratory.

Once a screening test is found to be abnormal, the next step is to corroborate the diagnosis. This can be done by determining whether the aldosterone level can be suppressed by either saline infusion or oral salt loading over 3 days. Other suppressive tests, such as with captopril, have been used in patients when salt loading may be dangerous. These suppressive tests often require referral to an endocrinologist or a hypertension specialist. Many studies now illustrate that moderate doses of spironolactone (25–50 mg/day) can dramatically reduce blood pressure (by 20–40 mmHg, systolic) in patients with primary aldosteronism, even when they were previously taking ACE inhibitors or other diuretics.

Once primary aldosteronism is confirmed with biochemical testing, the key diagnostic decision is whether the patient is suffering from a benign solitary adenoma, an adrenal adenocarcinoma, or bilateral adrenal hyperplasia. Adrenal computer tomography (CT) has several important limitations. Nonetheless, based in part upon the importance of excluding adrenocortical carcinoma, recent guidelines recommend adrenal computed tomography in all patients with confirmed primary aldosteronism [32]. Smaller, presumably benign lesions can be monitored expectantly, and the blood pressure can usually be safely controlled with adequate medical therapy that includes mineralocorticoid receptor antagonists, sometimes called aldosterone antagonists.

Due to short-comings of past imaging techniques, adrenal vein sampling has returned to favor as the best test to

determine whether an adenoma (or single adrenal gland) is hyper-functioning. In the modern era, most surgeons typically require this test prior to considering surgical removal of an adrenal mass due to the high prevalence of incidental adrenal masses in the general population. Lateralization of the adrenal vein aldosterone/cortisol ratio to the left or right adrenal gland upon baseline bilateral venous sampling, and also after ACTH stimulation, suggests the presence of a hyper-functioning lesion that may be appropriate for removal. The details of adrenal vein sampling and its interpretation were recently addressed in an expert consensus statement [33]. The merits of medical management versus surgical removal of a confirmed hyper-functioning adrenal lesion are still debated. On the one hand, hyper-aldosteronism *per se* may be harmful to the cardiovascular system, suggesting a theoretical rationale for surgical resection. Moreover, with the development of laparoscopic techniques, adrenalectomy is an increasingly attractive option for functional adenomas. Finally, patients may be able to avoid taking multiple medications, with their attendant risk of adverse effects, if a surgical cure of their hypertension is achieved (as in about 50% of cases, range 35–60%). On the other hand, if the adenoma is stable in size, smaller than 4 cm, and has benign characteristics upon imaging, the risk for malignant transformation is extremely small and long-term medical treatment can usually control the blood pressure. At this time, either approach is valid and can be considered appropriate depending upon the details of the case. As in all medical decision-making, patient preference is also an important consideration. Patients whose primary aldosteronism is due to bilateral adrenal hyperplasia are almost always treated medically with spironolactone, most often along with other antihypertensive medications. Eplerenone can also be considered. It is a more selective aldosterone antagonist that less often evokes bothersome anti-androgen side effects, such as gynecomastia. Alternatively, high doses of amiloride (10–50 mg/day) can sometimes be effectively used. In 2008, the Endocrine Society published an excellent guideline regarding the detection, diagnosis, and management of patients with primary aldosteronism [32]. Periodic monitoring of serum potassium and creatinine is essential when treating patients with mineralocorticoid receptor antagonists, amiloride, or other antihypertensive drugs that can alter potassium levels (e.g., other diuretics, ACE inhibitors, ARBs).

The recent PATHWAY-2 randomized, cross-over trial showed spironolactone was more effective compared to placebo, bisoprolol, or doxazosin as add-on therapy in resistant hypertension [34]. Patients known to have secondary hypertension were excluded from the trial, and plasma aldosterone was not predictive of response to spironolactone. Thus, even outside the setting of primary aldosteronism, spironolactone appears to be effective therapy for resistant hypertension.

Pheochromocytoma

The primary clues suggesting a pheochromocytoma come from the patient's history, but the symptoms of pheochromocytoma overlap considerably with those of numerous other diseases. Thus, it has been termed "the great mimicker". Most patients referred for evaluation will have an alternative cause for their symptoms, including panic attacks, atrial tachyarrhythmias, baro-reflex failure, paroxysmal hypertension syndrome, alcohol withdrawal, hyperthyroidism, perimenopausal hot flashes, or symptoms caused by intermittent compliance with hypertensive medications. The classic patient with a pheochromocytoma has wide, unprovoked fluctuations in blood pressure accompanied by tachycardia, pallor, sweating, headaches, and sometimes cardiac failure caused by progressive catecholamine-induced left ventricular failure. The paroxysms are not fleeting, usually lasting several minutes to hours in duration (not seconds), and occur intermittently from once or twice per day (not dozens of times) to only sporadically.

Due to the rarity of this disease (0.1–0.6% of general outpatient clinic patients with hypertension), a thorough evaluation for the many other causes of a "pseudo-pheochromocytoma" should be performed in most cases. In the majority of patients in whom pheochromocytoma is considered, other causes, such as paroxysmal hypertension, will be uncovered. Another relatively frequent mimic is baro-reflex failure, a condition usually caused by disruption of the afferent parasympathetic nerves allowing for unbuffered acute blood pressure variability. Baro-reflex failure is characterized by ultra-rapid excessive variability of blood pressure from minute-to-minute along with a hyper-exaggerated blood pressure increase to normal anxiety-provoking situations or pain, differentiating the condition from pheochromocytoma. Previous neck surgery, radiation, or carotid body tumors, along with strokes and autonomic neuropathies can cause failure of the baro-reflex. Patients generally respond extremely well to anti-sympathetic drugs (e.g. clonidine) and anxiolytic medications [35].

In patients with an appropriate history, the screening test of choice for pheochromocytoma has now become plasma free metanephrines and normetanephrines. Due to an extremely high sensitivity (~99%), these tests usually preclude the need to perform complicated 24-h testing or other procedures. Because these tumors continuously produce and release metanephrines and normetanephrines, unlike catecholamines which may be paroxysmally released, virtually all patients with a pheochromocytoma have elevated values. A negative result essentially eliminates the possibility of this diagnosis. However, due to a very low prevalence of this disease, most patients with a moderately elevated level (1.1 to fourfold elevation about normal values) have a false positive result. Repeat testing in the morning hours done in a fasting

state with blood drawn via an intravenous catheter is the next step. A normal results on any repeat test rules out pheochromocytoma in all but the rarest situations (e.g. hereditary pheochromocytomas). If repeat testing reveals similar borderline elevation, causes of false positive elevations should be considered (e.g. coffee, caffeine, tricyclic antidepressants, monoamine uptake inhibitors, severe stress, renal failure, heart failure, obesity). However, a particular advantage of these tests is a lower likelihood of false positive results compared to plasma or urine catecholamines. If repeat values continue to be moderately high and clinical suspicion for pheochromocytoma persists, then repeat testing in the fasting state with blood drawn via an IV placed in a patient resting supine for 30 min can usually eliminate false positives. In addition, the suppression of plasma normetanephrine levels after administration of 0.3 mg of clonidine can be tested in special centers. In patients with a pheochromocytoma, clonidine will fail to suppress plasma normetanephrine to normal levels (or fail to reduce levels by more than 50%).

Once there is clear biochemical evidence for a pheochromocytoma, the next step is to localize the tumor for resection. Eighty-five percent of pheochromocytomas are in the adrenal glands and most tumors can be demonstrated by CT or MRI with a very high sensitivity. In patients without obvious adrenal masses, full body MRI or CT imaging, or metaiodobenzylguanidine (MIBG) scanning with I^{131}–labeled benzylguanidine can localize an extra-adrenal tumor, which is usually found along the sympathetic chain or in the bladder. It is important to note that MIBG testing is very specific (90–99%) for a pheochromocytoma when an abnormal mass is identified by CT or MRI, but not particularly sensitive (<70–80%). Therefore, a negative result does not exclude the possible presence of an underlying pheochromocytoma, and MIBG is not the first imaging test to perform after biochemical testing is positive. Rarely, I^{123} MIBG imaging, positron emission tomography, and venous catheterizations for measurement of catecholamines at multiple body sites are required for localization when other imaging tests are unrevealing in patients with continued positive biochemical evidence.

Once localized, pheochromocytomas should be resected in most cases. A critical management point is appropriate perioperative blood pressure management, usually with phenoxybenzamine or selective alpha blockers plus other medications. Beta blockers should not be used prior to the establishment of alpha blockade since unopposed beta blockade may precipitate life-threatening crises in patients with pheochromocytoma. Due to highly variable and potentially life-threatening effects of a variety of common medications in these patients, a clinician with significant expertise in hypertension or endocrine tumors should be involved in the care of patients with pheochromocytoma. Malignant pheochromocytomas can be treated with various chemotherapy regimens, and with agents such as metyrosine and streptozocin. Recommendations arising from an international symposium on the diagnosis and management of pheochromocytoma have been published [36].

Cushing's Syndrome

Cushing's syndrome, an unusual cause of secondary hypertension, results from excess glucocorticoid secretion. The resulting hypertension can be severe and is associated with a lack of a normal nocturnal decline in blood pressure. This syndrome should be suspected in patients with depression, as well as in those with the physical features of Cushing's syndrome, such as central obesity and purple striae. In patients in whom Cushing's syndrome is suspected, a 24-h urine collection for free cortisol yields nearly 100% sensitivity. Confirmatory evaluation would include a dexamethasone suppression test and, if the result is positive, radiologic studies are used to localize the lesion to the pituitary or adrenal gland, or an ectopic tumor. If hypercortisolism is independent of adrenocorticotropic hormone (ACTH), the adrenal glands should be imaged by CT or MRI. If the hormonal tests suggest that the disease is ACTH-dependent, then the pituitary gland is the likely location of the tumor. Hypertensive patients with hypercortisolism are likely to benefit from referral to an endocrinologist for full evaluation, including evaluation for more unusual causes of cortisol or mineralocorticoid excess (e.g. congenital adrenal hyperplasia, 11β-OH steroid hydrogenase type 2 deficiency).

Thyroid and Parathyroid Abnormalities

Patients with symptoms of hyperthyroidism or hypothyroidism should be screened by thyroid-stimulating hormone (TSH) measurement. Patients with hypothyroidism often have a depressed cardiac output with a markedly increased peripheral vascular resistance, which results in hypertension. Similarly, patients with hyperthyroidism have tachycardia and increased inotropism and can be hypertensive for those reasons. Elderly patients often have atypical manifestations of thyroid dysfunction, and it is prudent to screen all elderly hypertensive patients for hypothyroidism or hyperthyroidism. Treatment of these patients can yield improvement in blood pressure, both systolic and diastolic.

Hyperparathyroidism can lead to left ventricular hypertrophy and hypertension. These conditions may be caused by increased vascular reactivity to catecholamines or long-term calcium deposition in the kidneys, which lead to renal parenchymal disease. Hyperparathyroidism should be considered in hypertensive patients with elevated serum calcium levels.

Obstructive Sleep Apnea

Obstructive sleep apnea is a common cause of secondary hypertension. In a recently published study, resistant hypertension patients were carefully evaluated for secondary causes of hypertension. Obstructive sleep apnea, found in 64% of the patients, was the most commonly identified secondary cause of hypertension among these resistant hypertension patients [37]. Observational studies have shown that systemic and pulmonary pressures rise during apneic episodes, which have also been associated with increased sympathetic activity. Screening patients with clinical signs of obstructive sleep apnea may identify a secondary cause of hypertension that can be easily reversed with weight loss and continuous positive airway pressure ventilation. Randomized, placebo controlled studies have shown that nocturnal continuous positive airway pressure can be successful in lowering both night and daytime blood pressures and aid in controlling previously refractory hypertension [38].

Aortic Coarctation

Significant aortic coarctation is generally diagnosed in childhood and is often amenable to balloon dilatation. However, patients with less severe coarctation often survive into adulthood without detection of the condition and develop hypertension through incompletely understood mechanisms. These patients often have activation of the renin-angiotensin system and excessive catecholamine increases during exercise. Adult patients with aortic coarctation often present with heart failure, bicuspid aortic value (aortic insufficiency), aortic rupture, bacterial endocarditis, or intracranial hemorrhage. The diagnosis can sometimes be made by evaluating the aortic contour on plain chest radiography, but it is more definitively made by CT, MRI, or surface and transesophageal echocardiography. At a minimum, all young patients (<35 years old) with hypertension must have lower extremity blood pressures checked in comparison to both right and left upper arm blood pressures. A thigh pressure lower than either arm value by more than 20 mmHg suggests a significant blood pressure gradient and should prompt specific evaluation. The prevalence of hypertension among adults with coarctation approaches 33%. Evaluation of young patients with hypertension should include consideration of aortic coarctation, not only because repair of the coarctation can improve the hypertension but also, more importantly, so that other sequelae of the coarctation and any associated congenital abnormalities can be minimized or prevented. Whether to repair with a surgical approach versus endovascular stenting will usually be determined on a case-by-case basis (e.g. associated aortic anatomy, age, valve problems).

Conclusions

In considering an evaluation for secondary causes of hypertension, it is important to realize that the overwhelming majority of patients with hypertension, even severe hypertension, have primary (essential) hypertension. Many other causes of apparent refractory hypertension should be assessed. It is important to fully evaluate the adequacy of a patient's medical regimen, with a special focus on its cost and the patient's ability to adhere to the regimen before labeling a patient's hypertension as "refractory to treatment." In addition, it is essential to look for exogenous causes of a patient's blood pressure elevation, because attention to these causes can result in reversal of much of a patient's hypertension and, in many ways, these causes are among the most treatable "secondary" causes of hypertension. Once it has been established that a patient's hypertension is truly refractory to treatment or has characteristics (either laboratory or clinical) suggestive of other secondary causes, prompt and complete evaluation can sometimes lead to marked improvement or even complete resolution of hypertension. It is important to bear in mind that an evaluation for hypertension should not merely focus on elevated numbers; it is also an opportunity—perhaps one that will not occur again in a decade—for a thoughtful examination of the patient's overall cardiovascular risk profile and for action to be taken to decrease cardiovascular risk.

Practical Points

- Approximately 90–95% of people with hypertension have primary (essential) hypertension.
- Clues to the presence of secondary hypertension are: hypertension refractory to an adequate three-drug regimen, a sudden alteration in blood pressure level or control, a paucity of risk factors to explain primary hypertension, young age, hypertensive emergency, suggestive symptoms or signs specific for an etiology (e.g. spells).
- Before beginning an evaluation for secondary causes of hypertension, the clinician must be certain that the blood pressure readings are accurate and indicative of the patient's true blood pressures during the majority of the day (rule out "white coat hypertension").
- Evaluation for various pseudohypertension syndromes is important in certain scenarios in order to avoid unrequired treatment of spurious blood pressure elevations.
- The clinician must also assess a patient's adherence to the medical regimen and the possible interfering effect of other prescription medications or over-the-counter pills.

- Renal parenchymal disease and reno-vascular hypertension are common causes of secondary hypertension. Aggressive combination medical therapy, particularly with appropriate diuretic usage, can control blood pressure in most patients.
- The role of renal artery revascularization, even in proven "reno-vascular hypertension," is increasingly in doubt and should be performed only after very careful consideration.
- Primary aldosteronism is one of the most common causes of refractory and/or secondary hypertension (5–15% of cases). A positive screening test (a serum aldosterone/plasma renin activity ratio >20–30 in most patients, even those on medications) requires further evaluation.
- Cushing's syndrome, hyperthyroidism, hypothyroidism, hyperparathyroidism, and pheochromocytoma are other potentially reversible endocrine causes of secondary hypertension that may be encountered.
- Plasma free normetanephrine is the screening test of choice for a pheochromocytoma. Due to its extremely high sensitivity (>99%), a normal result essentially eliminates this diagnosis. Most patients undergoing evaluation will prove to have other causes of labile or paroxysmal hypertension than a pheochromocytoma.
- Obstructive sleep apnea is a common, easily-diagnosed, and treatable cause of secondary hypertension.

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Heart Failure due to Left Ventricular Systolic Dysfunction

13

Brent C. Lampert, David B. S. Dyke, and Todd M. Koelling

Heart failure is a clinical syndrome in which abnormal cardiac function causes either a failure of the heart to pump blood at a rate matching the requirement of metabolizing tissues, or a situation in which filling pressures are elevated, or frequently both conditions simultaneously. Patients with impaired cardiac pumping function experience symptoms related to abnormal perfusion and retention of vascular fluid volume. The cardinal symptoms of heart failure include fatigue or exercise intolerance, dyspnea, and edema, although other related symptoms may also occur. Heart failure may be caused by disorders of the pericardium, myocardium, heart valves, or great vessels, but most patients manifest the syndrome through abnormalities in systolic function. Reduction in myocardial contractility is more commonly referred to as *systolic dysfunction* and may also coexist with chamber filling abnormalities, also referred to as *diastolic dysfunction.* This chapter focuses on patients with heart failure due to systolic dysfunction.

The term *heart failure* is now preferred to *congestive heart failure,* inasmuch as not all patients with heart failure are "congested," and experts believe that the latter description has limited diagnostic accuracy. Heart failure occurs commonly in clinical practice and represents the most common Diagnosis-Related Group discharge diagnosis in the Medicare (elderly) population. An estimated 5.1 million Americans have heart failure and it is projected that by 2030 this number will increase by 25%. Although heart failure can occur at any age, its incidence increases with advancing age. At 40 years of age, the lifetime risk of developing new heart failure is 20%. Despite a much shorter overall life expectancy, at 80 years of age the lifetime risk for development of new heart failure remains 20% [1].

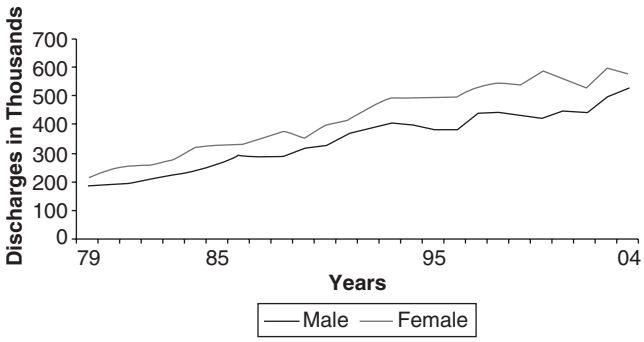

Fig. 13.1 Hospital discharges in the United States by sex from 1979 to 2010. (Data from Centers for Disease Control and Prevention/National Center for Health Statistics and the American Heart Association)

Heart failure is a common cause of mortality in the population; nearly 300,000 patients die of heart failure each year. Over the period from 1994 to 2004, deaths from heart failure increased by 28%. Between 1979 and 2005 hospitalizations for heart failure as a primary diagnosis rose by 175%, but have since leveled off (Fig. 13.1). While survival after a heart failure diagnosis has improved with time, the death rate remains high with an approximately 50% mortality within 5 years of the diagnosis. The annual estimated rate of new and recurrent heart failure events for white men aged 65–74 is 15.2 per 1000 population; for those aged 75–84, it is 31.7; and for those aged 85 and older, it is 65.2. For black men, the rates are 16.9, 25.5, and 50.6, respectively. For white women in the same age groups, the rates are 8.2, 19.8 and 45.6, respectively, and for black women, the rates are 14.2, 25.5, and 44.0, respectively. Because heart failure necessitates frequent hospitalizations in the population, the costs of caring for this syndrome are considerable. The estimated direct and indirect cost of heart failure in the United States for 2013 is $32 billion dollars and projections show that by 2030 the total cost will increase almost 120% to $70 billion [1].

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Usual Causes

It has been well recognized that the myocardium undergoes structural changes in response to cardiovascular disease states. Irrespective of the initial cause, myocardial damage results in reduced power output of the heart, which occurs in a varying time frame, depending on the severity of disease and the cause of myocardial damage. Myocardial ischemia is usually manifested initially by regional impairment of myocardial function. Nonischemic dilated cardiomyopathies caused by such insults as viral infections, exogenous toxins, regurgitant valvular lesions, and hereditary factors normally manifest with global left ventricular dysfunction. Abnormalities that begin by causing elevated myocardial strain include hypertension, aortic stenosis, and hypertrophic cardiomyopathy. Most patients with these abnormalities present with myocardial hypertrophy, either concentric (hypertension, aortic stenosis) or focal (hypertrophic cardiomyopathy). Although the types of insults that occur may be very different in the initial appearance of the myocardium, the chronic adaptations that occur in the body as a response to myocardial dysfunction reach a common pathway, as it is understood today (Table 13.1).

Specific Etiologies

The term *cardiomyopathy* is an ill-described, general category for a large group of unrelated disease processes that share only the clinical characteristic of substantially reduced cardiac pumping function and power output. Practical and graphic descriptions have been used to describe cardiomyopathy, and this classification is firmly anchored in the pathologic description of the heart. Thus, *dilated cardiomyopathy, hypertrophic cardiomyopathy,* and *infiltrative cardiomyopathy* are descriptive pathologic terms. Alternatively, cardiomyopathy is characterized by the specific clinical or disease process with which it is associated. Thus, terms such as *peripartum cardiomyopathy, diabetic cardiomyopathy,* and *toxic cardiomyopathy* are used. In clinical practice, the etiology of left ventricular systolic dysfunction can be identified in patients with coronary artery ischemia or infarction, infectious vectors, toxins, hereditary conditions, and conditions for which no cause can be identified (idiopathic) (Table 13.1). These disorders, in aggregate, account for the majority of cases of heart failure resulting from myocardial disease.

Ischemia

Ischemic cardiomyopathy is the most common cause of heart failure in developed countries. In patients with coronary artery disease, a cardiomyopathy can develop as the result of

Table 13.1 Causes of systolic heart failure

Primary myocardial diseases
Inherited (genetic) cardiomyopathic disorders
Dilated cardiomyopathy
Late remodeling stage of hypertrophic cardiomyopathy
Arrhythmogenic (right) ventricular cardiomyopathy
Left ventricular noncompaction
Muscular dystrophies
Secondary myocardial diseases
Energy supply deficit
Coronary atherosclerosis
Coronary dissection
Coronary embolus
Excess ventricular afterload
Hypertension
Aortic stenosis
Aortic coarctation
Excess ventricular preload
Mitral regurgitation, Tricuspid regurgitation
Aortic insufficiency, Pulmonic insufficiency
Tachycardia mediated
Atrial fibrillation/flutter
Supraventricular tachycardia
Infectious
Viral myocarditis
Post Rheumatic
Septicemia-related
Human immunodeficiency virus
Protozoal (Trypanosoma cruzi)
Endocrine
Hypothyroidism, hyperthyroidism
Pheochromocytoma
Diabetic
Obesity-related
Connective tissue diseases
Systemic lupus erythematosus
Infiltrative diseases
Sarcoidosis
Amyloidosis
Hemochromatosis
Wilson's disease
Toxins
Alcohol, cocaine
Anthracycline
Doxorubicin
Daunarubicin
Epirubicin
Paclitaxel
Trastuzumab (Herceptin)
Cyclophosphamide
Interferon
Interleukin-2
Chloroquine
Zidovudine
Thoracic radiation therapy
Congenital heart disease
Peripartum cardiomyopathy
Stress-induced "Tako-tsubo" cardiomyopathy
Idiopathic cardiomyopathy

one extensive myocardial infarction, multiple smaller myocardial infarctions, ongoing ischemia from severe triple-vessel disease, or coronary artery disease associated with significant mitral regurgitation. Myocardial dysfunction may also develop after coronary artery bypass surgery, even in the setting of otherwise technically adequate graft placement. Early identification of myocardial dysfunction associated with coronary artery disease is important, in view of the potential for reversal of dysfunction with effective management. When overt angina is not apparent, because of limited exercise capacity, subclinical myocardial ischemia may nonetheless produce abnormal systolic and diastolic ventricular dysfunction. Additional subclinical loss of viable myocardium may also occur.

When ischemia-related myocardial dysfunction prevents identification of reversible disease during exercise, viable hibernating myocardium may be identified by nuclear imaging studies. The predictive value of ^{201}Tl and ^{99m}Tc scintigraphy for detecting hibernating myocardium has been enhanced by newer redistribution and reinjection protocols, and these techniques are more readily available than positron emission testing at most institutions. Cardiac magnetic resonance imaging (MRI) enhanced with gadolinium is increasingly being used to assess viability. With its better resolution when compared to nuclear imaging, cardiac MRI may be more sensitive for predicting functional recovery in the most severely dysfunctional myocardial segments. Once identified, reversible ischemia caused by hibernation can be managed by interventional or surgical techniques, to prevent further deterioration of myocardial function.

Infections

A long list of infectious agents can be identified for this subgroup of myocardial disease. Myocardial dysfunction develops from a nonspecific immune or inflammatory response, or both, or from structural damage to cardiac myocytes. "Viral" myocarditis is frequently suspected among the patients who are otherwise classified as having idiopathic cardiomyopathy, although many of these patients may actually have an inherited cardiomyopathy. Myocarditis can be diagnosed by endomyocardial biopsy and has been shown to be present in 12% of patients presenting with dilated cardiomyopathy in the absence of coronary artery disease within 6 months of their original diagnosis [2]. With the exception of a few well-described viral causes that can be inferred from serial immune titers, isolation of a specific viral vector remains difficult. Molecular biologic techniques permit enhancement of viral messenger ribonucleic acid. However, in evaluations of myocardial tissue by histologic techniques, the occurrence of viral particles is equally distributed between patients with active myocarditis and those with nonspecific cardiomyopathy. Etiologic origin is therefore difficult to assign.

Diagnosing and treating active myocarditis remains a challenge. In general, the diagnosis can be confirmed only on myocardial biopsy, and the occurrence may be sporadic and related to fluctuation in Coxsackie virus prevalence. Endomyocardial biopsy can also be utilized for histologic documentation when there is a strong clinical suspicion of myocarditis. Endomyocardial biopsy evidence of myocarditis on the whole carries a prognosis similar to that for heart failure of idiopathic origin.

Among patients with history of a flu-like syndrome in the setting of clinical suspicion of myocarditis, biopsy evidence of inflammatory infiltrates is seen in approximately 25%, and yet almost half of these patients may have other concurrent disorders. Investigators have shown that the shorter the duration of illness, the greater the likelihood of a biopsy sample positive for inflammation; the likelihood reaches almost 90% in patients presenting within 4 weeks of their initial symptoms [3]. Seasonal and yearly variations exist in the clinical presentation. The Myocarditis Treatment Trial demonstrated better-than-expected prognosis in patients with myocarditis [4]. Specific immunosuppression did not alter outcome. Additional analyses are in progress to determine immunologic markers that identify patients who may benefit from immunosuppressive therapy.

Myocarditis may be present in cases in which the biopsy result is negative. One possible explanation is that the transvenous biopsy technique does not sample enough myocardial sites to detect each case of a disease that may have a focal or multifocal distribution. Acute myocarditis may occur as a regional process and can mimic acute myocardial infarction, with striking electrocardiographic changes. The regional nature of this disorder is evident with invasive and noninvasive assessment of ventricular performance. Depending on clinical presentation, this disorder may necessitate cardiac catheterization, which is the only means of definitively excluding epicardial coronary artery disease.

Myocardial dysfunction due to Chagas' disease remains the most common worldwide cause of cardiomyopathy [5]. Infection in humans is caused by a bite from the reduviid insect, which harbors the protozoa *Trypanosoma cruzi* in its gastrointestinal tract. *T. cruzi* is the infectious etiology of Chagas' disease and gains entry into a human host by fecal deposition after a bite from the reduviid. After initial infection, acute trypanosomiasis occurs, followed by a long latent period; chronic Chagas' disease appears up to 20 years later. Myocardial dysfunction and congestive heart failure develop during this time. *T. cruzi* parasites within a cellular infiltrate may be present during the acute phase, but cardiac manifestations occur during the chronic phase. There is no correlation between the severity of disease and parasitemia. T lymphocytes may destroy normal myocardial cells, and antibody-mediated responses to specific myocyte components, such as the sarcoplasmic reticulum, have been identi-

fied. In the Western Hemisphere, the greatest concentration of this disorder is in Central and South America, where 20 million people may be infected with the parasite [5]. However, with increasing migration from these regions to the United States, consideration must be given to this diagnosis in patients of Latin American or South American origin from endemic regions.

Toxins

Several exogenous toxins are well known to cause left ventricular systolic dysfunction and subsequent heart failure. The most common of these is alcohol, represented in 3.4% of cases of systolic heart failure in the absence of coronary artery disease. Myocardial toxicity due to anthracyclines (e.g., doxorubicin) is a common cause of systolic heart failure in patients with a prior history of receiving chemotherapy for the treatment of cancer [6]. Other exogenous toxins known to lead to systolic heart failure include cocaine, other chemotherapeutic agents (cyclophosphamide, and trastuzumab), interferon, interleukin-2, and chloroquine. In the mid-1960s, a clustering of cases of acute-onset cardiomyopathy developing in patients with heavy beer consumption led to the discovery that cobalt represented a myocardial toxin. When the practice of adding cobalt to beer was stopped, no further cases occurred.

Alcoholic Cardiomyopathy

Alcohol may be associated with heart failure in several different ways. Alcohol causes an acute depressant effect on myocardial contractility that can result in measurable dysfunction with binge drinking. Evidence suggests that the fundamental mechanism of injury induced by ethanol is structural and chemical disorganization of membranes, interference with ion transport, and derangement of various biochemical functions that possibly allow calcium to accumulate in the cell [7]. There may also be a genetic susceptibility to alcoholic cardiomyopathy, particularly certain polymorphisms of the gene that codes for angiotensin converting enzyme (ACE) [8]. Heavy alcohol consumption may also cause atrial tachyarrhythmias, termed *holiday heart,* which may contribute to the development of systolic dysfunction. The amount of alcohol necessary to cause this is unknown, because the testimony of alcoholic patients regarding intake cannot be validated. Studies have shown that ejection fraction correlates inversely with reported alcohol intake in alcoholic patients, and women may be more sensitive to the myocardial toxicity of alcohol than are men.

The pathologic and physiologic characteristics of alcoholic cardiomyopathy are similar to those of idiopathic dilated cardiomyopathy in gross appearance. The morphometric evaluation of endomyocardial biopsy does not provide adjunctive prognostic information in these patients. As many as one fourth of patients with systolic failure due to alcohol may present with elevated cardiac output, caused by concomitant liver disease and development of arteriovenous fistulae. Patients with alcoholic cardiomyopathy may have a favorable prognosis in comparison with those with idiopathic cardiomyopathy; approximately 50% of alcoholic patients experience improved left ventricular function once abstinence is established.

Athracycline and Anti-cancer Related Cardiomyopathy

Doxorubicin and daunorubicin are anthracycline analogues that are widely employed as chemotherapeutic agents. One important side effect caused by anthracyclines is cardiotoxicity. Cardiotoxicity due to anthracycline derivatives has been shown to be dependent on the cumulative dose [6]. Measurable left ventricular systolic dysfunction is rare in patients receiving less than 350 mg per square meter of doxorubicin but may be seen in as much as 30% of patients receiving more than 600 mg per square meter [9]. The peak levels of the drug may be a determinant for developing the disorder: Some evidence suggests that giving the same total dose weekly rather than every 3 weeks or administering the drug by slow continuous infusion rather than by bolus may reduce the incidence of cardiotoxicity. Other risk factors for development of doxorubicin-induced cardiomyopathy include age older than 70, use in combination with other chemotherapeutic agents (particularly paclitaxel and trastuzumab), concomitant or prior mediastinal radiotherapy, prior cardiac diseases, hypertension, liver disease, and whole body hyperthermia. Most authors on this topic have recommended monitoring patients serially with radionuclide ventriculography as patients are treated with anthracyclines [6]. However, despite variability with measurements, echocardiography is the most commonly used method to monitor systolic function because of its widespread availability and the absence of radiation exposure. Cardiac MRI may also be helpful in monitoring systolic function, particularly when other imaging techniques are suboptimal or unreliable. The diagnostic test with the greatest specificity and sensitivity for doxorubicin-induced cardiomyopathy is endomyocardial biopsy. Endomyocardial tissue from the right ventricle shows typical histopathologic changes, including loss of myofibrils, distention of the sarcoplasmic reticulum, and vacuolization of the cytoplasm and may appear before measurable changes in left ventricular systolic function occur. A biopsy scoring system has been described to show that patients in whom more than 25% of cells exhibit histopathologic changes will probably develop substantial changes in the ejection fraction, which suggests that treatment should be terminated [10]. However, it is still possible that patients with lower biopsy grades will develop cardiomyopathy 4–20 years later.

In addition to toxicity related to anthracyclines, several other anti-cancer therapeutics are associated with develop-

ment of cardiomyopathy, the most common of which is Trastuzumab (Herceptin), used for the treatment of breast cancer. In contrast to anthracycline related cardiomyopathy, trastuzumab cardiomyopathy is not dose-dependent, often resolves with treatment discontinuation, and rechallenge with the chemotherapy is often tolerated after recovery. The frequent use of multiple anti-cancer therapies (including radiation therapy) can greatly increase the future likelihood of developing cardiomyopathy.

Hereditary Influences

Studies have shed light on the role of the genetic background in the onset and the development of heart failure due to diastolic dysfunction (hypertrophic disease) and systolic dysfunction. Familial forms of dilated cardiomyopathy are common and have been described in 20 to over 50% of patients diagnosed with idiopathic DCM by clinical screening of family members [11]. This condition appears genetically highly heterogeneous with over 30 gene mutations identified. Inheritance patterns are usually autosomal dominant, but X-linked, autosomal recessive and mitochondrial inheritance have been described as well. Genetic abnormalities found to be associated with familial dilated cardiomyopathy include mutations in genes encoding cytoskeletal/sarcolemmal, sarcomere, nuclear envelope, and transcriptional coactivator proteins. It has been postulated that the molecular defects involved in hereditary forms dilated cardiomyopathy cause an abnormality in the transmission of contractile force. Polymorphisms in the Ile164 $beta_2$-adrenergic receptor have been shown to be associated with poor prognosis in patients with dilated cardiomyopathy [12]. In a study of 259 patients with dilated cardiomyopathy and NYHA Classes II to IV symptoms, patients with the Ile164 polymorphism displayed a striking difference in survival rates, with a relative risk of death or need for cardiac transplantation of 4.81. The 2009 Heart Failure Society of America (HFSA) genetic evaluation of cardiomyopathy practice guideline recommends obtaining a family history, screening family members, genetic counseling and genetic testing, and treatment for patients with a new diagnosis of idiopathic dilated cardiomyopathy [13]. However, other guidelines still recommend less detailed screening and genetic counseling. Further studies of the genetic determinants of dilated cardiomyopathy should allow better understanding of the underlying mechanisms that promote the progression of the disease, to identify subjects at risk of the disease who would benefit from early medical management and promote the development of pharmacogenetics.

Idiopathic Causes

Idiopathic remains the designation for many forms of dilated cardiomyopathy, when coronary artery disease and specific causes such as those listed earlier have been excluded. With the exception of primary causes, which are clinically identified, there are limited screening procedures that can identify a specific cause. Of these, perhaps the most fruitful is the screen test for thyroid disease, which may be particularly important in the evaluation of the elderly patient. Both hyperthyroidism and hypothyroidism may produce left ventricular dysfunction. Abnormalities of trace substances such as selenium have been suggested, but deficiencies do not routinely occur in Western diets. Patients may also present with left ventricular systolic dysfunction due to chronic tachycardia conditions, such as atrial fibrillation with rapid ventricular response. Rate control with beta blockers, digitalis, or both has been shown to lead to improvements in left ventricular function on follow-up testing.

Biologic Mechanisms and Disease Progression

Occurrence of the primary disorder leads first to myocyte injury or increased myocyte strain, or both; second, to myocardial remodeling in structure and function; and, third, to loss of systolic or diastolic function, which in turn leads to decreased cardiac output and elevated filling pressures. Structural changes in the myocardium and vasculature are important contributors to the progression of left ventricular dysfunction. Myocardial fibroblasts and vascular smooth muscle cells may hypertrophy or proliferate, or both, in response to a variety of stimuli. These structural effects lead to changes in the compliance of arteries that augment the left ventricular load and to increases in the volume and/or mass of the left ventricle [14]. The role of such ventricular remodeling in heart failure has been further described in patients who have had myocardial infarctions.

Many of the adaptive and maladaptive responses in congestive heart failure occur at sites distal to the initial myocardial damage. Decrements in cardiac output and elevations in central venous pressure result in reduced organ perfusion. Underperfusion of the kidney and underfilling of the arterial vasculature results in a cascade of adaptations that lead to neurohormonal alterations that have been found to have direct myocardial toxicity through myocyte hypertrophy, myocardial fibrosis, and/or apoptosis [15]. Nonetheless, these distal abnormalities are integrally related to reduction of systolic function. Because cardiac myocytes cannot replicate at a rate sufficient to contribute to repair a direct injury, the response to injury is limited primarily to hypertrophy and increased interstitial tissue alterations.

The mechanisms that lead to progression of disease in heart failure include neural and hormonal factors that increase the load on the left ventricle, stimulate growth of myocytes, and may have direct toxic effects on the myocardium. The concentrations of several neurohormones and

cytokines, including plasma norepinephrine, plasma renin activity, atrial natriuretic peptide (ANP), and tumor necrosis factor, have been shown to be increased in plasma in patients with congestive heart failure. The elevation in the levels of these compounds becomes more marked as clinical symptoms of heart failure advance and is associated with increased mortality rates. There also exists evidence that elevations of these compounds may be a more sensitive method of monitoring disease progression, as Benedict et al. [16] showed in the Studies of Left Ventricular Dysfunction (SOLVD) prevention trial that plasma norepinephrine levels continued to be predictive of mortality and development of clinical events related to the onset of heart failure despite the patients' being asymptomatic or minimally symptomatic.

Renin-Angiotensin-Aldosterone System

Activation of the renin-angiotensin-aldosterone system is one of the predominant abnormalities of heart failure. The degree of increase in plasma renin activity provides an indicator for prognosis in patients with heart failure [17]. Studies in mild and asymptomatic heart failure demonstrate relatively less activation, but even these values are increased in comparison to normal. The degree of renin activity is intensified in the presence of diuretic therapy. Angiotensin II causes constriction of the systemic vasculature and vasoconstriction of both the afferent and efferent renal arterioles. In some patients with severe heart failure, treatment with angiotensin-converting enzyme (ACE) inhibitors may cause a deterioration of renal function. This may be related to fixed renal artery disease or, alternatively, to selective blocking of the constrictor action of angiotensin II on the efferent arteriole [18]. Renin system components have been identified in the myocardium and vasculature, where they adversely affect fibrosis and remodeling, as well as cellular dysfunction. These findings suggest that the renin-angiotensin-aldosterone system has effects on cardiac function beyond altering sodium excretion and cardiac afterload. Not only is angiotensin II a potent vasoconstrictor, but it also causes a direct effect on hypertrophy of myocytes and may lead to energy supply mismatch as the capillary bed perfuses a larger bed.

In addition to vasoconstriction, angiotensin II stimulates aldosterone secretion by the adrenal gland, producing sodium retention and potassium excretion at the distal nephron. Elevations in the activity of aldosterone lead to a sodium-retentive state found in patients with heart failure. Although adrenergic stimulation and angiotensin II increase sodium transport in the proximal tubule of the kidney, patients with increased activity from aldosterone overcome this effect, and sodium delivery to the distal tubules is attenuated, leading to the edematous state. It has been shown previously that although ACE inhibition continues to suppress angiotensin II levels over the course of 1 year, levels of aldosterone are initially suppressed during the first 1–3 months of therapy but fail to be suppressed beyond 6 months of therapy [19]. This is thought to occur because stimuli in the form of glucocorticoids, hyperkalemia, hypermagnesemia, melanocyte-stimulating hormone, and endothelin continue to increase aldosterone secretion, although angiotensin II levels are low. Analysis of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) revealed that elevated levels of aldosterone were associated with the lowest rates of survival, and a reduction in plasma aldosterone during the course of therapy was associated with a favorable impact on survival [20]. Although elevated aldosterone levels may track the clinical state of patients with congestive heart failure, they may also be responsible in part for progression of myocardial dysfunction through mechanisms that lead to abnormal accumulation of collagen, which surrounds and encases myocytes, resulting in diastolic and systolic ventricular dysfunction. Such deposition of collagen may lead to pathologic hypertrophy of the myocardium and has been shown to be prevented by spironolactone in a rat model of arterial hypertension [21]. Spironolactone at doses of 25–50 mg per day can be used safely in conjunction with ACE inhibitors, diuretics, and digitalis. In a minority of patients, however, hyperkalemia may occur, leading to discontinuation of the drug. Findings of the Randomized Aldactone Evaluation Study (RALES) revealed that doses of spironolactone as low as 12.5 mg per day significantly reduce atrial natriuretic factor levels in patients with Classes II to IV heart failure without a significant effect on serum potassium levels [22]. Moreover, the RALES investigators also found that treatment groups had lower levels of aldosterone, norepinephrine, and plasma renin activity. More recently the PARADIGM-HF trial has shown that angiotensin-receptor and neprilysin inhibition with sacubitril and valsartan reduced cardiovascular mortality by 20% and overall mortality by 16%, as compared to enalapril for worsening heart failure patients with reduced ejection fraction.

Sympathetic Nervous System

The baroreceptor-mediated increase in sympathetic tone that occurs with ventricular dysfunction has several consequences, including increased myocardial contractility, tachycardia, arterial vasoconstriction and thus increased cardiac afterload, and venoconstriction with increased cardiac preload. Beta-adrenergic receptors in the heart either are down-regulated ($beta_1$-adrenegic receptors) or have abnormalities in signal-transduction activity that effectively uncouple them from effector mechanisms ($beta_1$- and $beta_2$-adrenergic receptors) [18]. Increased local and circulating concentrations of norepinephrine may contribute to myocyte hypertro-

phy, either directly through stimulation of alpha$_1$- and beta-adrenergic receptors or secondarily by activating the renin-angiotensin-aldosterone system. Norepinephrine is directly toxic to myocardial cells, an effect mediated through calcium overload, the induction of apoptosis, or both. Norepinephrine-induced death of myocytes can be prevented by concomitant nonselective beta-adrenergic blockade. Patients with plasma norepinephrine concentrations greater than 800 pg/mL (4.7 nmol/L) have a 1-year survival rate of less than 40% [23]. Through renal vasoconstriction, stimulation of the renin-angiotensin-aldosterone system, and direct effects on the proximal convoluted tubule, increased renal adrenergic activity contributes to the avid renal sodium and water retention that occurs in patients with heart failure.

Substantiating the importance of the sympathetic nervous system in the heart failure syndrome, multiple randomized controlled trials have demonstrated the benefits of beta-adrenergic blockade on clinical outcomes in patients with heart failure [24–26]. In the past, beta-adrenergic blockade was thought to be contraindicated in patients with heart failure. However, if patients can tolerate short-term beta-adrenergic blockade, ventricular function subsequently improves.

Natriuretic Peptides

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (or B-type natriuretic; BNP) impact sodium and water handling and pressure regulation in congestive heart failure and mitral regurgitation. Investigators have shown that these compounds are produced by cardiac myocytes and their levels correlate inversely with left ventricular ejection fraction, directly with left atrial pressure, and directly with New York Heart Association (NYHA) class and mortality [27]. Administration of exogenous ANP, 0.10 μg per kilogram per minute to normal subjects was found to increase sodium (450%) and free water (100%) excretion, while decreasing plasma renin (33%) and aldosterone (40%). Similar administration of ANP to patients with congestive heart failure had no effect on sodium or free water excretion, although significant decreases in pulmonary capillary wedge pressure (19%), systemic vascular resistance (13%), and plasma aldosterone (51%) and increases of cardiac index (17%) were noted. Randomized trials of nesiritide, an intravenous form of BNP, in acute decompensated heart failure have yielded conflicting results [28–30]. In the largest randomized trial in acute decompensated heart failure (ASCEND-HF), nesiritide produced a small improvement in dyspnea but caused more hypotension and did not effect rates of death or rehospitalization at 30 days [31]. Consequently, routine use of nesiritide in acute decompensated heart failure is not recommended. A trial of nesiritide may be considered as an alternative to other vasodilator therapy (nitroglycerin or nitroprusside) in hemodynamically stable patients who remain symptomatic despite routine therapy [32]. Serum level of endogenous BNP has been shown to be an independent prognostic indicator in patients with cardiac disease. Because of this, point-of-care BNP testing has also become part of routine clinical practice and is helpful for aiding in establishing a diagnosis in patients with new-onset dyspnea [33]. BNP guided therapy can also be useful to achieve optimal dosing of guideline directed medical therapy in clinically euvolemic patients in well-structured heart failure disease management programs [32, 34]. However, the usefulness of serial BNP measurements in acutely decompensated heart failure or to reduce hospitalizations is not well-established.

Endothelin

Endothelin (ET) is a family of potent vasoconstrictor peptides of vascular endothelial origin. Although it has been proposed that the vasoconstrictor effects of ET are produced at the local vascular level, increased plasma concentration of ET has been identified in cardiovascular disorders [35]. ET levels have been demonstrated to be nearly threefold higher in patients with congestive heart failure than in normal controls. ET was used a decade ago as a potent vasoconstrictor. The peptides were originally identified from rodent sources (ET-3) as well as human and porcine sources (ET-1). ET-1, ET-2, and ET-3 all have potent vasoconstrictor properties. ET-1 levels have a close association with pulmonary pressures, as well as the resistance ratio (pulmonary vascular resistance/systemic vascular resistance). Despite elevated plasma levels of ET being a negative prognostic indicator in patients with heart failure, clinical trials of ET receptor antagonist use in patients with heart failure with reduced ejection fraction have found no benefit and some evidence of harm including fluid retention and LFT abnormalities [36, 37]. This differs from patients with group 1 pulmonary arterial hypertension, where ET receptor antagnosists are one class of effective therapies.

Arginine Vasopressin

Arginine vasopressin (AVP) has affinity for two receptor subsets, V1 and V2, which govern free water clearance by the kidney and vasoconstriction, respectively. AVP production is increased in heart failure [38], as a result of angiotensin II stimulation and the indirect effect of thirst. Under resting conditions, AVP level is increased in patients with heart failure, in comparison with normal subjects and hypertensive patients. During the postural adjustment of head-up tilt, little additional modulation could be identified.

Additional physiologic studies have demonstrated that AVP exhibits the spectrum of abnormalities observed with other major hormonal pathways, while still maintaining responsiveness to adjustment of free water and other known physiologic changes. Preliminary clinical studies with AVP receptor antagonists have been performed. Design and outcomes of these studies have been determined by the receptor subtype against which the compound has physiologic activity. The spectrum of current compounds under experimental or clinical evaluation include primary V1, primary V2, and compounds with combined receptor activity.

The effects of tolvaptan, an oral vasopressin V2 receptor antagonist, have been studied in a randomized, placebo-controlled trial in patients hospitalized for heart failure. Although tolvaptan use was associated with improvements in hyponatremia, short term improvements in dyspnea, edema, and body weight, there were no effects on long-term mortality or heart failure-related morbidity [39].

Presenting Symptoms and Signs

The cardinal manifestations of heart failure are dyspnea, fatigue, and fluid retention. Both dyspnea and fatigue may limit exercise tolerance, and fluid retention may be demonstrated by peripheral edema, abdominal ascites, or pulmonary edema. All of these symptoms can impair the functional capacity and quality of life of affected individuals; however, these are not all necessarily present in patients with heart failure. Many patients with advanced heart failure do not show physical signs of pulmonary congestion, because of the chronic adaptive changes that occur in the pulmonary vasculature. These patients may have only symptoms of dyspnea and fatigue. Other patients may have overt signs of volume overload, with lower extremity edema and jugulovenous distention, but have minimal dyspnea. In these patients, the impairment of exercise tolerance may occur so gradually that it may not be noted unless the patient is questioned carefully and specifically about a change in activities of daily living.

New York Heart Association Classification

Functional status of patients has been standardized according to the NYHA classification system, a system that allows physicians to compare functional strata within the population of patients with heart failure (Table 13.2). This approach assigns patients to one of four functional classes, depending on the degree of effort that brings on either fatigue or dyspnea. Patients with NYHA Class I designation are without symptoms with any activity, except those that would bring on symptoms in normal individuals. NYHA Class II represents patients who develop fatigue or dyspnea on ordinary exertion (e.g., with one or more flights of stairs or with walking one or more blocks on a flat surface). NYHA Class III represents patients who develop symptoms at less than ordinary exertion (e.g., with less than one flight of stairs or with less than one block of walking on a flat surface). NYHA Class IV represents patients who experience symptoms at rest (e.g., sitting in a chair, lying in bed) or with minimal activity (e.g., eating, dressing, showering). Although much effort is made to assign a NYHA classification to patients, the functional status of a given patient need not be static. Patients may present in NYHA Class IV and, after appropriate medical therapy, change to being asymptomatic, or NYHA Class I. Nevertheless, assignment of a functional classification is important in the care of patients with heart failure, because current therapies indicated for treatment may have been tested only in patient populations selected on the basis of distinct NYHA classifications.

Table 13.2 New York Heart Association classification

Class I: Symptoms only at levels of activity that would produce symptoms in normal individuals; ordinary physical activity does not cause undue dyspnea or fatigue
Class II: Symptoms on ordinary exertion, resulting in mild limitation of physical activity
Class III: Symptoms on less than ordinary exertion, resulting in marked limitation of physical activity
Class IV: Symptoms at rest or minimal exertion, resulting in inability to carry on any physical activity without discomfort

Exercise tolerance and functional status are not necessarily determined by resting left ventricular function; instead, they correlate better with exercise cardiac reserve. Patients with very low ejection fraction may be entirely asymptomatic, whereas others with mild to moderate dysfunction are symptomatic at rest or with mild exertion. Many factors contribute to exercise tolerance, including skeletal muscle function, respiratory function, peripheral vascular function, ventillatory disturbances, and psychologic factors. Cardiopulmonary exercise testing (peak VO2) is the most objective measure of functional capacity in patients with heart failure and one of the best predictors of when to list a patient for cardiac transplantation.

American College of Cardiology/American Heart Association Stages of Heart Failure

Because NYHA classification is a designation in flux, the American College of Cardiology and American Heart Association (ACC/AHA) Task Force on Practice Guidelines, in the ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, originally published in 2001 and most recently updated in 2013 [32], established a staging system to act as a complement to the NYHA classification. The ACC/AHA stages represent

Table 13.3 American College of Cardiology/American Heart Association stages of heart failure

Stage A: Patients at risk for developing a structural disorder of the heart
Stage B: Patients with a structural disorder of the heart but without symptoms
Stage C: Patients with a structural disorder of the heart and with prior or current symptoms of heart failure (New York Heart Association Classes II–IV)
Stage D: Patients in the end stage of chronic heart failure who require repeated or prolonged hospitalizations or specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care

the evolution and the progression of heart failure (Table 13.3). Stage A represents patients who are at high risk for developing a structural disorder of the heart but have not yet done so. This stage includes patients with hypertension, coronary artery disease risk factors, or a family history of cardiomyopathy. Stage B represents patients with a structural disorder of the heart but without symptoms. These patients are analogous to those represented by NYHA Class I. Stage C represents patients with a structural disease of the heart and with prior or current symptoms of heart failure. This stage includes patients represented by NYHA Classes II to IV. Stage D represents patients in the terminal phase of the disease who require repeated and prolonged hospitalizations or specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care. These patients have marked symptoms of heart failure at rest despite maximal medical therapy and may require specialized interventions. The classification scheme recognized that heart failure has established risk factors; that the evolution of heart failure has asymptomatic and symptomatic phases, and that interventions may be necessary at every stage to help prevent the progression of the disease and to help relieve the suffering of the patient.

Clinical Features and Laboratory Tests

History

The usual reason the patient seeks medical attention is breathlessness or fatigue that limits exercise tolerance. Sometimes the first recognized manifestation of heart failure is orthopnea or paroxysmal nocturnal dyspnea; in other patients, pedal edema may be the first recognized abnormality. Thus, the secondary manifestations of heart failure (such as circulatory congestion) bring the patient to medical attention, rather than the primary cardiac contractile abnormality. A complete history and review of systems are crucial for understanding the cause of heart failure. Direct inquiry may reveal prior evidence of myocardial ischemia, infarction, or both; valvular disease; toxin use or exposure; or a family history of heart ailments.

When documenting a history from the patient with heart failure, the examiner should begin by identifying the dominant symptom of the patient, whether it is fatigue, dyspnea, chest discomfort, palpitations, syncope or near syncope, edema, cough, or wheezing. Clarifying the conditions in which the symptom occurs is critical: whether they occur at rest, with recumbency, or with mild, moderate, or heavy exertion; how long the episodes have been occurring; how frequently the episodes last; how severe the symptoms are; and what relieves the symptoms. Establishing the activity level of the patient is important, because many patients will report no symptoms and yet they have assumed a sedentary lifestyle to avoid experiencing the effects of their heart condition. Patients with modest limitations of activity should be asked about their participation in sports or their ability to carry out strenuous exercise, whereas patients with substantial limitations of activity should be asked about their ability to get dressed without stopping, take a shower, climb stairs, or carry out specific routine household chores. Documenting a dietary history is helpful, particularly for the patient with edema, because some patients may be consuming large amount of sodium and free water that may override attempts to establish euvolemia. Patients should be asked about a history of hypertension, diabetes, hypercholesterolemia, coronary disease, valvular disease, peripheral vascular disease, rheumatic fever, chest irradiation, and exposure to cardiotoxic agents. Patients should be questioned carefully regarding illicit drug use, alcohol consumption, tobacco use, and exposure to sexually transmitted diseases. A travel history may be helpful in identifying patients exposed to trypanosomes, which lead to Chagas' disease. The history should also include questions related to noncardiac diseases such as collagen vascular diseases, infections, and thyroid excess or deficiency.

Physical Examination

General Appearance

Asymptomatic patients may not have distinguishing characteristics on general appearance. Patients with chronic heart failure have features of chronic disease, such as pallor and general weakness. In more advanced stages of the disease, wasting of limb-girdle and facial muscles is common, and there may be the appearance of overall cachexia. The abdomen may be distended from hepatomegaly and ascites. Long-standing peripheral edema is accompanied by darkened skin as a result of chronic hemosiderin deposition and scarring from chronic skin lesions. Body weight may be misleading in documentation of heart failure. Accumulation

of edema may be insidious and balanced by loss of lean body mass, thereby masking fluid retention. Virtually any weight abnormality may be present, and the presence of obesity certainly will completely obscure any attempt to characterize weight in relation to the severity of heart failure.

Pulse and Blood Pressure

Tachycardia, in the absence of other known causes, represents chronotropic compensation for the reduced cardiac output of pump failure. A two-to-one ratio of apical to radial pulse may reflect pulses alternans, can be seen in patients with severe heart failure. Alternatively, very slow peripheral pulses may represent sinus node dysfunction (structural or secondary to medications) or heart block. An irregular pulse most typically reflects atrial fibrillation. A narrow pulse pressure is consistent with a low stroke volume or inadequate diastolic filling time. Assessment of the carotid arteries and pulses therefore provides information regarding ventricular contraction and the overall circulatory status.

The measurement of systolic and diastolic blood pressure provides important clues to the origin of heart failure. If blood pressure exceeds 140/90 mmHg on repeated measurements, lowering the blood pressure is mandatory in patients with heart failure. In contrast, many patients with long-standing heart failure have hypotension, which is accentuated with upright posture ("orthostatic hypotension"). When documented, this should be correlated with symptoms of dizziness and fatigue. In general, most therapies for heart failure produce low blood pressure and may require adjustment in the setting of symptomatic orthostatic hypotension.

Venous System

The magnitude of jugular venous distention provides an estimate of cardiac filling pressure and circulatory volume status. It is most convenient to use the right atrium as the reference point for this measurement by measuring at the midaxillary point at the nipple level. The simplest stress test is the hepatojugular reflux test, performed by exerting constant firm pressure over the right upper quadrant of the abdomen. A positive result of the hepatojugular reflux test may be interpreted as evidence for impaired right ventricular response to volume load, a dilated heart that can be compressed by a rising diaphragm, and a volume overload state. An alternative approach to stressing the circulation is leg raising or exercise. In evaluating the peripheral venous system, the examiner should look for varicose veins or prior surgical scars, which may increase the tendency for edema, particularly in an asymmetric manner. Peripheral pitting edema secondary to heart failure should be distinguished from the heavy ankles of lipedema. The pitting quality of edema distinguishes it from lymphedema.

Lungs

Tachypnea is a typical finding of heart failure and may be present under resting conditions during the physical examination. Dyspnea in the course of a patient interview is a finding of inadequate cardiac compensation. The Cheyne-Stokes ventillatory pattern can be observed, usually in patients with advanced heart failure.

The most characteristic finding on pulmonary examination is the presence of rales, indicative of increased pulmonary capillary pressure and transudation of fluid into the alveolar airspace. In general, rales provide an estimate of the severity of left ventricular decompensation, inasmuch as the height of the rales in the lung fields is proportionate to the severity of the decompensation. However, many patients with chronic heart failure do not show physical signs of pulmonary congestion, because of the chronic changes that occur in the pulmonary vasculature and lymphatics, even despite a markedly elevated left atrial pressure. Rales can be obscured by the presence of pleural effusion, which is more often a marker of chronic decompensation. In addition, occasionally edema of the airways may lead to wheezing, as is seen in the patient with "cardiac asthma."

Cardiac Findings

Precordial palpation provides valuable information in heart failure, indicating the extent of cardiac enlargement and providing information regarding the degree of contractile impairment and valvular function. Displacement of the apical impulse away from the midsternal line is typical of heart failure. A diffuse apical impulse is characteristic of ventricular enlargement, and a heaving quality may indicate ventricular dyskinesis or underlying left atrial lift. The palpation of thrills may provide a clue to the presence of valvular disease. Auscultation of the heart should confirm the abnormalities already identified by observation and palpation. In particular, the examiner should check for the presence of murmurs or diastolic filling sounds. Mitral regurgitation is common in patients with heart failure and may result in an apical murmur that radiates toward the axilla. Tricuspid regurgitation may also be present on auscultation. An accentuated pulmonic closure sound (P_2) suggests pulmonary hypertension, a fourth heart sound (S4) indicates abnormal atrial-ventricular filling characteristics, and a third heart sound (S3) indicates ventricular dysfunction or decompensation.

Evaluative Testing

Electrocardiography

Prior or acute myocardial infarction can be identified by Q waves on the electrocardiogram. Myocardial hypertrophy almost invariably accompanies heart failure, and so increased voltage or conduction abnormalities are often present. Left

ventricular hypertrophy and cardiomyopathy may manifest with what appears to be localized loss of electrical forces that may be mistaken for a prior myocardial infarction. Evidence of atrial conduction delay–related prolongation of the PR interval, QRS duration, and QT interval are common in patients with heart failure. These changes may predispose patients to cardiac arrhythmias. Both atrial and ventricular dysrhythmias are common manifestations of heart failure, and evidence for their existence may be detected on a random electrocardiogram. Monitoring for longer periods, especially 24-h Holter monitoring, or patient-triggered event recording, is likely to detect these arrhythmias.

Chest Radiography

The chest radiograph provides an estimate of ventricular chamber size, but it often serves as a screening technique to identify the presence of heart disease. The cardiothoracic ratio measured on a standard posteroanterior chest film provides an estimate of overall heart enlargement. The degree of left ventricular enlargement is better assessed by lateral or oblique views. In the presence of a high pulmonary capillary pressure secondary to left ventricular failure, pulmonary blood volume often is redistributed to the upper lobes in an upright film, producing the cephalization characteristic of left-sided heart failure. Pulmonary infiltrates and fibrosis occasionally masquerade as heart failure.

Exercise Testing

Exercise testing can be conducted safely in the patient with heart failure, and the information obtained from this test is important in diagnostic and therapeutic efforts. An exercise test can be performed either informally in the examining room, by having the patient perform a 6-min walk test, or formally with the use of a cardiopulmonary exercise test with either a bicycle ergometer or a treadmill, simultaneously with respiratory gas analysis. The cardiopulmonary exercise test provides more detailed information regarding the cause of the exercise limitation. Monitoring the electrocardiogram during exercise provides additional information that can give a clue to the presence of ischemic heart disease. Stress testing with measured gas exchange allows for more precise assessment of anaerobic threshold, peak oxygen consumption, ventillatory efficiency, as well as other parameters that have prognostic value. Its added value is in distinguishing among cardiac, pulmonary, deconditioning, and nonmotivational disability.

Echocardiography and Radionuclide Ventriculography

Ventricular function can be quantitated by imaging techniques, either echocardiography or radionuclide ventriculography. A left ventricular ejection fraction of less than 45% at rest is considered abnormal. Echocardiography provides information about valve function and regional wall motion as well as quantitative assessment of the dimensions, geometry, and thickness of the left ventricle. Qualitative information about right ventricular size and function is available from echocardiography. Doppler flow measurements also identify the functional significance of observed stenotic and regurgitant valve lesions, which provides a better global assessment of the impact of heart failure on cardiac function, as well as etiologic information. The comprehensive evaluation offered by echocardiography is helpful in assessing the patient with heart failure, inasmuch as it is not uncommon for patients to have more than one abnormality contributing to the heart failure syndrome. Radionuclide ventriculography offers enhanced precision in measuring left ventricular ejection fraction in comparison with echocardiography and may be more useful when monitoring ventricular function serially is important in the care of the patient (i.e., monitoring patients treated with anthracyclines).

Magnetic Resonance Imaging

The techniques of cardiac magnetic resonance imaging (CMRI) have matured over the last several years. Highly detailed images of cardiac structures allow for very accurate estimation of ventricular performance including ejection fraction, as well as evaluation of structural abnormalities. Magnetic resonance imaging is particularly well suited to evaluation of subtle abnormalities within the myocardium, such as those seen with infiltrative diseases (sarcoidosis, amyloidosis, hemochromatosis), as well as evaluation for myocardial viability and/or presence of myocardial fibrosis. Pericardial structures are also well visualized with magnetic resonance imaging. Unfortunately, many patients are unable to undergo CMRI because of the presence of metallic structures such as pacemakers, defibrillators, and mechanical prosthetic valves.

Coronary Arteriography and CT Angiography

Coronary artery disease is responsible for 50–60% of cases of heart failure due to left ventricular systolic dysfunction in the United States. Because of this, coronary angiography and/or CT angiography is often necessary to clarify the origin of left ventricular dysfunction. It may be useful to define the presence, anatomic characteristics, and functional significance of coronary artery disease in patients with heart failure. This may be particularly useful in three types of patients: (a) those with known coronary artery disease and angina; (b) those with known coronary artery disease without angina; and (c) those in which the possibility of coronary artery disease has not been evaluated. Identification of high-grade coronary artery disease should prompt analysis for revascularization in patients with angina, because ongoing ischemia is a prominent cause of left ventricular dysfunction and heart failure. For patients without angina, functional

testing with nuclear imaging or stress echocardiography may be able to identify viable myocardium or ischemic myocardium that may respond favorably with revascularization. In patients with left ventricular systolic dysfunction and unknown coronary anatomy, cardiac catheterization may be able to identify lesions amenable for revascularization that could change the course of the disease. This applies in particular to patients with regional dysfunction, episodic heart failure symptoms, and chest discomfort or anginal equivalent. Although there are no clear guidelines for coronary arteriography in patients with heart failure due to left ventricular systolic dysfunction and no anginal equivalent, many of these patients would benefit from evaluation of the coronary anatomy, inasmuch as the sensitivity of noninvasive functional studies is limited and many patients with ischemic disease have clinically silent events. In patients in whom coronary artery disease has previously been excluded as the cause for left ventricular dysfunction, repeated invasive or noninvasive assessment for ischemia is generally not indicated.

Right-Sided Heart Catheterization

With quality echocardiography and Doppler studies, as well as other non-invasive techniques for evaluating cardiac function, right-sided heart catheterization is not required in all patients. Most drugs used for the treatment of heart failure are prescribed on the basis of proven mortality reduction, or symptomatic relief, rather than hemodynamic measurements. Therefore the benefits of hemodynamic monitoring in the management of patients with heart failure remain uncertain. In fact, a large randomized study of right-sided heart catheterization against a non-invasive strategy demonstrated no substantial benefit to patients who underwent the invasive approach [40]. Nevertheless, invasive hemodynamic monitoring may assist in the determination of volume status and cardiac output in patients with complex disease, particularly when cardiac transplantation or implantation of a left ventricular assist device is being contemplated. It can also be helpful in distinguishing heart failure from other disorders such as pulmonary disease or sepsis. Although hemodynamic measurements can be estimated with the use of noninvasive methods such as transthoracic bioimpedance, routine use of those techniques cannot be recommended until they have been shown to improve outcomes in the population of patients with heart failure.

Endomyocardial Biopsy

The usefulness of endomyocardial biopsy is not well established. Most patients with nonischemic cardiomyopathy show nonspecific changes on biopsy (hypertrophy, cell loss or apoptosis, and fibrosis). Biopsy specimens showing lymphocytic infiltration consistent with myocarditis are of diagnostic but, at present, not of therapeutic value. Many patients with myocarditis improve without specific therapy, and directed immunosuppression has not been shown to be helpful in these patients. Biopsy specimens showing giant-cell myocarditis are of prognostic utility, because this disease has been shown to have a malignant course. Nonetheless, therapies for giant cell myocarditis are, at present, anecdotal. The biopsy findings can be used to make a diagnosis of sarcoidosis, amyloidosis, hemochromatosis, eosinophilic myocarditis, Loeffler's syndrome, and endocardial fibroelastosis. However, evidence that biopsy results lead to successful therapies in these conditions is lacking. There is no evidence that outcomes would be improved by performing biopsies to screen for these diseases. Although the risk of serious complication is less than 1%, endomyocardial biopsy is not indicated in the routine evaluation of cardiomyopathy and should be performed only when there is a strong reason to believe that the results will have a meaningful impact on subsequent therapeutic decisions.

Laboratory Testing

The most important blood studies in the patient with heart failure are the serum electrolyte and renal function measurements. A low serum sodium concentration indicates a stimulated renin-angiotensin system as well as increased vasopressin levels and is observed in patients requiring large doses of loop diuretics. A low serum potassium level and contraction alkalosis may also be observed in patients receiving diuretic therapy. An elevated blood urea nitrogen or serum creatinine level suggests either organic or functional renal impairment, caused by vasoconstriction, and decreased cardiac output. Liver function abnormalities may suggest hepatic congestion. Thyroid-stimulating hormone should be measured at the initial evaluation, because both hypothyroidism and hyperthyroidism can be a primary contributor to the cause of heart failure. In the setting of an acute presentation of heart failure, measurement of creatine phosphokinase and isoenzymes, as well as troponin I or troponin T may indicate the presence of active inflammation or ischemic injury to the heart. Serum ferritin and transferrin saturation measurements may be useful for detecting hemochromatosis, although they are of limited yield in the absence of other manifestations of hemochromatosis such as diabetes, liver disease, and skin changes. Screening for human immunodeficiency virus is recommended for patients with high-risk exposures or history of sexually transmitted diseases, with manifestations of infection with the virus such as lymphopenia, anemia, cachexia, or history of opportunistic infections.

Interest has been developing in using the measurement of BNP to diagnose heart failure in the setting of unexplained dyspnea and to monitor patients with chronic heart failure. In

the past, measurement of BNP has required a complex radioimmune assay, and in many hospitals, this meant that the test needed to be sent to a referral center for analysis. More recently, results of studies of the use of a portable apparatus capable of rapid analysis of blood samples have shown the utility of measuring samples on site in the emergency department [33, 41]. Natriuretic peptide levels have been shown to distinguish heart failure from pulmonary causes of dyspnea and to enable examiners to correctly classify the severity of heart failure [27]. As stated previously, serial measurements of BNP can be useful to achieve optimal dosing of guideline directed medical therapy, but their role in acute decompensated heart failure or reducing hospitalizations is not well defined.

Differential Diagnosis

Determination of the underlying cause of systolic heart failure may provide additional avenues for therapies that can lead to improvement of the condition of the patient. Because of the prevalence of atherosclerosis in the population, the first diagnosis that must be considered is ischemia or infarction. Because coronary artery disease is the causal factor in more than half the cases of systolic heart failure, measures taken to distinguish the remaining causes are less likely to produce a diagnosis. During the initial evaluation of the patient, the clinician should be able to identify patients with primary valve disorders (such as aortic stenosis, aortic insufficiency, and mitral regurgitation) causing heart failure. For patients with aortic stenosis, and in many cases of aortic insufficiency, valve surgery can result in a vast improvement of the heart failure syndrome. Although prior reports advised against mitral replacement in the setting of mitral regurgitation and systolic heart failure, repair of the mitral valve (sparing the papillary muscle function and ventricular geometry) has been shown to improve symptoms in these patients in uncontrolled series [42]. The MitraClip, a percutaneous device that focally approximates the mitral leaflet edges, has been shown to be less effective at reducing mitral regurgitation than conventional surgery, but the procedure is associated with superior safety and similar improvements in clinical outcomes [43]. This device is commercially available in Europe, but remains investigational in the United States. Patients with uncontrolled hypertension should be treated with maximally titrated doses of ACE inhibitors, beta blockers, and, if necessary, amlodipine and other antihypertensives.

Evaluation of the patient should uncover exposure to cardiac toxins, such as alcohol or cocaine. Detoxification from alcohol and prolonged abstinence may allow for recovery of cardiac function. Patients with tachyarrhythmias such as atrial fibrillation with rapid ventricular response should be treated with cardioversion or rate control, because ventricular function may improve once the tachycardia ceases. Both hypothyroidism and hyperthyroidism may result in systolic heart failure, which merits a check of thyroid-stimulating hormone on initial presentation. It is well documented that treatment of these disorders leads to clinical improvement. Initial assessment of the laboratories of patients with systolic heart failure may reveal evidence of hypocalcemia or uremia, both documented causes of dilated cardiomyopathy capable of improvement with correction of the abnormality. Other nutritional (selenium) and metabolic (carnitine) deficiencies have been described as leading to dilated cardiomyopathy. These deficiencies, when corrected, may lead to improvements in cardiac function.

Endomyocardial biopsy is not recommended in the routine evaluation of patients with systolic heart failure. However, treatment of patients presenting with signs and symptoms highly suggestive of diagnoses that may be made through biopsy (particularly if the diagnosis has a proven therapy) may benefit by endomyocardial biopsy and the directed therapy that ensues. Patients presenting with fever, myalgias, or pleuritic chest pain may be suffering from myocarditis or myopericarditis. Findings on electrocardiography may also be suggestive of myocarditis or myopericarditis. At the time of this writing, however, no effective therapies for myocarditis beyond supportive therapy and medical therapy for heart failure have been identified. Patients with a history of extracardiac sarcoid or signs of atrioventricular block may be suffering from cardiac sarcoid. Reports of improvements in these patients have been made with the use of corticosteroids. Patients with concomitant liver disease, especially in the setting of diabetes and skin bronzing, may have systolic heart failure as a result of hemochromatosis, a diagnosis that can be made by endomyocardial biopsy. Investigators have also shown utility of magnetic resonance imaging in the diagnosis of cardiac hemochromatosis. Some patients with pheochromocytoma have dilated cardiomyopathy, which is reversible in at least some cases with operative removal of the tumor. Patients presenting with symptoms of sweating, tachycardia (also common in other forms of cardiomyopathy), or headaches may benefit from measurement of plasma and urinary catecholamines and their metabolites and from imaging of the abdomen with computed tomography.

In the absence of identifiable causes of systolic heart failure, patients are assigned a diagnosis of “idiopathic” dilated cardiomyopathy. In series of 1230 patients presenting with nonischemic dilated cardiomyopathy, 50% were assigned a diagnosis of idiopathic dilated cardiomyopathy [44]. Because no etiologic agent can be identified with these patients, no specific therapy is available beyond medical therapies proved to benefit patients with systolic heart failure as a group, which are outlined later in this chapter.

Complications

Morbidity and mortality are, unfortunately, common complications in patients suffering from systolic heart failure. One of the most common complications in heart failure is the need for hospitalization for the treatment of worsening heart failure. There are over one million hospitalizations and over 1.8 million physician office visits annually for a primary diagnosis of heart failure [1]. These hospitalizations result from acute worsening of the chronic condition or from gradual worsening that is refractory to outpatient management. The rate of hospitalization varies, depending on the severity of the illness. Of ambulatory patients (largely in NYHA Classes II to III) enrolled into the placebo arm of the U.S. Carvedilol trials, 19.6% were hospitalized over a mean follow-up period of 6.5 months, in comparison with 14.1% of the patients receiving carvedilol [24]. Patients in the RALES study who were in NYHA Class IV at the time of enrollment or in NYHA Class III but had been in NYHA Class IV within the previous 6 months were more likely to be hospitalized; 40% of the placebo group required hospitalization over the 24-month follow-up period, and 31.6% of the patients received spironolactone.

Patients with heart failure may suffer from heart rhythm disturbances. More than 10% of patients with heart failure and systolic dysfunction suffer from concomitant atrial fibrillation. Ventricular tachyarrhythmias are also common, inasmuch as approximately 10% of patients with advanced heart failure experience syncope or high-grade ventricular ectopy that necessitates the placement of an implantable cardiac defibrillator. Lower grades of ventricular ectopy, such as nonsustained ventricular tachycardia, are seen more commonly; approximately one third of patients show at least three beats of ventricular tachycardia on ambulatory electrocardiographic monitoring.

Cerebrovascular accidents, a dreaded complication of heart failure, can occur because of the presence of left atrial mural thrombus, usually associated with atrial fibrillation, or left ventricular mural thrombus, usually associated with akinesis or dyskinesis of the anterior and/or apical segments in the setting of low-flow and stasis. The incidence of stroke can be reduced with the use of warfarin in certain patients with heart failure. Because of the complications associated with anticoagulant use, routine use of warfarin in patient with heart failure is not currently recommended in absence of known risk factors for thromboembolism, such as atrial fibrillation, mechanical prosthetic valves, prior thromboembolic event, known mural thrombus, or recent anterior wall/apical myocardial infarction.

Low cardiac output in advanced heart failure may lead to complications resulting from poor organ perfusion. Renal insufficiency, hepatic insufficiency, gastroenterologic dysfunction, and central nervous system dysfunction are commonly seen as disease severity progresses. These complications can compound the problem of heart failure in that they exacerbate fluid retention, lead to metabolic derangements, and interfere with compliance with medical and dietary therapies. Quality of life and prognosis progressively decline when heart failure is associated with multisystem organ failure. Palliation with intravenous inotropic medications in this setting may improve the clinical status of the patient temporarily.

Therapy for Heart Failure due to Left Ventricular Systolic Dysfunction

The goals of treatment for congestive heart failure include identification of correctable causes and cofactors, prevention of disease progression, maintenance of physical activity, reversal of sodium retention, and reduction of the risk of mortality. Of course, some of these factors can be achieved or optimized only through medical therapy for heart failure, particularly as the disorder reaches advanced stages. ACE inhibitors are recommended for all stages of heart failure, not only for treatment but also to prevent progression of ventricular dysfunction. Spironolactone, an aldosterone antagonist, has been shown to significantly reduce mortality rates when added to standard therapy. Diuretic therapy is used for the symptomatic and clinical relief of edema, but there are no data that identify a primary role in prevention of disease progression. Most clinicians believe that digoxin is safe and effective in reducing the risk of hospitalization. More recently, beta-adrenergic blockade has emerged as important therapy for heart failure, dispelling previous misconceptions regarding lack of benefit, or even additive risk.

Diet and Lifestyle Issues

The effective therapy of heart failure requires compliance with dietary limitations and other lifestyle issues. Sodium restriction is a highly debated area of heart failure management and current guidelines categorize it as “reasonable for patients with symptomatic heart failure to reduce congestive symptoms [32].” Fluid restriction can also be helpful. As the disease progresses, more aggressive management of fluid intake is usually required, and should be established in a range of less than 64 oz per day. If hyponatremia is present, even more aggressive fluid restriction may be required. In the absence of dietary restrictions, patients consuming liberal amounts of sodium and water can overcome the even the most potent diuretic regimens.

Cessation of smoking should be aggressively encouraged in all patients with heart failure, particularly those with underlying ischemic disease. In addition, alcohol consump-

tion should be kept to one or fewer drinks a day, and in any patient with a history of alcohol dependence or cardiomyopathy associate with alcohol use, abstinence should be advised.

In patients with heart failure in whom the cause is coronary artery disease and the lipid profile is abnormal, dietary and pharmacologic reduction of cholesterol and triglyceride levels is recommended per established guidelines. Despite strong evidence of benefit for statins in most patients with established cardiovascular disease, two large randomized trials found no benefit from initiating statin therapy in patients with symptomatic systolic heart failure (ischemic or nonischemic) [45, 46]. Therefore, statins are not recommended as an adjunctive therapy when prescribed solely for the diagnosis of systolic heart failure without any other indication for their use [32].Obesity can be a major confounding factor in the successful management of heart failure, in view of the direct effects of obesity on ventricular geometry and function. In fact, patient who are obese are more likely to develop cardiovascular disease, including heart failure. Despite this, and of some degree of controversy, is the recently described "obesity paradox" in which patients who are modestly overweight appear to have improved survival once heart failure is established. However, studies that have demonstrated this paradox are very likely flawed by issues of differences in duration of disease as well as disease severity between patient groups. A reasonable goal is that of focusing on heart-smart dietary compliance and adequate physical activity, instead of absolute weight reduction. Unless extreme obesity exists, rapid and aggressive weight loss is probably not warranted in most patients with heart failure, but rather a common sense approach towards permanent lifestyle changes and modest weight reduction is probably a reasonable goal.

Exercise

Historically, bed rest was recommended for the management of acute heart failure, particularly when the cause was myocarditis. This is no longer recommended beyond the initial first days of management of acute decompensation. Current studies indicate that cardiac rehabilitation and a supervised exercise prescription are important for the maintenance of overall circulatory conditioning and skeletal muscle function, and can reduce the degree of exercise intolerance and improve quality of life in patients with heart failure. In the largest trial for patients with heart failure with systolic dysfunction, HF ACTION, a formal exercise program was associated with modest improvements in peak VO2 and 6-min walk distance and overall lower healthcare related costs [47]. Development of a cardiac rehabilitation program should be considered for all patients, as part of the long-term management of heart failure.

Specific Drug Classes

Since the mid-1980s, there has been a radical shift in the accepted endpoints for safety and efficacy of drug therapy for patients with heart failure. Although acute and chronic hemodynamic endpoints are important for characterizing the pharmacologic response to a new drug, more desirable long-term endpoints include reduction of symptoms (improved quality of life), improved exercise or exertional capacity, reversal of abnormal neurohormonal profile, and reduction of mortality. The studies in heart failure that dominated the late 1980s and the early 1990s were large, multicenter clinical trials. These trials were powered to detect the effect of pharmacologic therapy on mortality, efficacy endpoints, and meaningful side effect profiles. Ancillary data derived from these studies included the influence of therapy on subclasses of patients, changes in ventricular arrhythmias, quality of life, symptoms, and concomitant drug usage. Frequently, these studies did not provide information regarding mechanism of pharmacologic action, specific details of pathophysiologic processes, or clear explanations for drug failure when they occurred. General guidelines for the treatment of systolic heart failure according to ACC/AHA stage are given in Tables 13.4, 13.5, 13.6, 13.7, and 13.8 [32].

Diuretics

Diuretics are evaluated with the efficacy endpoint of weight reduction and reversal of edema and pulmonary vascular congestion and are a traditional therapy for the edema of heart failure. Although there have been no long-term randomized controlled studies showing the effects of diuretic therapy on morbidity and mortality in heart failure, shorter term studies have shown that diuretics improve symptoms and exercise tolerance in patients with volume overload. Diuretic choices include loop diuretics (e.g., furosemide, bumetanide, and torsemide), thiazide diuretics [e.g., HydroDIURIL (hydrochlorothiazide) and metolazone], and potassium-sparing diuretics (e.g., spironolactone, triamterene, and amiloride). Loop diuretics act in the proximal tubule and maintain their efficacy unless renal function is severely impaired. Thiazide diuretics tend to be less potent when used alone and are not effective in patients with mod-

Table 13.4 Recommendations for patients at high risk of developing heart failure (Stage A)

Class I (recommended)
1. Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines
2. Other conditions that may contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *LV* left ventricular
From Yancy et al. [32]

Table 13.5 Recommendations for patients with asymptomatic systolic left ventricular dysfunction (Stage B)

Class I (recommended)
1. In patients with history of myocardial infarction and reduced EF, ACE inhibitors or ARBs should be used to prevent heart failure
2. In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF
3. In patients with MI, statins should be used to prevent HF
4. Blood pressure should be controlled to prevent symptomatic HF
5. ACE inhibitors should be used in all patients with a reduced EF to prevent HF
6. Beta blockers should be used in all patients with a reduced EF to prevent HF
Class IIa (probably indicated)
1. ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, LVEF less than or equal to 30%, and on guideline directed medical therapy (see text)
Class III (*not* recommended)
1. Calcium channel blockers with negative inotropic effects

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *LV* left ventricular, *ICD* internal cardioverter defibrillator
From Yancy et al. [32]

Table 13.6 Recommendations for treatment of symptomatic left ventricular systolic dysfunction (Stage C)

Class I (recommended)
1. Diuretics in patient with fluid retention
2. ACE inhibitors for all patients
3. ARBs for patients who are ACE inhibitor intolerant
4. Use of 1 of 3 beta-blockers proven to reduce mortality for all stable patients (see text)
5. Aldosterone receptor antagonists for NYHA class II-IV with LVEF ≤35%
6. Aldosterone receptor antagonists following acute MI with LVEF ≤40% with symptoms of HF or DM
7. Hydralazine and isosorbide dinitrate for African Americans with NYHA class III-IV on guideline directed medical therapy
8. Patients with chronic HF with atrial fibrillation and an additional risk factor for cardioembolic stroke should receive chronic anticoagulation; The selection of anticoagulant agent should be individualized
9. ICD therapy for primary prevention of sudden cardiac death in patients >40 days post-MI with LVEF ≤35%, NYHA class II or III symptoms on guideline directed medical therapy, and who are expected to live >1 year
10. CRT for patients with LVEF ≤35%, sinus rhythm, LBBB ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on guideline directed medical therapy
11. ICD therapy for primary prevention of sudden cardiac death in patients >40 days post-MI with LVEF ≤30, NYHA class I symptoms on guideline directed medical therapy, and who are expected to live >1 year
Class IIa (probably indicated)
1. ARBs are reasonable alternative to ACE inhibitors as first line therapy
2. Hydralazine and isosorbide dinitrate can be useful in patients who cannot be given ACE inhibitors or ARBs
3. Digoxin may be beneficial to reduce hospitalizations
4. Chronic anticoagulation is reasonable for patients with chronic HF and atrial fibrillation without any additional risk factors for cardioembolic stroke
5. Omega-3 PUFA is reasonable to use as adjunctive therapy to reduce mortality and hospitalizations
6. CRT can be useful for patients with LVEF ≤35%, sinus rhythm, non-LBBB pattern with QRS ≥150 ms, and NYHA class III/ambulatory class IV symptoms on guideline directed medical therapy
7. CRT can be useful for patients with LVEF ≤35%, sinus rhythm, LBBB with QRS 120–149 ms, and NYHA class II, III, or ambulatory class IV symptoms
8. CRT can be useful in patients with atrial fibrillation and LVEF ≤35% on guideline directed medical therapy if (a) patient requires ventricular pacing or otherwise meets CRT criteria and (b) AV nodal ablation or rate control allows near 100% ventricular pacing
9. CRT can be useful in patients on guideline directed medical therapy who have LVEF ≤35% and are undergoing new or replacement device implantation with anticipated ventricular pacing
Class IIb (might be considered, but usefulness not well established)
1. Addition of ARB in persistently symptomatic patients on guideline directed medical therapy in whom an aldosterone antagonist is not indicated or tolerated
2. ICD is of uncertain benefit to prolong survival in patients with high risk of nonsudden death such as frequent hospitalizations, frailty, or severe comorbidities
3. CRT may be considered for patients with LVEF ≤35%, sinus rhythm, non-LBBB pattern with QRS 120–149 ms, and NYHA class III/ambulatory class IV on guideline directed medical therapy
4. CRT may be considered for patients with LVEF ≤35%, sinus rhythm, non-LBBB pattern with QRS ≥ 150 ms, and NYHA class II on guideline directed medical therapy
5. CRT may be considered for patients with LVEF ≤30%, ischemic etiology of HF, sinus rhythm, LBBB with QRS >150 ms, and NYHA class I symptoms on guideline directed medical therapy
Class III (*not* recommended)
1. Routine combined use of ACE inhibitor, ARB, and aldosterone antagonist
2. Inappropriate use of aldosterone antagonists in patients with significant renal dysfunction and/or hyperkalemia
3. Anticoagulation in patients without atrial fibrillation, a prior thromboembolic event, or a cardioembolic source
4. Statins as adjunctive therapy when prescribed solely for HF
5. Nutritional supplements as treatment for HF
6. Hormonal therapies other than to correct deficiencies
7. Drugs known to adversely affect the clinical status of patients with HF (eg, most antiarrhythmics, NSAIDS, or thiazolidinediones)
8. Long term use of infused positive inotropic drugs except as palliation for patients with end-stage disease
9. Calcium channel blocker are not recommended as routine treatment
10. CRT is not recommended for patients with NYHA Class I or II symptoms, non-LBBB pattern, and QRS <150 ms
11. CRT is not indicated for patients whose comorbidities and/or frailty limit survival to <1 year

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *LV* left ventricular
From Yancy et al. [32]

Table 13.7 Recommendations for patients with refractory heart failure (Stage D)

Class I (recommended)
1. Inotropic support to maintain systemic perfusion and preserve end-organ function in cardiogenic shock pending definitive therapy or resolution
2. Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite guideline directed medical therapy, device, or surgical management
Class IIa (probably indicated)
1. Fluid restriction (1.5–2 L/day), especially in patients with hyponatremia
2. Continuous intravenous inotropes as a "bridge therapy" in patients awaiting MCS or device therapy
3. MCS in carefully selected patients with stage D HF in whom definitive management (e.g., cardiac transplantation) is anticipated
4. Nondurable MCS as a "bridge to recovery" or a "bridge to decision" for carefully selected patients with HF and acute profound disease
5. Durable MCS to prolong survival for carefully selected patients with stage D HF
Class IIb (might be considered, but usefulness not well established)
1. Short term, continuous intravenous inotrope support for threatened organ dysfunction in hospitalized patients
2. Long-term support with continuous intravenous inotrope support as palliative therapy
Class III (*not* recommended)
1. Routine intravenous infusion inotrope use, either continuous or intermittent, for reasons other than palliative care
2. Short-term intravenous inotrope use in hospitalized patients without evidence of shock or threatened end-organ performance

MCS mechanical circulatory support
From Yancy et al. [32]

Table 13.8 Dosages of medications used in heart failure

Medication	Starting dose	Peak dose
Diuretics		
Loop diuretics		
Furosemide	20 mg daily	200 mg twice daily
Bumetanide	0.5 mg daily	4 mg twice daily
Torsemide	5 mg daily	100 mg twice daily
Thiazide diuretics		
Hydrochlorothiazide	25 mg daily	50 mg daily
Chlorthalidone	50 mg daily	100 mg daily
Metolazone	2.5 mg daily	10 mg twice daily
K^+-sparing diuretics		
Spironolactone	25 mg daily	25–50 mg daily
Amiloride	5 mg daily	10 mg daily
Triamterene	50 mg daily	100 mg twice daily
Angiotensin-converting enzyme inhibitors		
Captopril	6.25 mg t.i.d.	50 mg t.i.d.
Enalapril	2.5 mg q.d.	10–20 mg b.i.d.
Lisinopril	2.5–5 mg q.d.	20–40 mg q.d.
Fosinopril	5–10 mg q.d.	40 mg q.d.
Ramipril	1.25–2.5 mg q.d.	10 mg b.i.d.
Quinapril	5 mg b.i.d.	20 mg b.i.d.
Beta blockers		
Metoprolol Succinate	12.5–25 mg q.d.	200 mg q.d.
Bisoprolol	1.25 mg q.d.	10 mg q.d.
Carvedilol	3.125 mg b.i.d.	25 mg b.i.d. (50 if weight >85 kg)
Carvedilol CR	10 mg q.d.	80 mg q.d.
Digitalis		
Digoxin	0.125 mg q.d.	0.125–0.25 mg q.d.

erately impaired renal function. Because patients with chronic heart failure tend to have at least mild abnormalities of renal function, loop diuretics generally tend to be the diuretic of first choice in view of mild renal impairment in this population. However, this does not exclude use of thiazide-type diuretics in milder heart failure. In more severe heart failure, loop diuretics are much more efficacious when combined with a thiazide-type diuretic, as they block different sites in the nephron and have an additive effect. The goal is optimization of diuresis, prevention of hypokalemia, and assessment of the risk of hyperkalemia. In the absence of signs or symptoms of volume overload, diuretics are not necessary.

When diuretic therapy is initiated in a stable but volume-overloaded patient with heart failure, furosemide, 20–40 mg daily, is preferred. Baseline chemistry profiles should be drawn and rechecked 5–7 days after initiation of the drug, to assess for signs of hypokalemia and volume contraction. If the baseline serum potassium level is in the lower range of normal, then supplemental potassium chloride is added along with the diuretic. The patient should be advised on weight monitoring every morning after voiding and to record the result. The goal weight change should rarely be in excess of 0.5–1.0 kg per day. The patient should be contacted within a week of starting the initial diuretic dose to determine whether further upward titration is necessary. Dosages are normally titrated upward by doubling the baseline dose until an adequate diuretic response is achieved; this usually results in urination within 30–60 min of taking the dose and increased urination should be noted for 3–6 h after the dose is taken. If euvolemia is achieved, then dosages need not be increased, and attention should be paid to signs and symptoms of dehydration. If the patient remains volume overloaded despite an adequate diuretic response, then the regimen can be increased to twice a day. If twice-a-day loop diuretic does not result in euvolemia, then addition of a thiazide diuretic should be considered (e.g., hydrochlorothiazide, 25–50 mg daily). Intermittent doses of high-dose diuretics (metolazone) are not recommended, because these result in large volume shifts and in episodes of hypokalemia that can precipitate ventricular dysrhythmias.

Patients may become resistant to diuretics as a result of intestinal edema, hypoperfusion, or renal mechanisms. In general, patients with diuretic resistance respond better to higher doses of drug or addition of a thiazide diuretic, or both. Because the bioavailability of furosemide may be affected by changes in intestinal edema, bumetanide and

torsemide may be more reliably absorbed in these patients. Patients with inadequate response to all oral diuretics should be treated with intravenous diuretics. Diuretic responsiveness may be restored after alleviation of the edematous state.

Digoxin

Although forms of digitalis glycosides have been used by physicians to treat edematous states for more than 200 years, its efficacy has been a point of dispute until much more recently. Digitalis exerts its effect through the inhibition of Na^+-K^-adenosine triphosphatase (ATPase). Inhibition of this enzyme leads to augmentation of the myocardial contractility but also blocks vagal afferent nerve function, thereby leading to sensitization of cardiac baroreceptors. Baroreceptor responses to physiologic maneuvers are normalized in many patients. By slowing the ventricular response in atrial fibrillation, digoxin improves ventricular filling, coronary perfusion time, and myocardial oxygen consumption. Inhibition of Na^+-K^-ATPase in the kidney reduces the renal tubular reabsorption of sodium, thereby leading to natriuresis. Digitalis therapy administration decreases plasma renin activity and plasma aldosterone. Acutely, catecholamines are also reduced with digitalis.

Two studies evaluated the effect of digoxin withdrawal on clinical and exercise parameters. These were the Randomized Digoxin and Inhibitor of Angiotensin Converting Enzyme (RADIANCE) and the Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) trials [48, 49]. In both trials, patients randomly assigned to undergo withdrawal of digoxin experienced reduction of exercise performance and clinical deterioration. Deterioration was evident within 4–8 weeks, consisting of subjective clinical deterioration, requirement for medication change, and increase of outpatient and inpatient medical management. More recently, the Digitalis Investigation Group (DIG), a long-term trial of 7500 patients randomly assigned to receive digoxin or placebo, showed no mortality benefit with digoxin. However, the risk of hospitalization was reduced by 8% in these patients [50].

Patients with heart failure who are at risk for hospitalization (NYHA Classes II to IV) should be considered for treatment with digoxin. Therapy with beta blockers should not be withheld to facilitate the initiation of digoxin, however. Therapy with digoxin is initiated and maintained at a dose of 0.125–0.25 mg per day. Lower doses (0.125 mg every other day) may be given to elderly patients or patients with impaired renal function. Previously, the therapeutic range of digoxin was thought to be up to a serum level of 2.0 ng/mL. Analysis of data from the DIG trial, however, has shown that patients achieving these levels are more likely to experience adverse effects, and are likely at a higher risk for mortality, potentially of arrhythmogenic origin. Current AHA/ACC guidelines recommend that lower plasma levels (0.5–0.9 ng/mL) are more likely to be associated with benefit [32]. Periodic monitoring of plasma levels should be performed, particularly in the setting of changes in renal performance, or chronic kidney disease.

Renin-Angiotensin System Suppression

Angiotensin converting enzyme inhibitors (ACE inhibitors), in contrast to direct-acting vasodilators, have been highly successful in all stages of congestive heart failure. Although ACE inhibitors have vasodilator properties, their mechanism of action extends to other effects of suppressing angiotensin II and modulation of additional vasoactive substances. ACE serves to catalyze the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and stimulant for aldosterone release. ACE also acts as a kininase, and inhibition of this enzyme leads to decreased breakdown of bradykinin. It is the kininase activity that may explain the advantage of ACE inhibitors over angiotensin receptor blockers.

Many studies have identified the clinical and mortality benefit of ACE inhibitors for all stages of heart failure. The CONSENSUS trial investigators reported in 1987 that the addition of enalapril in patients with NYHA Class IV symptoms led to a 31% reduction in mortality. A significant improvement in NYHA classification was observed in the enalapril recipients, together with a reduction in heart size and a reduced requirement for other medications for heart failure [51]. The effects of ACE inhibitors on patients with asymptomatic heart failure (NYHA Class I) and mild to moderate (NYHA Classes II and III) were demonstrated in the SOLVD trial, which also evaluated the ACE inhibitor enalapril. The treatment substudy evaluated the efficacy of enalapril versus placebo for the treatment of established heart failure [52]. In this group, enalapril was associated with a reduction of overall mortality (16% reduction), although rates of mortality attributed to sudden death were not substantially altered. In a separate prevention substudy in patients with asymptomatic left ventricular dysfunction, enalapril prevented progression of congestive heart failure [53]. Overall mortality rates were not improved in comparison with those for placebo. Enalapril recipients also experienced a lesser incidence of subsequent clinically evident myocardial infarction, in comparison with those receiving placebo. Subsequent studies of ACE inhibitors used in patients with systolic heart failure have demonstrated that the benefits provided are not restricted to any particular compound, but instead represent a "class effect."

In addition to studies that have documented the benefit of ACE inhibitors in mild or asymptomatic heart failure, studies have demonstrated the benefit of ACE inhibitors in patients who have experienced an acute myocardial infarction. The Survival and Ventricular Enlargement (SAVE) study assessed the effects of captopril in an asymptomatic post-infarction population with ejection fractions of less than 40% [54]. This

study also demonstrated reduction of recurrent myocardial infarction with captopril. Subsequent studies of ramipril in a symptomatic postinfarction population showed reduction in mortality with the addition of an ACE inhibitor [55]. More recently, ramipril has been shown to reduce the risk of cardiovascular events (HOPE trial), including a 23% reduction in the risk of developing heart failure, in a population without preexisting heart disease but with cardiovascular risk factors [56]. It is overly simplistic to label these drugs vasodilators, because patients in this study had an average systolic/diastolic pressure drop of only 3/2 mmHg with the active drugs. The drugs appear to have effects on the vasculature, heart, and kidneys that go far beyond their rather small blood pressure–lowering effects. Inhibition of the renin-angiotensin-aldosterone system at the tissue level allows the vasculature, heart, and kidneys to escape some of the ravages of long-term activity of angiotensin II and aldosterone, including growth, hypertrophy, proliferation, deposition of collagen, and tissue remodeling.

The choice of ACE inhibitor dosage should be based on individual patient characteristics, such as baseline blood pressure and serum creatinine and serum sodium levels. Development of mild hypotension (e.g., systolic blood pressure of 80–90 mmHg) and azotemia (serum creatinine concentration of 2.0–2.5 mg per deciliter) may be encountered during drug titration and should be tolerated in the absence of symptoms to attain the benefits offered by the drug. Symptomatic hypotension, progressive azotemia, or an intolerable cough, however, occasionally forces the discontinuation of the ACE inhibitor. Other side effects, including rash and angioedema, are rare. The optimal dosage of an ACE inhibitor and the treatment target (blood pressure vs. trial goal doses) has not been established. Evidence suggests that aspirin and nonsteroidal antiinflammatory drugs can block the favorable effects and increase the likelihood for renal insufficiency of ACE inhibitors, and their use should be minimized; patients with coronary artery disease should reduce their aspirin dose to 81 mg/day.

Angiotensin receptor blockers (ARBs) have similar pharmacologic effects as ACE inhibitors, but there are key differences as well. Theoretically, by blocking the actual angiotensin receptors, a more complete blockade of the renin-angiotensin system can be achieved. Several clinical trials have tested the hypothesis that this action would be associated with better survival than traditional therapy with ACE inhibition, but this has not been demonstrated in well-powered mortality trials. However ARBs, although more expensive than ACE inhibitors, are associated with less cough—an occasional but frequently intolerable side-effect of ACE inhibition. There is also a decreased, but not absent, likelihood of angioedema with ARBs over ACE inhibitors. Current AHA/ACC guidelines recommend ACE inhibitors as first-line therapy in basically all stages of heart failure, even in patients with asymptomatic left ventricular dysfunction, and that ARBs can be used in patients who are ACE intolerant because of cough or angioedema. However both classes of drugs are occasionally contra-indicated because of poor renal function or hyperkalemia [32]. Occasionally, an ARB can be added on top of an ACE inhibitor for patients with persistent symptoms despite adequate doses of conventional therapy who cannot tolerate an aldosterone antagonist. Triple-therapy with an ACE inhibitor, and ARB and an aldosterone antagonist is *not* recommended because of risk for hyperkalemia and/or renal failure [32].

Aldosterone Blockade

Although therapy with ACE inhibitors may initially lead to reductions in elevated aldosterone levels in heart failure patients, some patients may develop "aldosterone escape" after a period of months. Serum aldosterone levels have been shown to correlate with NYHA class. Elevated levels of aldosterone have been shown to correlate with myocyte hypertrophy and fibrosis in animal models of heart failure [57].

The addition of spironolactone, an aldosterone inhibitor, to the combination of digoxin, loop diuretic, and ACE inhibitor in patients with severe heart failure (those in NYHA Class IV and those in NYHA Class III who have had symptoms at rest within the previous 6 months) has been evaluated in the RALES trial [58]. The addition of low doses of spironolactone (12.5–50 mg daily) reduced the risk of death by 30% in these patients. More recently, the EMPHASIS-HF trial demonstrated the benefit of aldosterone antagonists in mild heart failure (NYHA class II) in reducing the risk of death and hospitalization for heart failure [59].

The most common reported adverse reactions to spironolactone are hyperkalemia and gynecomastia. Because spironolactone causes the potassium level to rise by an average of 0.2 mmol per liter, attention should be paid to concomitant doses of supplemental potassium. Serum potassium levels should be checked at baseline and again 5–7 days after spironolactone therapy is initiated. Patients with serum potassium levels greater than 5.0 mmol per liter and serum creatinine levels greater than 2.5 mg per deciliter should have these abnormalities corrected before initiating spironolactone therapy. If the serum potassium level rises between 5.0 and 6.0 mmol per liter after therapy begins, then the dosage should be reduced by half and the laboratory measurements should be checked in 5–7 days. If the serum potassium level rises above 6.0 mmol per liter, then the drug should be discontinued until the abnormality resolves before a lower dosage is attempted.

Eplerenone, a newer aldosterone antagonist with fewer estrogenic effects than spironolactone, has been evaluated in patients with post-infarction heart failure and mild heart failure (NYHA class II), and is associated with a decrease in mortality that is similar to that seen with spironolactone [59,

60]. Eplerenone is a reasonable, albeit more expensive, alternative to spironolactone, particularly for patients who have difficulty with spironolactone-associated gynecomastia. Similar monitoring for serum potassium levels and renal function should be established.

Current AHA/ACC guidelines recommend aldosterone blockade in patients with a reduced ejection fraction who have mild to severe symptoms (NYHA class II-IV) as long as monitoring of serum potassium levels and renal function is feasible [32]. These guidelines do not recommend concomitant use of an ACE inhibitor, and ARB, *and* an aldosterone antagonist because of excessive risk for hyperkalemia and/or renal failure.

Direct Vasodilators

Despite conventional wisdom that "vasodilators" are a mainstay of chronic heart failure therapy, only the combination of hydralazine and isosorbide dinitrate has a favorable efficacy and mortality benefit in heart failure. By older classifications, hydralazine was considered a direct arterial vasodilator, and nitrate preparations such as isosorbide dinitrate were considered venodilators. Such arbitrary classification of vasodilators does not withstand current scrutiny. Hydralazine does exert an effect on vascular smooth muscle cells that is direct. The marked increases of cardiac output and heart rate produced by hydralazine may suggest a direct inotropic effect, although confirmatory studies are needed. Although nitrates are venodilators, it is clear that they are also arterial vasodilators, inasmuch as they mimic endothelium-dependent nitric oxide vasodilation. This combination of therapy is effective in all forms of congestive heart failure. A Veterans Administration Cooperative Study, the Vasodilator–Heart Failure Trial (V-HeFT) in moderate heart failure, was the first trial to demonstrate a favorable effect on mortality when the combination of hydralazine and isosorbide dinitrate was compared with placebo [61]. The V-HeFT II trial compared the combination of hydralazine and isosorbide dinitrate with enalapril in patients with moderate congestive heart failure, without a placebo arm [62]. Mortality in the hydralazine-isosorbide dinitrate group was virtually superimposed with the hydralazine-isosorbide dinitrate group in the V-HeFT I trial. Although treatment with enalapril produced a greater reduction in mortality, treatment with hydralazine–isosorbide dinitrate resulted in a greater improvement in exercise tolerance and a significant increase of ejection fraction.

The combination of hydralazine and isosorbide dinitrate has more recently been tested in a well-powered randomized, placebo controlled trial in an African American population with systolic heart failure. A 43% reduction in mortality, a reduction in hospitalization and an improvement in quality of life was demonstrated with a bidil, a combination pill consisting of these two medications [63]. The combination pill Bidil remains available, but is not actively marketed. Individual doses of hydralazine and isosorbide dinitrate remain a useful treatment option. The current AHA/ACC guidelines recommend using this combination in African American patients with NYHA class III or IV symptoms who are receiving optimal medical therapy with ACE inhibitors and beta-blockers. This combination can also be considered in patients in whom ACE inhibitors and ARBs are contraindicated because of renal dysfunction, drug intolerance, or hypotension [32]. The alpha-antagonist prazosin, with potent vasodilator properties, has been tested extensively in patients with heart failure. The original V-HeFT study demonstrated that the prazosin treatment did not confer a mortality benefit, in comparison with placebo. Activation of the renin system and adverse stimulation from "unopposed beta"–adrenergic effects has been implicated. As a class of drugs, alpha antagonists are not currently used in chronic therapy for heart failure. Other types of vasodilators such as epoprostenol prostaglandin (Flolan), minoxidil, moxonidine, and nifedipine have all shown detrimental effects in patients with systolic heart failure. The disappointing results of trials with these drugs that provide potent vasodilatory effects have shown that a treatment strategy to provide vasodilation to patients with systolic heart failure has a weak foundation. Medications that have been shown to be successful in reducing deaths and hospitalizations in patients with systolic heart failure have demonstrated significant effects on the neurohormonal adaptations that occur in the disease, rather than pure hemodynamic effects.

Sympathetic Nervous System Blockade

The sympathetic nervous system is activated in patients with advanced heart failure. Evidence for this change rests in observations that norepinephrine levels correlate with mortality in heart failure, and low-frequency heart rate responses by heart rate spectral analysis are augmented in patients with severe heart failure. In view of failed trials of dobutamine and other positive inotropic agents on clinical outcomes, relatively small studies performed in Europe initially hinted at the beneficial effects of beta blockade in heart failure [64]. The Metoprolol in Dilated Cardiomyopathy (MDC) trial evaluated progressive increase of metoprolol dosage in patients with moderate to severe dilated cardiomyopathy; patients with coronary artery disease were excluded. Metoprolol improved functional status and was associated with a reduction of combined endpoints (combined mortality or listing for cardiac transplantation) in comparison with placebo. Despite these results, skepticism regarding the use of beta blockers in the treatment of heart failure prevailed until the U.S. Carvedilol trials demonstrated a 65% reduction in mortality with carvedilol, a nonselective beta blocker with additional alpha-blocking properties, in patients with largely NYHA Classes II and III symptoms [24]. After this, trials

using selective beta$_1$ blockade (metoprolol) and nonselective beta blockade in the absence of alpha blockade (bisoprolol) have demonstrated that the benefits of beta blockade in heart failure are largely a class effect [25, 26]. Only the Beta blocker Efficacy and Survival Trial (BEST) failed to demonstrate a benefit of a beta blocker (bucindolol) over placebo in heart failure. Most recently, the Cardivol Prospective Randomized Cumulative Survival (COPERNICUS) trial showed that beta blockade with carvedilol reduces mortality in patients with NYHA class IV heart failure—rest symptoms without signs of volume overload [65].

As a class, beta blockers produce the greatest increase in ejection fraction during therapy in comparison with other forms of therapy. Reduction of heart rate and improved diastolic filling time may contribute to this benefit. Beta blockers directly suppress renin release and thereby interrupt the renin system at its origin. The antioxidant properties of carvedilol may also contribute to its efficacy in heart failure, either by direct chemical redox effects or by indirect effects as a consequence of decreased oxygen consumption or oxidative stress.

Patients with NYHA Class II and III symptoms and patients with rest symptoms who do not have signs of volume overload should be treated with beta blockade unless a contraindication exists. During the initiation of beta blockers, and with each dose titration, patients may experience a temporary reduction in functional status and worsening of fluid retention. This period generally lasts for 2–4 weeks and is usually tolerated without additional diuretics. Beta blockers should not be started by patients who are hospitalized for the treatment of volume overload. Patients with heart rate less than 60 beats per minute should receive beta blockers with caution. Patients with low systolic blood pressure generally tolerate beta blockade; trials have generally shown little to no blood pressure reduction in patients with low to normal blood pressure at baseline. Patients with significant bronchospastic disease may either not tolerate beta blockade, or may be better able to tolerate bisopolol or metoprolol (less beta-2 blockade) than the nonselective carvedilol. Patients with heart failure and wheezing as a manifestation of pulmonary congestion should be considered candidates if the wheezing resolves with diuresis.

Treatment with carvedilol should be initiated at 3.125–6.25 mg twice daily, bisoprolol should be started at 1.25 mg daily, and metoprolol succinate should be initiated at 12.5–25 mg daily. The dose of beta blocker may be titrated upward by doubling the dose every 2–4 weeks as tolerated. Patients should report symptoms of weight gain, breathlessness, or hypotension that might delay upward titration. Carvedilol should be titrated upward to the maximally tolerated dose with a goal of achieving 25 mg twice daily or, for patients weighing more than 85 kg, 50 mg twice daily. However, doses as low as 6.25 mg twice daily have demonstrated mortality benefit in comparison with placebo. Patients treated with metoprolol should be targeted to receive a daily dose of 200 mg. Patients admitted to the hospital for the treatment of volume overload during treatment with beta blockade should receive intravenous diuretics. Beta-blockers should be continued during a symptomatic exacerbation of heart failure in the absence of hemodynamic instability or contraindications. If beta-blocker use is limited, the physician may try to reduce the dose, rather than discontinue the beta blocker abruptly. Initiation of beta-blockers is recommended during a hospitalization after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents [32].

Current AHA/ACC guidelines recommend beta blockers for all patients with a history of myocardial infarction, and basically all patient with left ventricular dysfunction, even if asymptomatic, unless specifically contraindicated [32].

Calcium Channel Antagonists

Calcium channel antagonists have not been successful in the treatment of congestive heart failure, and largely do not have a role in therapy of heart failure patients except in patients with coexistent hypertension or active myocardial ischemia. Hypotheses for the lack of efficacy in congestive heart failure include a direct negative inotropic effect and activation of adverse neurohormonal pathways. This class of compounds is pharmacologically diverse. Verapamil and diltiazem do not increase heart rate, whereas the dihydropyridines increase both resting and peak exercise heart rate. Plasma catecholamines are also increased in response to many of the dihydropyridines. Newer dihydropyridines may not produce these adverse effects. Both felodipine and amlodipine have been shown to be safe but not efficacious in patients with heart failure [66].

Inotropic Therapy

Several randomized trials comparing the effects of inotropic therapies (dobutamine, milrinone, vesnarinone, pimobendan, ibopamine, enoximone, and others) to standard therapy for heart failure have shown that these agents increase the likelihood of death. The presumed mechanism for the added risk is through increased ventricular dysrhythmias, but these agents may also hasten the progression of heart failure by creating a mismatch between myocardial energy supply and demand and through neurohormonal mechanisms. These positive inotropic drugs should be avoided in patients with heart failure if at all possible. Patients with advanced heart failure, who require frequent hospitalizations despite adherence to dietary restrictions, treatment with medical therapies known to improve clinical outcomes, and optimization of volume status, may be candidates for continuous intravenous inotropic support for palliative purposes or as "bridge therapy" for those awaiting mechanical circulatory support or

cardiac transplantation only. The goal of such therapy should be to increase systemic blood flow to improve organ perfusion, improve appetite, and enhance the likelihood that volume status can be maintained so that these patients can enjoy their remaining days outside the hospital. There is no role for intermittent administration of positive inotropic medications to patients with heart failure.

Implantable Cardiac Defibrillators

Many patients with heart failure due to left ventricular systolic dysfunction die unexpectedly from sudden cardiac death (in the setting of ventricular fibrillation, pulseless ventricular tachycardia, or severe bradycardia). Implantable cardiac defibrillators have the capacity to continuously monitor the cardiac electrogram and deliver therapy (cardioversion, antitachycardia pacing, or backup cardiac pacing) on the basis of the program algorithm. Two primary prevention trials have demonstrated that patients with ischemic heart disease, left ventricular systolic dysfunction, and nonsustained ventricular tachycardia benefit from implantable defibrillators if malignant ventricular arrhythmias can be induced during electrophysiologic testing [67, 68]. Even without inducible arrhythmias, the risk of sudden cardiac death is substantial in patients with ischemic cardiomyopathy [67]. Furthermore, in the absence of electrophysiologic testing, patients with ischemic left ventricular dysfunction, an ejection fraction of 30% or less, with NYHA class I-III symptoms have been demonstrated to derive survival benefit from implantation of an implantable defibrillator [69].

Less is known about the utility of ambulatory electrocardiographic monitoring in the nonischemic population. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) enrolled patients with ischemic and nonischemic cardiomyopathy, NYHA Class II or III symptoms, and left ventricular ejection fractions of less than 35%. Patients were randomized to either conventional therapy, therapy with amiodarone or an implantable defibrillator. Therapy with amiodarone did not appear to decrease mortality over placebo, whereas therapy with an implantable defibrillator decreased mortality by 23%. This effect was seen not only in patients with ischemic disease, but also in patients with non-ischemic cardiomyopathy [70].

Current AHA/ACC guidelines *recommend* implantation of a defibrillator in patients with heart failure with reduced systolic function who are at least 40 days post-infarction, have an ejection fraction of 35% or less and class II-III symptoms on guideline directed medical therapy as long as there is a reasonable expectation of survival with good functional status for more than 1 year. These guidelines also *recommend* an implantable defibrillator in similar patients with NYHA class I symptoms and an ejection fraction of 30% or less. In addition, an implantable defibrillator is of uncertain benefit in patients with a high risk of non-sudden death such as frequent hospitalizations, frailty, or severe comorbidities [32].

Patients with true refractory heart failure (Stage D disease) generally should not receive defibrillators, and those who have them should receive counseling about the option of inactivation of the defibrillation function of their device. Sudden death is painless, and may spare the patient continued existence with the severe and intolerable symptoms associated with end-stage heart failure.

Cardiac Resynchronization Therapy (CRT)

Many patients with systolic heart failure have ventricular dyssynchrony that is caused by an intraventricular conduction delay or (left) bundle branch block. Left ventricular pacing can be offered through specially designed pacemakers and combination defibrillator/pacemakers that allow for the placement of a lead into the coronary sinus, terminating in the anterior interventricular vein or the middle cardiac vein. Studies have shown that biventricular pacing or cardiac resynchronization therapy can improve this dyssynchrony in patients with left bundle branch block and can lead to higher cardiac output, higher blood pressure, and improved exercise tolerance. The CARE-HF trial, which randomized patients with NYHA class III-IV symptoms to either routine medical therapy or therapy with a multisite pacemaker designed to reduce dyssynchrony, demonstrated not only improvements in functional capacity and quality of life, but also a 36% decrease in mortality [71]. Better methods for estimation of true mechanical dyssynchrony (as opposed to isolated electrical dyssynchrony) using a variety of echocardiographic techniques, including tissue Doppler mapping, are currently a topic of great interest, as approximately 1 out of 3 patients are non-responders to therapy, despite the presence of electrical dyssynchrony.

Current AHA/ACC guidelines recommend implantation of a CRT device for any patient with NYHA class II, III or ambulatory class IV symptoms, an ejection fraction of $\leq$35%, sinus rhythm, and left bundle branch block with QRS $\geq$150 ms. CRT may be useful for patients with NYHA class III-IV symptoms, left bundle branch block, but QRS duration of only 120–149 ms and those with non-left bundle branch pattern and QRS $\geq$150 ms. Finally, CRT may be considered in patients with ischemic cardiomyopathy, LVEF <30%, NYHA class I symptoms, and left bundle branch block with QRS $\geq$150 ms. CRT should not be considered for patients with NYHA class I or II symptoms, non-left bundle branch pattern, and QRS <150 ms or in patients in whom comorbidities and/or frailty limit survival to less than 1 year [32].

Surgical Therapy

Traditional surgical procedures can be considered in certain patients with heart failure. Coronary artery surgery, one of the most commonly performed surgical procedures in the United States, is frequently performed in patients with left ventricular dysfunction. This should be reserved for those with appropriate coronary anatomy, and demonstration of either ischemia, or viability, or a large burden of at-risk myocardium, such as seen in left main disease.

Valvular procedures, particularly the case for aortic stenosis, can also be helpful, so long as the left ventricular function has not deteriorated past the point of no return. Transcatheter aortic valve replacement (TAVR) has been recently developed as a treatment for patients with severe symptomatic AS with unacceptably high risk for surgical aortic valve replacement. In highly selected patients, TAVR and surgical aortic valve replacement are associated with similar rates of 1-year survival, but stroke and vascular complications are more frequent with TAVR [72, 73]. Mitral valve replacement has generally not been met with favorable results in patients with cardiomyopathy and functional mitral regurgitation. Mitral valve repair, on the other hand, can be done with a very low mortality even in ventricles with significant dysfunction. This procedure is associated with improved symptoms in highly selected patients [42], but there is, as of yet, no well designed clinical trial demonstrating an improvement in mortality.

Although partial left-ventriculectomy ("Batista procedure"), a surgical procedure aimed at restoration of left ventricular geometry by reducing the radius of the left ventricular cavity, theoretically should be beneficial, it has not been met with long-term success. Even though this procedure has been largely abandoned, several other procedures with similar concepts continue to be investigated. Patients with large akinetic or dyskinetic segments may undergo the so-called surgical ventricular restoration procedure. The abnormal segments are re-shaped with a combination of a circumferential purse-string stitch and/or patch exclusion in order to restore the left ventrical toward normal shape, thus reducing the radius and therefore the wall tension via the law of Laplace. In general, ventricular reconstruction does not appear to be of benefit but current guidelines still note that it may be considered in carefully selected patients with heart failure for specified indications, including retractable HF and ventricular arrhythmias [32]. A variety of externally applied cardiac support devices that restore ventricular geometry via a similar mechanism have been investigated. The best studied thus far is the CorCap device which is a bidirectional woven "net" that is applied surgically—usually in combination with other surgical therapies such as mitral valve reconstruction. Five year follow up of this device limited to patient who did not receive concurrent mitral surgery demonstrated a sustained decrease in LV diastolic volume and improvement in NYHA functional class, but failed to show any difference in mortality [74]. However, the CorCap was never approved and its manufacturer went out of business.

Cardiac Transplantation

Cardiac Transplantation is the "gold standard" therapy for end-stage heart failure, at least in highly-selected patient populations. Survival rates after cardiac transplantation are approximately 86% at 1 year, and approximately 50% at 10 years post-transplant. Survival is limited by a combination of mortality from allograft vasculopathy (an accelerated form of coronary artery disease), malignancy, infection, renal dysfunction, and primary graft failure. Despite the limitations, most patients have an excellent quality of life after transplantation, and many resume a relatively normal life.

Unfortunately, donor supply will always limit this therapy to a relatively small number of patients. Fewer than 2500 heart transplants per year are performed in the United States annually, and there is no evidence that this number will increase—in fact, the number of annual transplants has been essentially stable for the past two decades.

Mechanical Circulatory Support

Mechanical circulatory support (MCS) is a rapidly growing field. The large gap between the number of available donor organs and the large numbers of patients with advanced heart failure led the development of durable mechanical circulatory support. Mechanical circulatory support was initially developed as a bridge to transplantation to support patients who were listed for transplant, but had significant deterioration of their hemodynamics despite optimal medical therapy. The initial devices were pulsatile volume displacement pumps. These devices were shown to normalize hemodynamics, improve end-organ dysfunction, and provide an acceptable quality of life [75]. They were approved by the FDA for bridge to transplantation in 1994.

With the initial positive results in the bridge to transplant population, interest grew is applying MCS as permanent support for patients who were ineligible for cardiac transplantations. This led to the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial in which the pulsatile HeartMate XVE demonstrated an impressive doubling of 1 year survival to 52% when compared to medical therapy [76]. The FDA approved the device in 2003 and established destination therapy (DT) as a separate indication from bridge to transplantation.

Despite the improved survival, the first generation pulsatile pumps were associated with significant limitations such as their large size, numerous adverse events, and frequent need for pump replacement. Additionally, while greatly improved over medical therapy, the survival in the REMATCH study at 2 years was still poor (24%). Technology improved with the development of continuous flow devices. These pumps are smaller, contain no valves, use less power, and have fewer moving parts. Direct comparison of the second generation continuous flow pumps (HeartMate II) with the pulsatile pumps demonstrated further significant increases in survival (68% vs. 55% at 1 year; 55% vs. 24% at 2 years), fewer adverse events, and impressive improvements in functional capacity and quality of life [77–79]. These findings led to FDA approval of the HeartMate II for bridge to transplantation in 2008 and destination therapy in 2010. Since approval for destination therapy, MCS has become more widely adopted and there has been over a tenfold increase in its use. Recently, a second continuous flow pump, the HeartWare, was approved for bridge to transplantation and results from a destination therapy trial are still pending.

Even with the substantial improvements in outcomes with continuous flow pumps, significant challenges remain. Patients require systemic anticoagulation and gastrointestinal bleeding is a common adverse event. Stroke is an acute and chronic risk for patients with MCS. Acute right ventricular dysfunction after implant is a continued concern and is associated with worsened morbidity and mortality. Finally, the continuous flow devices require an external power source that necessitates a percutaneous driveline. The driveline is a chronic nidus for infection and a significant weakness for prolonged MCS. Efforts at miniaturizing the devices, finding less invasive methods of implantation, and developing transcutaneous energy systems that eliminate the driveline are ongoing.

Prognosis

The prognosis of patients suffering from congestive heart failure has improved significantly since the mid-1980s. Patients with NYHA Class IV heart failure symptoms enrolled in the placebo arm of the CONSENSUS trial had a 44% rate of mortality at 6 months of follow-up [80]. The patients treated with enalapril in this study had a 40% reduction in mortality at 6 months. The RALES trial showed in 1999 that the addition of spironolactone to the medication regimen of patients with severe heart failure reduced the risk of death by 30%. Most of the patients in the RALES trial were taking ACE inhibitors at baseline. More recently, the COPERNICUS trial demonstrated that carvedilol reduces the risk of all-cause mortality by approximately 35%. Although most patients in the COPERNICUS trial were receiving ACE inhibitors at baseline, only a minority of the patients was receiving spironolactone. However, if the effects of these three classes of drugs are assumed to be additive, the expected mortality of patients with NYHA Class IV symptoms would be reduced by 72% (12% rate of 6-month mortality) in comparison with the group enrolled in the CONSENSUS trial.

Although statistics can be gleaned from clinical trials in regard to the expected survival of populations of patients with systolic heart failure, predicting the prognosis of an individual patient is difficult. Predictions regarding how many months a patient has to live should be avoided, because they are invariably wrong. Nonetheless, patients with heart failure benefit from understanding their general prognosis, as it helps them understand the need to prepare for end-of-life events.

Perhaps the best-documented predictor of prognosis is functional status, usually with the NYHA classification. Asymptomatic patients with heart failure enrolled in the SOLVD Prevention Trial had a 15% rate of mortality over an average of 37 months of follow-up. Patients with NYHA Classes II and III symptoms enrolled in the treatment arm of the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) had a 7.2% rate of mortality at 12 months of follow-up. In contrast, patients with NYHA Class IV symptoms enrolled in the COPERNICUS trial had an 18% mortality rate over 12 months of follow-up. Ejection fraction has also been shown to be a potent predictor of mortality in a heterogeneous population of patients with heart failure, but it is less helpful when groups of patients with severe left ventricular systolic dysfunction are compared [80]. Several additional predictors of prognosis have been identified, including peak exercise oxygen consumption, cardiothoracic ratio as measured by chest radiograph, left ventricular end-diastolic volume, QRS interval, heart rate, mean arterial blood pressure, presence of coronary artery disease, presence of mitral regurgitation, ventricular arrhythmias as identified by Holter monitoring, pulmonary capillary wedge pressure, serum sodium, and levels of plasma norepinephrine as well as other neurohormones/cytokine levels (e.g., BNP, ET, tumor necrosis factor).

Statistical models have been derived and validated for the purposes of predicting prognosis in patients referred for evaluation for transplantation, but they are cumbersome, and frequently require testing that is not universally available. The Heart Failure Survival Score [81] is one such model, is relatively easy to use, but does require cardiopulmonary exercise testing (including gas exchange). More recently, web-based models have become available which utilizes routinely available clinical, laboratory, and demographic information. The Seattle Heart Failure Model [82] allows for evaluation of a patient within minutes, and can be done online at the following website: http://depts.washington.edu/shfm/. Caution should be employed, however, as this model was derived from patients with moderate heart failure, and

applicability to other populations may not give accurate estimates. Nonetheless, such applications can be used to risk-stratify patients, can help the practitioner to counsel the patient as to whether he or she should be referred to a center with advanced therapeutic options, and can help a patient understand his or her disease process. This can be helpful for planning for life events such as need for continued standard medical therapy, referral for transplantation or left ventricular assist device, or when appropriate, end-of-life planning.

Follow-Up and Disease Management Systems

Care of patients with systolic heart failure requires close follow-up and attention to detail to prevent decompensation, need for hospitalization, and death. Outpatient visits are necessary for monitoring subtle changes in signs and symptoms and for titrating medications to achieve the optimal medical regimen. Laboratory testing to monitor renal function and serum potassium level should be performed within 1 week of medication changes, because changes in renal perfusion and electrolyte excretion may lead to unwanted side effects. Because care of the patient with systolic heart failure patient requires significant time and resources to provide sufficient education and planning for follow-up laboratory testing, specialized multidisciplinary disease management programs designed to care for patients with heart failure may provide a distinct advantage over management by a single practitioner. Trials designed to study the benefits of multidisciplinary care delivery to elderly patients with heart failure have clearly been shown to improve clinical patient outcomes, as well as to lead to reduction in cost of care [83].

Recommendations for End-of-Life Planning

Education of patients with heart failure and their families regarding prognosis should be done at the time of initial evaluation and at subsequent times of follow-up care when conditions have changed so the parties can have a chance to plan for end-of-life events. Advanced planning should include treatment preferences such as implantable cardiac defibrillator placement, intravenous inotropic administration, surgical interventions, and transplantation. Because patients with systolic heart failure may experience sudden death, attention should be paid to living wills and advanced directives early in the treatment course. Patients with severe heart failure symptoms refractory to maximal medical therapy and who are ineligible for surgical interventions should be approached regarding preferences for resuscitation. Hospice services may be helpful for patients in the process of dying from severe heart failure.

Practical Points

- In all patients with symptoms of heart failure, their left ventricular systolic function should be assessed.
- Coronary angiography should be performed in patients with heart failure and symptoms of angina or with risk factors for atherosclerosis.
- Patients with heart failure and a left ventricular ejection fraction less than 40% should be treated with an ACE inhibitor unless it is contraindicated.
- Patients with heart failure and a left ventricular ejection fraction less than 40% should be treated with a beta blocker, unless they are intolerant of this medication or unless rest symptoms and signs of volume overload are present.
- Patients with current or recent NYHA Class II-IV symptoms should be treated with spironolactone.
- All patients with heart failure should be advised to weigh themselves daily and report significant weight changes (more than 3–5 lb) to their physicians.
- Patients requiring diuretic therapy or who have a history of volume overload should be instructed to limit daily dietary sodium intake to 2–3 g and limit daily dietary fluid intake to 48–64 oz.
- Patients with refractory heart failure symptoms require frequent office visits and meticulous management of medical therapy.
- Eligible patients with NYHA Class III or IV symptoms despite optimal medical care should be referred for cardiac transplantation and/or mechanical circulatory support evaluation.
- Patients with heart failure should understand how their disease influences their prognosis and should be advised to consider end-of-life issues.

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Paroxysmal Supraventricular Tachycardia

14

Hakan Oral and Fred Morady

Supraventricular tachycardias arise in or involve at least some part of the atrium or atrioventricular junction. Supraventricular tachycardias develop as a result of abnormal automaticity, triggered activity or, most commonly, reentry. Both atrial flutter and atrial fibrillation are supraventricular tachycardias; however, because of the differences in their mechanisms and clinical manifestations, they are grouped separately from other types of supraventricular tachycardias, commonly referred to as paroxysmal supraventricular tachycardia (PSVT).

Usual Causes and Mechanisms of Supraventricular Tachycardia

The most common forms of PSVT are atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reciprocating tachycardia (AVRT), and atrial tachycardia. Together these constitute more than 95% of all PSVT. Uncommon mechanisms of PSVT include sinus node reentry, junctional ectopic tachycardia, intra-Hisian reentry, and nodoventricular or nodofascicular reentrant tachycardias (Table 14.1). In addition, the symptoms of PSVT sometimes are mimicked by sinus tachycardia.

Table 14.1 Paroxysmal supraventricular tachycardias

Mechanism	Prevalence (%)
Atrioventricular nodal reentrant tachycardia	60
Orthodromic reciprocating tachycardia due to an accessory pathway	30
Antidromic reciprocating tachycardia due to an accessory pathway	<5
Atrial tachycardia	10
Sinus node reentry	<1
Junctional tachycardia	<1

Atrioventricular Nodal Reentrant Tachycardia

AVNRT is the most common type of PSVT encountered in clinical practice, accounting for approximately two thirds of all cases. AVNRT is more commonly seen in women, with a female-to-male gender ratio of 2:1. It may occur at any age but most commonly manifests during the fourth and fifth decades of life.

AVNRT is caused by reentry. In patients with AVNRT, the atrioventricular junction has two or more functionally discrete pathways. One of these functional pathways, the "fast pathway," conducts impulses rapidly but has a relatively long effective refractory period. The other pathway, "slow pathway," has a slower conduction velocity but a shorter effective refractory period than the fast pathway [1, 2]. In typical AVNRT, an atrial premature depolarization (APD) conducts to the atrioventricular junction through the atrium. Because it is premature, it may encounter a refractory fast pathway and conduct through only the slow pathway. Because the slow pathway has a longer conduction time, by the time the depolarization travels through the slow pathway and arrives at the compact atrioventricular junction, the fast pathway may have recovered excitability, so that the depolarization travels in a retrograde manner through the fast pathway and back down the slow pathway. If this reentry process continues, a sustained tachycardia occurs (Fig. 14.1) [3–5]. Because the fast pathway has a rapid conduction velocity, the ventriculoatrial conduction time during typical AVNRT is very short. Therefore, on the surface electrocardiogram (ECG), retrograde P waves may be buried within the QRS complexes and not be visible or may be partially visible at the end of the QRS complex (Fig. 14.1). P waves are typically inverted in the inferior leads (II, III, and aV_F) and may be manifest as pseudo-S waves, and upright in V_1, leading to a pseudo-r′ appearance.

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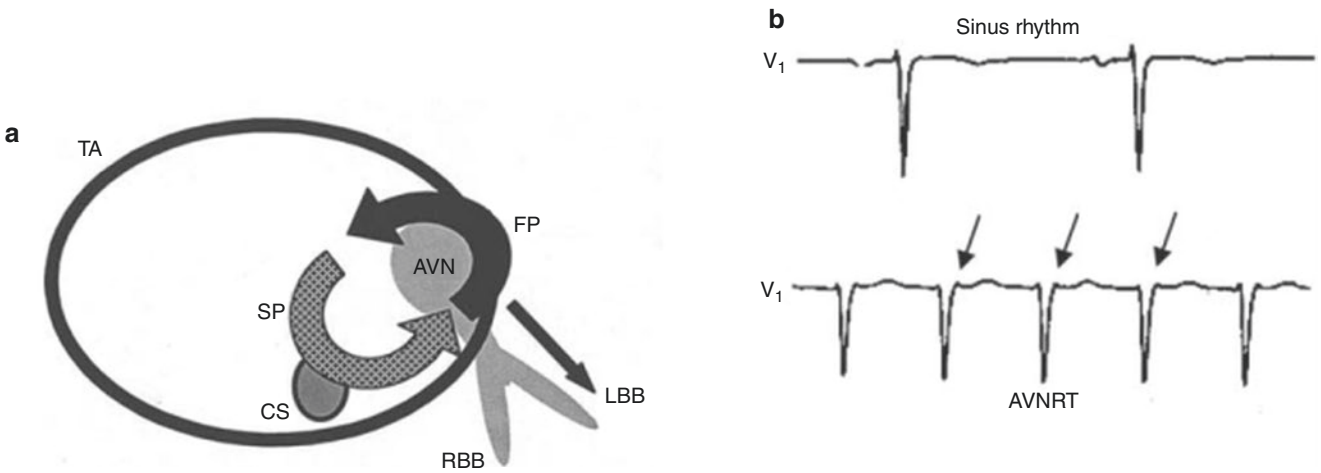

Fig. 14.1 Mechanism of atrioventricular nodal reentrant tachycardia (AVNRT) is shown (**a**). Right atrium and right ventricle are illustrated in the left anterior oblique view. During AVNRT, electrical depolarization conducts in an antegrade manner through the slow pathway (SP, *hatched arrow*) to the compact atrioventricular node (AVN) and in a retrograde manner through the fast pathway (FP, *solid arrow*). (**b**) Pseudo-r′waves caused by retrograde P waves during AVNRT (*arrows*). *AVN* atrioventricular node, *CS* coronary sinus, *FP* fast pathway, *LBB* left bundle branch, *RBB* right bundle branch, *SP* slow pathway, *TA* tricuspid annulus

In the atypical form of AVNRT, the fast pathway is utilized as the anterograde limb and the slow pathway as the retrograde limb of the reentrant circuit. Therefore, the ventriculoatrial conduction time is prolonged. The ECG reveals inverted P waves in the inferior leads and a long RP interval (RP interval exceeds PR interval). Atypical AVNRT accounts for fewer than 10% of cases of AVNRT.

Atrioventricular Reentrant Tachycardia (AVRT)

In normal individuals, the only electrical connections between the atria and the ventricles are the atrioventricular node and the His-Purkinje system. In patients who have an accessory pathway, there is an extra muscular tissue between the atrium and the ventricle. Accessory pathways may conduct electrical impulses in an anterograde or retrograde manner or in both directions. Accessory pathways that conduct only in the retrograde direction are called *concealed* accessory pathways, because no delta waves are present on the ECG. Anterograde conduction over an accessory pathway leads to ventricular preexcitation, with the typical ECG manifestations of a short PR interval and delta waves (Wolff-Parkinson-White pattern). Depending on the relative timing of the activation of the ventricles through the atrioventricular junction, the His bundle, and the accessory pathway, there may be different degrees of ventricular preexcitation, and the delta waves may be subtle or pronounced.

The mechanism of PSVT due to an accessory pathway is reentry. An APD may block in the accessory pathway in an anterograde manner and then activate the ventricle through the atrioventricular node and the His bundle. By the time the impulse reaches the ventricular insertion site of the accessory pathway, the pathway may have regained excitability and may conduct in a retrograde manner, initiating the tachycardia. This type of reentry, in which the atrioventricular node and the His bundle are used as the anterograde limb and the accessory pathway as the retrograde limb, is called *orthodromic reciprocating tachycardia* (ORT) (Figs. 14.2a and 14.3). Approximately 30% of PSVT arise from orthodromic reciprocating tachycardia (Table 14.1). The type of reentry circuit, in which the accessory pathway is utilized as the anterograde limb and the atrioventricular node–His Purkinje system is utilized as the retrograde limb, is referred to as *antidromic reciprocating tachycardia* (ART) (Figs. 14.2b and 14.4).

The anatomic location of the accessory pathway may be anteroseptal, midseptal, posteroseptal, right free wall, or left free wall. Free-wall sites are subgrouped as anterior, anterolateral, lateral, posterolateral, or posterior in relation to the mitral or tricuspid annulus. Left free-wall pathways account for 60% of all pathways, followed by posteroseptal (30%) and right free-wall pathways (10%). The anteroseptal and midseptal pathways are rare. Multiple accessory pathways exist in 5% of patients with the Wolff-Parkinson-White syndrome. Multiple accessory pathways are more prevalent among patients with congenital heart disease, particularly Ebstein's anomaly.

The most common type of supraventricular tachycardia in patients with an accessory pathway is ORT. ART accounts for fewer than 10% of accessory pathway–mediated PSVTs.

An unusual PSVT is the permanent form of junctional reciprocating tachycardia, an ORT in which a slowly conducting, concealed posteroseptal pathway is used as the retrograde limb of the reentrant circuit. This tachycardia has a

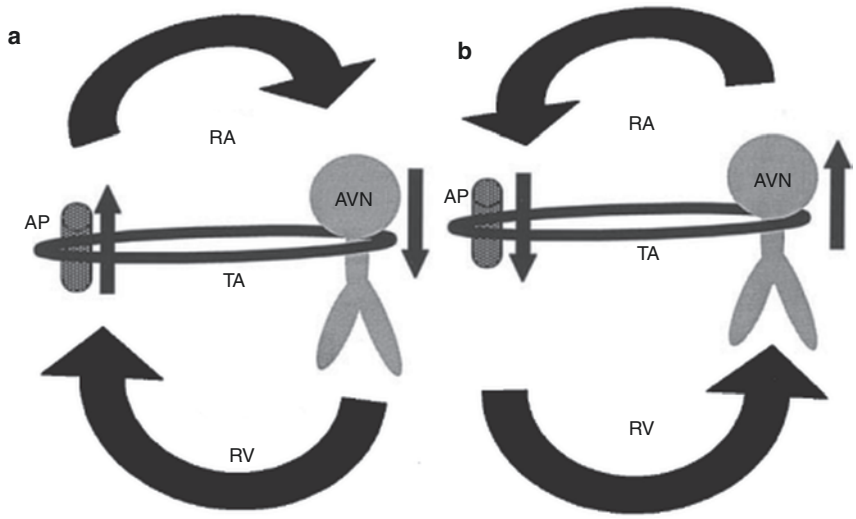

Fig. 14.2 (**a**) Orthodromic reciprocating tachycardia. Electrical impulse propagates in an antegrade manner through the atrioventricular node, His bundle, and bundle branches and conducts in a retrograde manner to the atrium through the accessory pathway. (**b**) Antidromic reciprocating tachycardia. Electrical impulse propagates in an antegrade manner through the accessory pathway to the ventricle and conducts in a retrograde manner to the atrium through the His bundle and the atrioventricular node. *AP* accessory pathway, *AVN* atrioventricular node, *LBB* left bundle branch, *RA* right atrium, *RBB* right bundle branch, *RV* right ventricle, *TA* tricuspid annulus

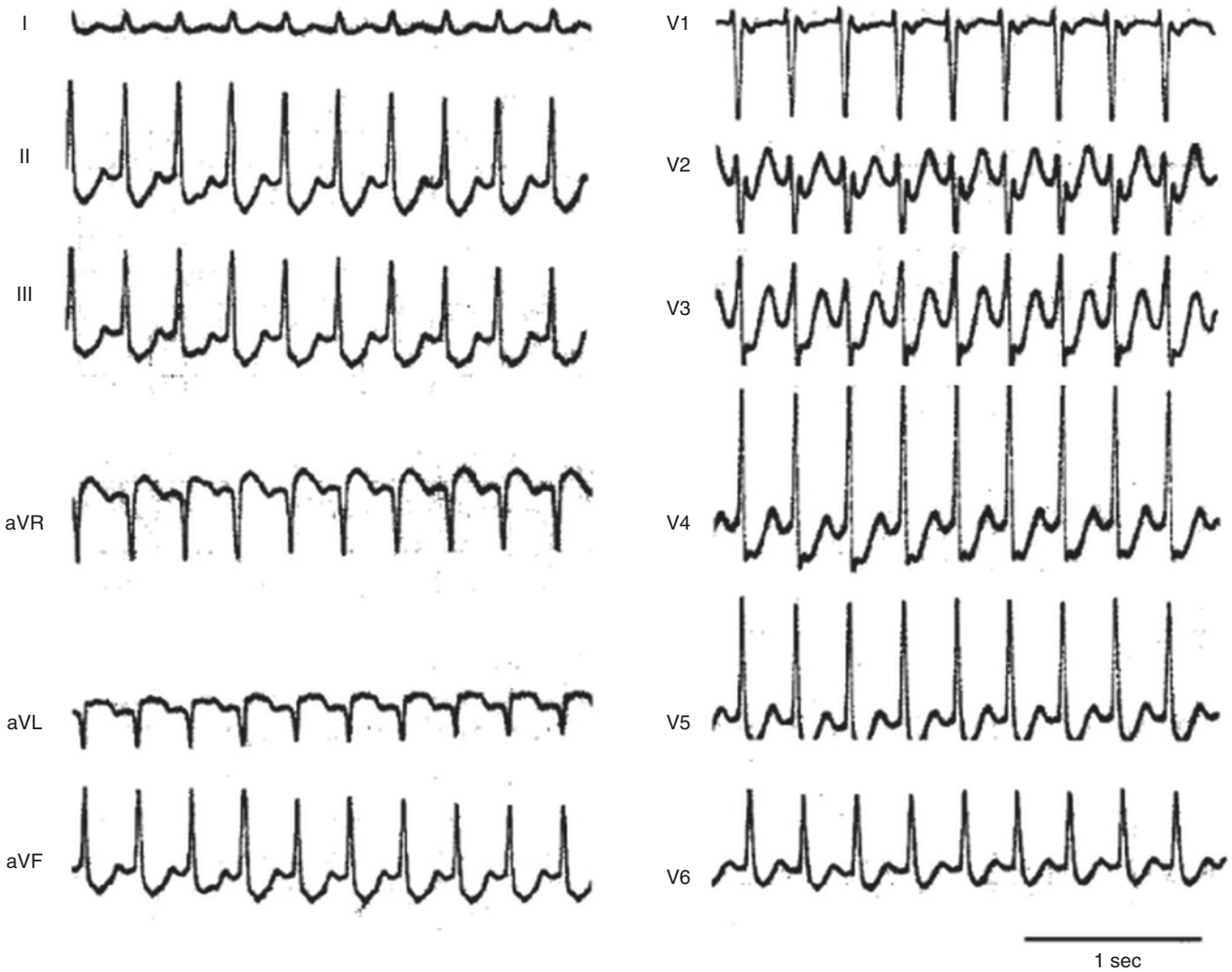

Fig. 14.3 A 12-lead electrocardiogram during paroxysmal supraventricular tachycardia (PSVT) in a patient with a concealed accessory pathway. The mechanism of PSVT was orthodromic reciprocating tachycardia. P waves can easily be visualized in the ST segment, particularly in the inferior leads

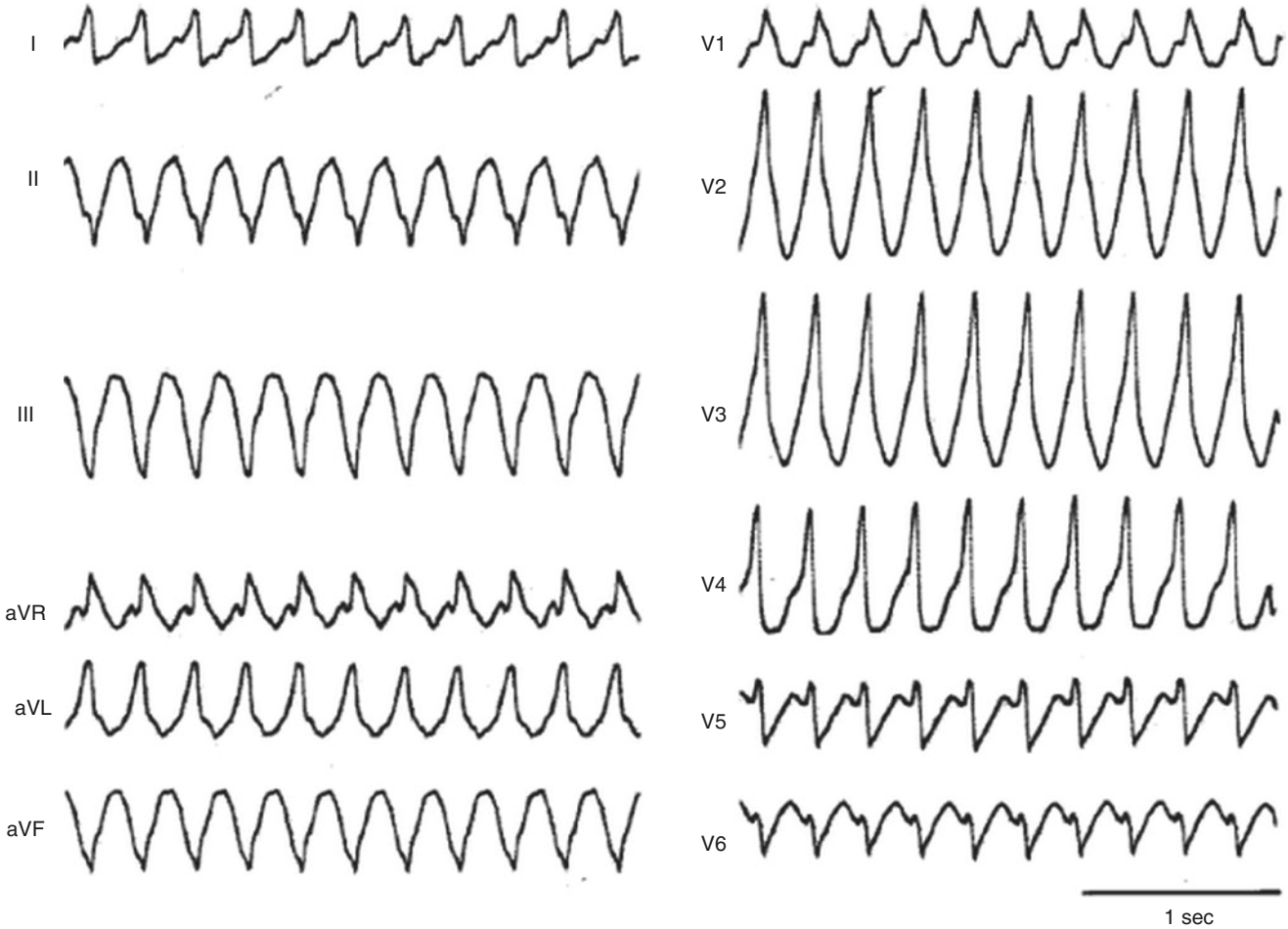

Fig. 14.4 A wide QRS complex tachycardia in a patient with Wolff-Parkinson-White syndrome. Because of ventricular preexcitation over the accessory pathway, QRS complexes are wide. The mechanism of this tachycardia was antidromic reciprocating tachycardia

long RP interval, with inverted P waves in the inferior leads. It may be incessant and may cause tachycardia-induced cardiomyopathy (Fig. 14.5).

Atrial Tachycardia

Atrial tachycardias account for approximately 10% of all PSVT. In contrast to AVNRT and AVRT, which are caused by reentry, the mechanism of atrial tachycardia may be abnormal automaticity, triggered activity, or reentry, particularly in patients with scarred atrial myocardium. Atrial tachycardia may originate in the right atrium, typically along the crista terminalis, or in the left atrium. In patients with atrial tachycardia, there may be variable atrioventricular conduction, and atrial tachycardia persists even when there is atrioventricular block. In contrast, ORT and ART cannot continue when there is atrioventricular block.

Presenting Symptoms and Signs

PSVT has an abrupt onset and termination. The symptoms associated with PSVT depend on the mechanism of the tachycardia, the rate of the tachycardia, and the presence of underlying structural heart disease. Most affected patients experience palpitations. Dyspnea, chest discomfort, lightheadedness, and weakness also are common. Syncope is unusual. In some patients, presyncope and syncope may be caused by a vasodepressor response to the tachycardia. Incessant forms of PSVT may lead to development of tachycardia-mediated cardiomyopathy. Sudden death due to supraventricular tachycardia is extremely rare. However, sudden death may occur in patients with rapidly conducting accessory pathways. In these patients, very rapid ventricular rates during atrial fibrillation may trigger ventricular fibrillation.

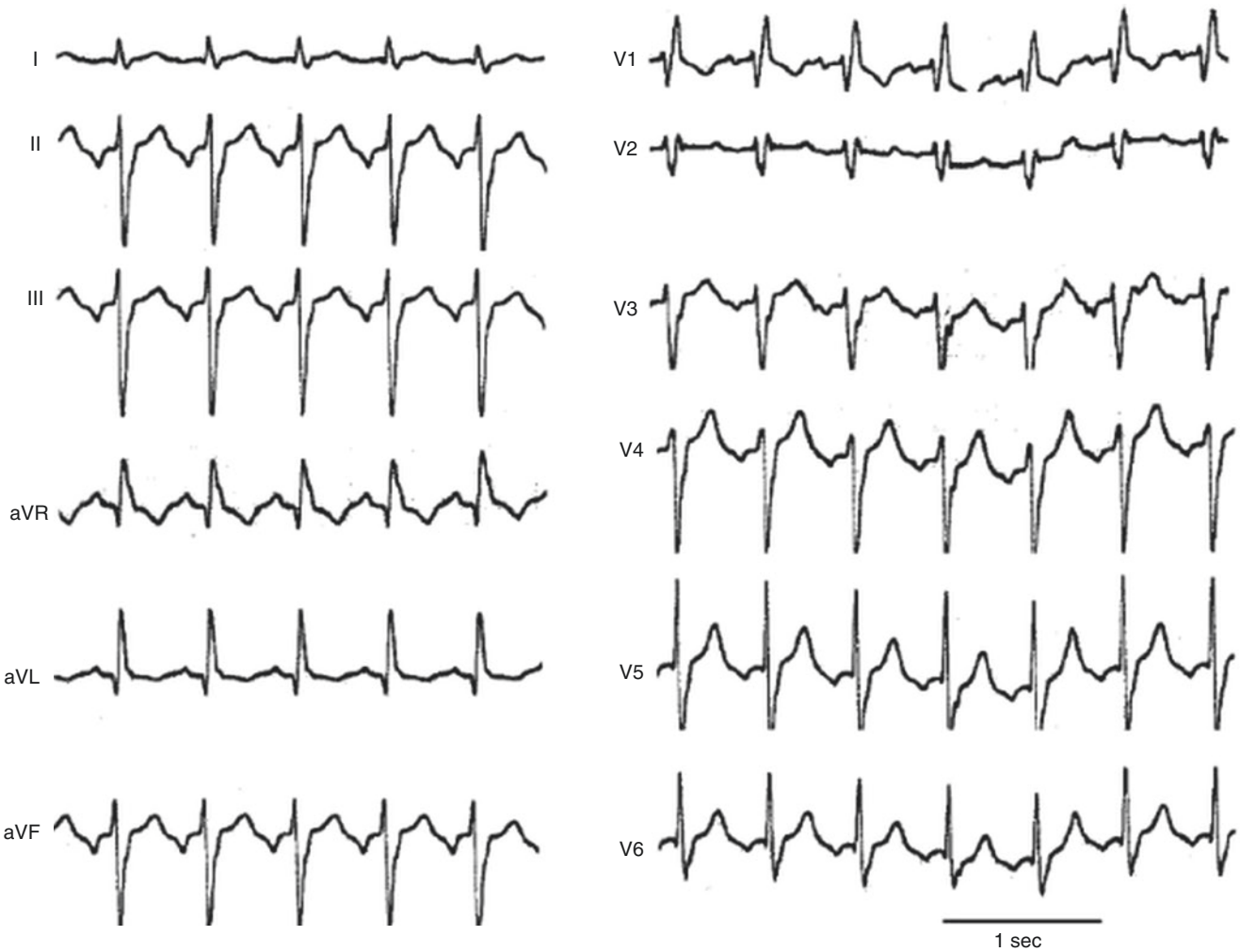

Fig. 14.5 A 12-lead electrocardiogram during paroxysmal supraventricular tachycardia. The mechanism of this tachycardia was permanent form of junctional reciprocating tachycardia, caused by a slowly conducting posteroseptal accessory pathway. The RP interval was longer than the PR interval. P waves were inverted in the inferior leads, II, III, and aV_F

Helpful Diagnostic Tests and Differential Diagnosis

A 12-lead ECG may be helpful in determining the mechanism of PSVT. The P wave and QRS morphologic features and their relation to each other may provide important clues. The hallmark of PSVT is narrow QRS complexes. However, in patients with underlying intraventricular conduction delay or bundle branch block, in patients with a rate-related bundle branch block during the tachycardia, or in patients with ventricular preexcitation, PSVT is characterized by wide QRS complexes.

If the P waves are visible, the P wave axis provides information on the site of atrial activation. Negative P waves in leads I and aV_L indicate either a left atrial tachycardia or activation of the left atrium through a left-sided accessory pathway. If the P waves occur in the left half of the RR cycle and are separate from the QRS complex, ORT is more likely than typical AVNRT to be present (Fig. 14.3). During typical AVNRT, P waves usually are buried within the terminal portion of the QRS complexes and often cannot be visualized (Fig. 14.2b).

If there is atrioventricular block during the tachycardia, with more P waves than QRS complexes, atrial tachycardia is very likely to be present. Atrioventricular block during PSVT excludes a tachycardia caused by an accessory pathway. There is one-to-one relationship between the P waves and QRS complexes in most cases of AVNRT; however, two-to-one atrioventricular block can occasionally be observed.

If a record is available, the initiation and termination of a PSVT may provide diagnostic clues. Reproducible initiation of a PSVT with an APD that conducts with a long PR interval may suggest initiation of typical AVNRT, with anterograde conduction over the slow pathway. Termination of a

tachycardia with a P wave without a subsequent QRS complex—spontaneously, during carotid sinus massage, or during adenosine administration—makes the presence of atrial tachycardia very unlikely.

In approximately 20% of cases, the mechanism of PSVT cannot be determined from the surface ECG [6]. Furthermore, in many patients with PSVT, a 12-lead ECG of the tachycardia is not available. An ambulatory event recorder that is patient activated may be useful in documenting whether PSVT is the cause of symptoms. These devices can be used for 30–60 days. If the symptoms occur on a daily basis, a 24-h Holter monitor is useful.

An electrophysiologic test is the gold standard for determining the mechanism of PSVT. Once the mechanism has been established, radiofrequency catheter ablation can often be performed during the same procedure.

Therapy

Acute Management

During PSVT in which the atrioventricular node is part of the reentrant circuit (AVNRT or AVRT), maneuvers or pharmacologic agents that temporarily slow or block atrioventricular conduction may terminate the tachycardia. A Valsalva maneuver or carotid sinus massage should be considered initially in hemodynamically stable patients. Among pharmacologic agents, adenosine has emerged as a useful diagnostic and therapeutic agent [7, 8]. Adenosine induces transient atrioventricular block and terminates most AVNRTs and AVRTs. Adenosine is contraindicated in patients with reactive airway disease. Adenosine may precipitate atrial fibrillation, and caution is necessary with its use in patients with the Wolff-Parkinson-White syndrome, because atrial fibrillation may be associated with extremely rapid ventricular rates. If adenosine is contraindicated or not available, then intravenous beta blockers such as esmolol, metoprolol, or propranolol or intravenous calcium channel blockers such as verapamil or diltiazem can be used. In patients with atrial fibrillation and the Wolff-Parkinson-White syndrome, intravenous procainamide should be considered as the initial antiarrhythmic agent. Drugs that selectively block atrioventricular conduction should not be used, because they may result in an increase in conduction over the accessory pathway and acceleration of the ventricular rate [9, 10]. If there is evidence of significant hemodynamic compromise, synchronized direct-current cardioversion should be considered.

Long-Term Therapy

Long-term treatment in patients with PSVT depends on the frequency, duration, and severity of symptoms. In symptomatic patients, radiofrequency catheter ablation is often a first-line therapeutic modality, because of a very favorable risk/benefit ratio. In addition, one study has shown that radiofrequency catheter ablation is the most cost-efficient treatment strategy in patients with PSVT [11]. In addition to patient preference, radiofrequency catheter ablation is indicated in patients with frequent episodes of PSVT that are refractory to drugs, in patients with PSVT associated with severe symptoms such as presyncope or syncope, and in patients with the Wolff-Parkinson-White syndrome who have an accessory pathway that is capable of rapid conduction [12].

The efficacy of radiofrequency catheter ablation in curing AVNRT has been reported to be 98–100% [13–16]. The recurrence rate is less than 2%, and complications such as atrioventricular block are rare (1% or less).

Radiofrequency catheter ablation has been shown to be effective in 85–100% of patients with an accessory pathway [12, 17–20]. The risk of complications such as atrioventricular block or pericardial tamponade is less than 1% [12].

In patients with atrial tachycardia, radiofrequency catheter ablation has a success rate of 80–90%. The lower efficacy than for other types of PSVT is attributable in part to an increased propensity for atrial tachycardias to be multifocal [12, 21]. However, radiofrequency catheter ablation may be appropriate for patients whose condition has been refractory to drug therapy or who prefer catheter ablation over chronic drug therapy.

In patients with symptomatic episodes of PSVT who prefer not to have radiofrequency catheter ablation, medical therapy also is an option. Agents that block atrioventricular nodal conduction—that is, beta blockers or calcium channel blockers—may be useful for AVNRT and ORT [22]. However, in patients with the Wolff-Parkinson-White syndrome, these agents may facilitate conduction over the accessory pathway during atrial fibrillation. Class IA (quinidine, procainamide, disopyramide) [23–25], IC (propafenone, flecainide) [26, 27], and III (amiodarone, sotalol) [28–31] drugs can be considered for patients whose condition is refractory to beta blockers or calcium channel blockers, for patients with atrial tachycardia, or for patients with the Wolff-Parkinson-White syndrome. The efficacy of these agents in preventing PSVT is unpredictable and variable. Side effects may limit the use of antiarrhythmic drug therapy.

In patients with infrequent and brief episodes of PSVT, no specific drug therapy may be needed. In patients with occasional episodes of PSVT that are long enough or symptomatic enough to warrant therapy, drug therapy can be used on an as-needed basis, instead of on a daily basis. For example, a 20- to 40-mg dose of propranolol taken at the onset of PSVT may lessen the severity of symptoms and shorten the duration of the episode, without causing the side effects that may be associated with daily use of beta blockers.

Practical Points

- AVNRT, AVRT, and atrial tachycardia constitute more than 95% of all PSVT.
- AVNRT is the most common type (60%). The surface ECG may show retrograde P waves buried at the end of the QRS complex. P waves are typically inverted in the inferior leads (II, III, and aV_F) and may be manifest as pseudo-S waves, and upright in V1, leading to a pseudo-r′ appearance.
- Accessory pathways may conduct electrical impulses in an anterograde manner (manifest), in a retrograde manner (concealed), or in both directions. Anterograde conduction over an accessory pathway leads to ventricular preexcitation, with a short PR interval and delta waves (Wolff-Parkinson-White pattern). Approximately 30% of PSVT is due to accessory pathways. Multiple accessory pathways are more prevalent in patients with congenital heart disease, particularly Ebstein's anomaly.
- Atrial tachycardias account for approximately 10% of all PSVT. In patients with atrial tachycardia, there may be variable atrioventricular conduction, and atrial tachycardia persists even in the presence of atrioventricular block.
- PSVT have an abrupt onset and termination. Most patients experience palpitations. Dyspnea, chest discomfort, lightheadedness, and weakness also are common. Syncope is unusual. In some patients, presyncope and syncope may be caused by a vasodepressor response to the tachycardia.
- The hallmark of PSVT is narrow QRS complexes. However, in patients with an underlying intraventricular conduction delay or bundle branch block, in patients with a rate-related bundle branch block during the tachycardia, or in patients with ventricular preexcitation, PSVT is characterized by wide QRS complexes.
- In approximately 20% of cases, the mechanism of PSVT cannot be determined from the surface ECG. An electrophysiologic test is the gold standard for determining the mechanism of PSVT. Once the mechanism has been established, radiofrequency catheter ablation can often be performed during the same procedure to eliminate the tachycardia permanently.
- Radiofrequency catheter ablation usually is the most effective and cost-efficient treatment strategy in patients with symptomatic PSVT.

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Atrial Fibrillation and Atrial Flutter

15

Toshimasa Okabe, Aman Chugh, Frank Pelosi Jr, and Fred Morady

Atrial fibrillation is the most common cardiac arrhythmia necessitating hospitalization in the United States [1]. Although not immediately life-threatening, atrial fibrillation is associated with significant rates of morbidity and mortality. Furthermore, recurrences of arrhythmia and complications from therapy present a challenge for both the patient and the clinician.

Usual Causes

Based on the current clinical and experimental data, there are probably multiple mechanisms that are responsible for initiating and maintaining atrial fibrillation. Classically, atrial fibrillation is thought to be perpetuated by the presence of multiple self-sustaining waves of atrial depolarization, or *wavelets* (Table 15.1) [2, 3]. In recent years, the concept of drivers and rotors has been proposed as a major mechanism in the pathophysiology of atrial fibrillation. When the rapid periodic activity of a rotor encounters atrial tissue incapable of maintaining 1:1 activation, fibrillatory conduction results. The rotor hypothesis predicts that there is a frequency gradient between the source and more remote atrial tissue. Indeed, evidence of left-to-right gradients has been reported in both animal models and clinical studies [4, 5]. Whatever the mechanism may be, as episodes of atrial fibrillation become more frequent or long lasting, electrophysiologic and structural properties of the atrium are altered and become maladaptive. Although atrial fibrillation may be initially *paroxysmal,* or self-terminating, this remodeling process may result in atrial fibrillation in becoming *persistent*, which indicates that either pharmacologic or electrical conversion (i.e., cardioversion) is required to restore sinus rhythm. When the patient and the clinician decide to stop further attempts to restore sinus rhythm and pursue ventricular rate control as a management strategy, it is termed *permanent* or *chronic* atrial fibrillation [6].

Approximately 1–2% of the general population has atrial fibrillation; however, the prevalence of atrial fibrillation increases with age from less than 1% among persons younger than 50 years up to 9% for those older than 80 years [7, 8]. There is no distinct preponderance with regard to gender.

Table 15.1 Cardiac and noncardiac conditions associated with atrial fibrillation

Cardiac diseases associated with atrial fibrillation
Coronary artery disease
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Valvular heart disease
Rheumatic
Nonrheumatic
Cardiac arrhythmias
Atrial tachycardia
Atrial flutter
Atrioventricular nodal reentrant tachycardia
Wolff-Parkinson-White syndrome
Sick sinus syndrome
Pericarditis
Noncardiac disease associated with atrial fibrillation
Systemic hypertension
Diabetes mellitus
Hyperthyroidism
Pulmonary diseases
Chronic obstructive pulmonary disease
Primary pulmonary hypertension
Acute pulmonary embolism
Obstructive sleep apnea

Adapted from Pelosi and Morady [87]

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Atrial fibrillation has a significant association with structural heart disease. Twenty-five percent of patients with atrial fibrillation also have concomitant coronary artery disease [8]. Although only about 10% of all myocardial infarctions are associated with atrial fibrillation, its presence is associated with a mortality rate of up to 40% [9]. Approximately, one third of patients undergoing cardiac surgery experience atrial fibrillation, and the combined coronary artery bypass grafting (CABG) and valvular surgery has the highest risk of postoperative atrial fibrillation [10]. Postoperative atrial fibrillation adds to hospital length of stay and cost and is associated with increased short- and long-term mortality [11, 12].

The association of atrial fibrillation and valvular heart disease is well established. Rheumatic valvular disease greatly increases the chance of developing atrial fibrillation and quadruples the risk of thromboembolic complications. Of the patients with left ventricular dysfunction, approximately one in five have atrial fibrillation [13]. This arrhythmia may also be part of the initial presentation of acute pericarditis and rare cardiac tumors, such as atrial myxoma.

Other cardiac arrhythmias, such as those related to the Wolff-Parkinson-White syndrome, may be associated with atrial fibrillation. Catheter ablation of the accessory pathway that causes this syndrome also eliminates atrial fibrillation in 90% of cases [14]. Other arrhythmias associated with atrial fibrillation include atrial tachycardia, atrioventricular nodal reentrant tachycardias, and bradyarrhythmias such as sick sinus syndrome and other sinus node dysfunction.

Atrial fibrillation is associated with otherwise noncardiac systemic diseases. Systemic hypertension is found in 45%, and diabetes mellitus in 10% of patients with atrial fibrillation [8]. Although associated thyroid disease accounts for about 2% of cases of atrial fibrillation, it is one of a few reversible causes of this arrhythmia and should not be overlooked [15]. The presence of atrial fibrillation and chronic obstructive pulmonary disease is associated with an increased rate of mortality. Patients with acute pulmonary embolism may initially present with atrial fibrillation. Obesity and obstructive sleep apnea have also been recognized as modifiable risk factors for atrial fibrillation [16–19].

No apparent cause may be identified in approximately 3% of patients with atrial fibrillation [20]. This *lone* atrial fibrillation is not associated with a high thromboembolic risk in younger age groups, but as a person ages or develops other associated conditions, the risk may increase. While low-to-moderate exercise and weight control have been shown to reduce an incidence of atrial fibrillation, long-term practice of strenuous endurance training has been associated with increased risk of atrial fibrillation in otherwise healthy trained athletes [21]. Proposed pathophysiology of atrial fibrillation in this subgroup of patients include atrial remodeling, increased inflammation, altered parasympathetic/sympathetic balance and increased pulmonic vein ectopy [22].

Signs and Symptoms

The presenting symptoms of atrial fibrillation are quite variable. Palpitations, fatigue, or dyspnea with exertion are common. Atrial fibrillation may exacerbate symptoms of myocardial ischemia in the presence of underlying coronary artery disease. Loss of atrial contractile function during atrial fibrillation lowers cardiac output and may lead to congestive heart failure in patients with left ventricular dysfunction. Atrial fibrillation rarely causes syncope; therefore, syncope attributed to such a diagnosis should be called into question. Asymptomatic episodes may occur in otherwise symptomatic patients with atrial fibrillation; therefore, reliance on symptoms may underestimate the arrhythmic burden attributable to atrial fibrillation [23].

History and physical examination of a patient with atrial fibrillation should first be directed at determining the degree of clinical compromise (Table 15.2). The pulse is classically described as "irregularly irregular," but a very rapid ventricular rate may make this difficult to detect. Blood pressure is typically normal, and hypotension is unusual in the absence

Table 15.2 Components of clinical evaluation of atrial fibrillation

Component	Findings
History	Determine duration of atrial fibrillation
	Determine severity of symptoms
	Palpitation
	Fatigue
	Dyspnea, particularly upon exertion
	Lightheadedness
	Identify symptoms of ischemia or congestive heart failure (CHF)
Physical examination	Pulse: rate and irregularity
Vital signs	Blood pressure
Neck	Jugular venous distention
Pulmonary	Rales suggestive of CHF
Cardiac	S_3 gallop suggestive of CHF
	Presence of murmurs suggestive of valvular disease
Abdominal	Hepatomegaly suggesting right-sided heart failure
Extremities	Peripheral edema suggestive of CHF
Laboratory tests	Hematocrit (anemia), thyroid-stimulating hormone (thyroid disease)
	Cardiac enzymes if ischemia is suspected
Electrocardiography	Confirm atrial fibrillation
	Identify ischemia, left ventricular preexcitation, preexcitation syndromes (Wolff-Parkinson-White syndrome)
Echocardiography	Left ventricular function, valvular function, outflow obstruction, cardiac chamber size
Exercise testing	Identify cardiac ischemia
	Determine adequacy of rate control
Ambulatory monitoring	Determine adequacy of rate control
Sleep study (polysomnography)	Correlate symptoms with arrhythmia Evaluate underlying obstructive sleep apnea if clinically suspected

of left ventricular outflow tract obstruction. The clinician should look for signs of congestive heart failure such as pulmonary rales, a third heart sound (S_3), or peripheral edema. Cardiac auscultation may reveal cardiac murmurs, right ventricular lift, or displaced point of maximum impulse suggestive of structural heart disease.

Helpful Tests

Electrocardiography is the most helpful means of establishing a diagnosis of atrial fibrillation. The electrocardiogram is characterized by an irregular ventricular rate with no clear pattern ("irregularly irregular"), although this may be obscured by rapid rates (Fig. 15.1). Replacement of the normal P waves with disorganized, fibrillatory atrial activity is the hallmark of atrial fibrillation but may be concealed by artifact or rapid ventricular rates. In the presence of complete atrioventricular block, the ventricular rate can be regular. The diagnosis of classic atrial flutter is made by the presence of *flutter waves,* a more organized atrial activity appearing as a regular sawtooth pattern of atrial activity best seen in the inferior limb leads II, III, and aVF (Fig. 15.2). Ventricular rates are typically regular at a fixed ratio to the flutter rate (e.g., 2:1, 3:1); however, variable block in the atrioventricular node can result in variable ventricular rates. The presence of ST segment or T wave abnormalities may suggest ischemia or treatment with digitalis. Prolongation of the QRS duration can be suggestive of distal conduction system disease, left ventricular hypertrophy, or preexcitation syndromes such as Wolff-Parkinson-White syndrome.

Chest radiography may identify abnormalities in cardiac silhouette or confirm the presence of pulmonary congestion.

Echocardiography is helpful for identifying associated structural heart disease and guiding management in patients with atrial fibrillation. Associated conditions such as valvular heart disease or cardiomyopathy may be revealed, which has significant impact on treatment decisions. The presence

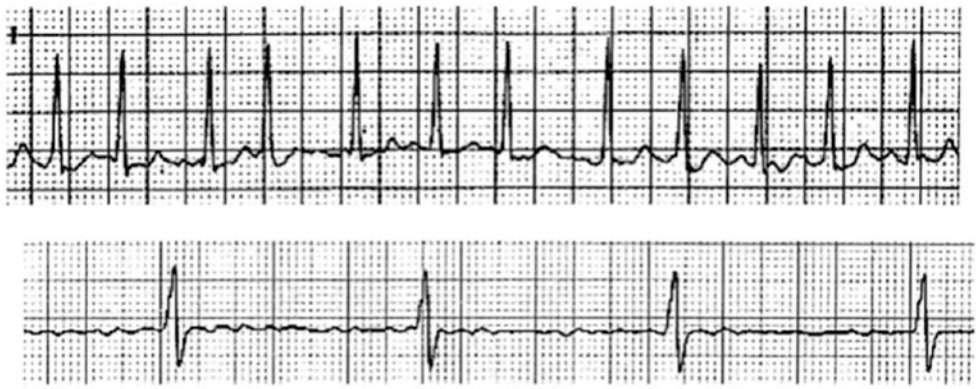

Fig. 15.1 Top, A patients with atrial fibrillation. Note the fibrillatory atrial activity. Bottom, Atrial fibrillation with complete heart block. Although atrial fibrillation is clearly present, complete heart block and a junctional escape rhythm results in a regular ventricular rhythm

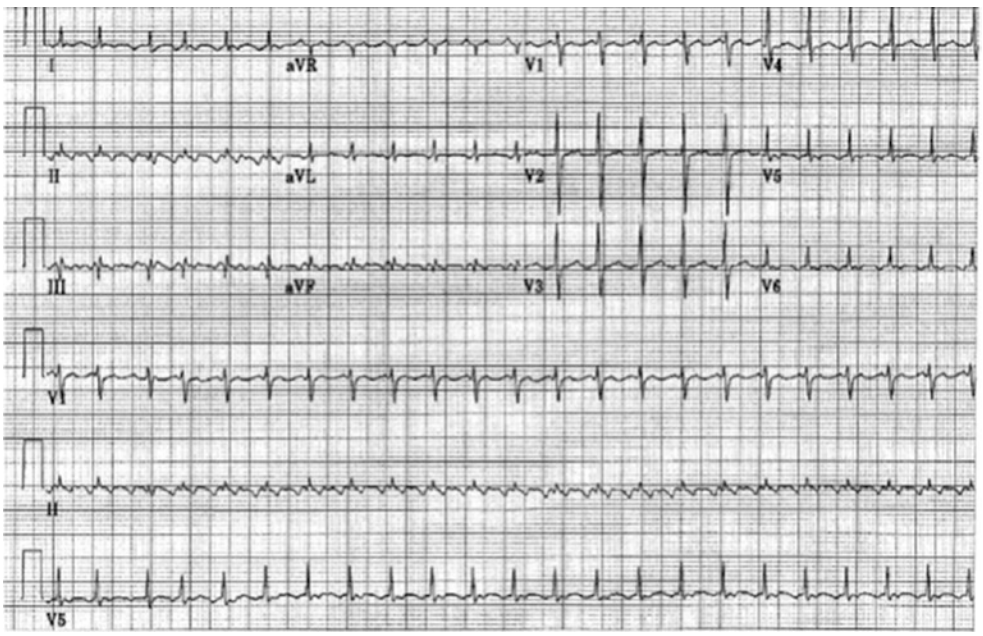

Fig. 15.2 A 12-lead electrocardiogram showing atrial flutter and 2:1 atrioventricular conduction. Flutter waves appear as a sawtooth pattern best seen in leads II, III, and aVF

of significant left atrial enlargement is associated with a low likelihood of maintenance of normal rhythm over the long term [24].

Exercise testing should be considered for patients with coronary risk factors or anginal symptoms. Exercise testing can also be used to determine the adequacy of ventricular rate control during initial presentation and therapy. In addition, stress testing may be helpful in selecting an antiarrhythmic agent in patients with symptomatic atrial fibrillation. For example, if large perfusion defects or other evidence of coronary disease are found on noninvasive testing, class IC agents (e.g., propafenone, flecainide) should be avoided because of the risk of ventricular proarrhythmia [25]. A sleep study (polysomnography) to evaluate obstructive sleep apnea is recommended for selected patients. The prevalence of obstructive sleep apnea is high in patients with atrial fibrillation, and untreated obstructive sleep apnea is associated with the risk of recurrent atrial fibrillation after cardioversion and catheter ablation [26–28].

Complications

Although not immediately life-threatening, atrial fibrillation has several complications associated with increased rates of morbidity and mortality. In some patients with Wolff-Parkinson-White syndrome and rapidly conducting accessory pathways that bypass the atrioventricular node, a very rapid ventricular rate during atrial fibrillation with ventricular preexcitation may lead to ventricular fibrillation and sudden death (Fig. 15.3). For this reason, radiofrequency ablation of the accessory pathway is recommended when ventricular preexcitation during atrial fibrillation is present. Atrial fibrillation with rapid ventricular rates associated with left ventricular outflow tract obstruction or mitral stenosis may lead to hypotension and rapid clinical deterioration. Similar complications may occur with atrial flutter with rapid ventricular rates. Uncontrolled rapid ventricular rates may be associated with left ventricular dysfunction and heart failure related to a persistently elevated heart rate [29–31].

Of the more common complications of atrial fibrillation, the most devastating is that of thromboembolism, especially stroke. Stroke attributed to atrial fibrillation is associated with death or severe debilitation at a rate twice that of stroke from other causes [32, 33]. The incidence of stroke increases with age, thereby making recovery more difficult for those afflicted. Large multicenter trials have established clinical variables with nonvalvular atrial fibrillation that are independently associated with stroke. The CHA_2DS_2-VASc score is the most widely used risk prediction model for assessing thromboembolic complications associated with nonvalvular atrial fibrillation. The score consists of congestive heart failure/left ventricular dysfunction, hypertension, age, diabetes, stroke/transient ischemia attack/thromboembolism, vascular disease, and female sex [34] (Table 15.3). Echocardiographic predictors, such as left atrial size and left ventricular hypertrophy, have also been reported to be risk factors [24]. Additionally, chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, increases the risk of thromboembolic complications associated with atrial fibrillation [35].

Therapy

The management goals of atrial fibrillation or flutter are directed at three objectives: (a) prevention of thromboembolic events, (b) control of accelerated ventricular rates, and (c) restoration and maintenance of sinus rhythm. The decision to restore sinus rhythm is often based on the presence of symptoms.

The presence of atrial fibrillation confers a risk of thromboembolic events four times that of the general population in selected groups [36]. This risk is significantly greater in the presence of *rheumatic mitral valve disease, mitral stenosis or prosthetic valves ("valvular atrial fibrillation").* Multiple clinical trials have demonstrated that warfarin significantly reduces the risk of stroke [36–40]. Chronic warfarin therapy, however, generally requires frequent laboratory monitoring for PT-INR (Prothrombin Time-International Normalization Ratio), and it can be difficult to maintain an appropriate therapeutic range (PT-INR: 2–3). More recently, safety and efficacy of direct-acting oral anticoagulants (DOACs) have been demonstrated for patients with nonvalvular atrial fibrillation in pivotal clinical trials, and these drugs are now widely used in clinical practice [41]. Currently, 1 direct thrombin inhibitor (dabigatran) and 3 factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) are approved for thromboembolic prophylaxis in patients with nonvalvular atrial fibrillation [42–45]. These drugs do not require routine drug level monitoring, and dose adjustment is unnecessary unless patients have renal impairment. A major disadvantage of DOACs is the lack of a widely available reversing agent in case of major or life-threatening bleeding. The use of DOACs is not approved for patients with valvular atrial fibrillation.

The 2014 Atrial Fibrillation guidelines recommend the use of antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preference [6]. In patients with nonvalvular atrial fibrillation, the CHA_2DS_2-VASc score is recommended to assess thromboembolic risk. The CHA_2DS_2-VASc score identifies seven risk factors (congestive heart failure/left ventricular dysfunction, hypertension, advanced age [age ≥ 75 years or 65–74 years], diabetes, stroke/transient ischemia attack/thromboembolism, vascular disease, and female sex). Each risk is assigned 1 point except for a history of prior stroke/transient ischemic

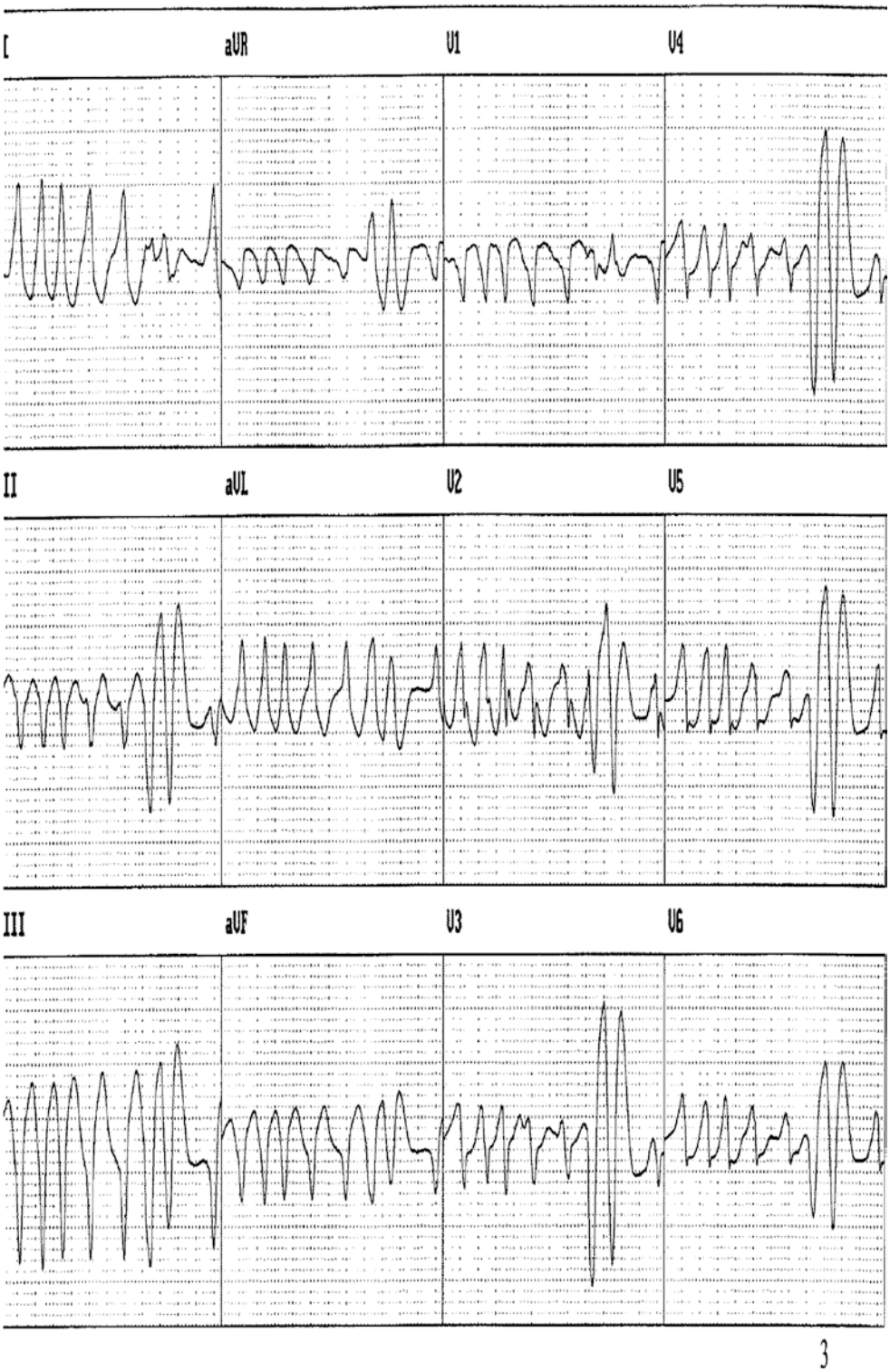

Fig. 15.3 A 12-lead electrocardiogram showing atrial fibrillation with ventricular pre-excitation from Wolff-Parkinson-White syndrome. Note the wide QRS duration

attack and age ≥ 75 years, which are assigned 2 points, respectively (the maximum score is 9) (Table 15.3). Antithrombotic therapy with either warfarin or DOACs is recommended for patients with nonvalvular atrial fibrillation and the CHA_2DS_2-VASc score of 2 or greater. Patients with nonvalvular atrial fibrillation and the CHA_2DS_2-VASc score of 0 considered truly at low risk for stroke, and antithrombotic therapy can be omitted. Either no antithrombotic therapy or treatment with an oral anticoagulant or aspirin can be selected for patients with CHA_2DS_2-VASc score of 1 (Table 15.4). It should be emphasized that the CHA_2DS_2-VASc is not applicable to patients with valvular atrial fibrillation and those

Table 15.3 CHA_2DS_2-VASc risk stratification score

Risk factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/Transient ischemic attack/Thromboembolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65–74 years	1
Sex (female)	1
	Maximum score = 9

Table 15.4 Recommendations for antithrombotic therapy for patients with atrial fibrillation and flutter

Risk category	Recommended therapy
No risk factors	No antithrombotic therapy
One risk factor	No antithrombotic therapy, Aspirin, warfarin or DOACs
Previous stroke/TIA or CHA2DS2-VASc score ≥2	Warfarin (INR, 2–3) or DOACs
Rheumatic mitral stenosis, mechanical or bioprosthetic heart valves (valvular atrial fibrillation)	Warfarin (INR 2–3[a])

DOAC direct-acting oral anticoagulant, *INR* International Normalization Ratio, *TIA* transient ischemic attack
[a]The target INR for a mechanical valve is generally 2.5–3.5

with hypertrophic cardiomyopathy. Antithrombotic therapy is recommended in these patients independent of the CHA_2DS_2-VASc score [6, 46]. Lastly, although some emerging data suggest slightly lower risk of thromboembolism in patients with paroxysmal atrial fibrillation compared to those with non-paroxysmal subtypes, the current guidelines recommend that the decision on antithrombotic therapy should be made irrespective of whether atrial fibrillation is paroxysmal, persistent or permanent [6, 46].

Assessing an individual patient's bleeding risk can be challenging and several risk prediction schemas are available to support clinical decision-making (ATRIA, HAS-BLED, ORBIT, HEORRA2HAGE2) [47, 48]. The HAS-BLED score is a simple and practical tool to predict 1-year risk of major bleeding, incorporating readily available clinical factors (hypertension, abnormal renal/hepatic function, stroke, bleeding history or predisposition to bleeding, labile PT-INR, age > 65 and concomitant use of drugs [aspirin and NSAIDs] and/or alcohol). A score of ≥3 indicates potentially "high risk" population for bleeding and careful assessment of benefit and risk as well as close monitoring of anticoagulation is warranted [49].

Although atrial flutter has been presumed to carry a lower risk of thromboembolic complications, accumulating evidence indicates that patients with atrial flutter have a greater thromboembolic risk than those with sinus rhythm, and an antithrombotic strategy similar to that for atrial fibrillation is recommended [6, 50].

Many of the symptoms of atrial fibrillation, including those attributable to ischemia or congestive heart failure, may be relieved with control of rapid ventricular rates. Lenient heart rate control (resting heart rate < 110 beats per minute) is reasonable in the absence of symptoms or left ventricular dysfunction [51].

Control of ventricular rates is directed primarily at slowing conduction of the atrioventricular node. Many agents are available both in oral and intravenous formulations. In order to rapidly control ventricular rates, an agent is commonly administered intravenously and converted to an oral form once rates have been stabilized. Secondary causes of rapid rates, such as anemia, congestive heart failure, ischemia, or thyrotoxicosis, should be managed. Beta blockers are preferred for patients with coronary artery disease and cardiomyopathy but must be used carefully because of their negative inotropic effects. Calcium channel blockers, such as verapamil and diltiazem, can also be used for short-term therapy, but the safety of long-term use in the presence of coronary artery disease or cardiomyopathy has not been established. Calcium channel blockers in the dihydropyridine group, such as nifedipine, have little role in controlling accelerated ventricular rates. Although digoxin is commonly used to control ventricular rates, its effect on atrioventricular nodal conduction is indirect and can be overcome by clinical states associated with increased adrenergic tone, such as exertion or congestive heart failure. It is beneficial in patients with left ventricular dysfunction, but it is otherwise a relatively poor choice as a single agent for rate control of atrial fibrillation.

If medical therapy fails to control ventricular rates adequately, nonpharmacologic therapy in the form of ablation of the atrioventricular node may be considered. This is performed by advancing an ablation catheter to the atrioventricular junction through one of the central veins. Radiofrequency energy is applied to the atrioventricular junction until complete heart block is achieved. A permanent pacemaker is then necessary to maintain appropriate heart rates at rest and during exertion. This therapy has been shown to improve symptoms and quality of life for individuals with atrial fibrillation and symptomatic rapid ventricular rates refractory to pharmacologic therapy [52–54].

The same agents used to control ventricular rates in the presence of atrial fibrillation are also used for atrial flutter. However, catheter ablation should be considered early for atrial flutter in appropriate patients given its excellent efficacy and safety profile [55].

The restoration of sinus rhythm has immediate impact on control of ventricular rates and relieves patient's symptoms. Although restoration of sinus rhythm can usually be achieved with electrical or pharmacologic cardioversion, maintenance of sinus rhythm is far more challenging.

The conversion of atrial fibrillation to sinus rhythm, known as cardioversion, is most commonly achieved with the use of direct current electrical energy delivered as a synchronized shock through an external defibrillator. This method restores sinus rhythm in approximately 85% of cases [56]. Contemporary defibrillators in which biphasic defibrillation waveforms are used have demonstrated improved success rates. The procedure is performed while the patient is adequately sedated to prevent discomfort. An external defibrillator is used with defibrillator patches placed in the sternal-apical or anterior-posterior configurations. Direct current energy is usually delivered at 200 J and increased to up to 360 J if conversion of sinus rhythm is not achieved. Although conversion to sinus rhythm is usually achieved quickly, recovery of atrial function may take several weeks. For this reason, the high risk of thromboembolic complications persists; therefore, several weeks of adequate anticoagulation is required. Anticoagulation with warfarin with an INR of 2–3 or uninterrupted DOAC must be maintained for 21 days before cardioversion and continued for at least 4 weeks after cardioversion if warfarin is chosen for oral anticoagulation.

There are some situations in which adequate anticoagulation before cardioversion is not possible or feasible. If the physician suspects that atrial fibrillation is associated with hemodynamic instability, cardioversion to sinus rhythm can be performed if the possible benefits outweigh the risks. Transesophageal echocardiography to identify thrombus in the left atrial appendage is useful for safely performing cardioversion; however, continuous anticoagulation for at least 28 days or longer after cardioversion is necessary to prevent complications as atrial function improves [57]. Because atrial function appears to be preserved during atrial fibrillation of short duration, the thromboembolic risk in this population is considered low and anticoagulation before and after cardioversion for atrial fibrillation lasting less than 48 h is optional for patients *without* conventional thromboembolic risk factors [58–60]. A suggested algorithm for anticoagulation before and after cardioversion is found in Fig. 15.4. For patients with atrial flutter, the same precautions as those for atrial fibrillation should be pursued [6, 50, 61].

Pharmacologic agents for cardioversion may obviate the need for sedation. The agent most commonly used is the Vaughan Williams Class III antiarrhythmic agent ibutilide, which can convert atrial fibrillation in as high as 64% of cases [62]. The previously mentioned regimen of anticoagulation should be used, because the risk of thromboembolic complications after cardioversion is not related to the method. Ibutilide is very useful as a facilitator to improve efficacy of direct-current cardioversion, improving efficacy of cardioversion to as high as 100% [63]. Ibutilide is also associated with a 3–10% risk of polymorphic ventricular tachycardia (torsades de pointes) and should not be used in patients with prolonged QT intervals on electrocardiogram or severe left ventricular dysfunction [63]. All patients receiving ibutilide should be monitored for several hours. Other antiarrhythmic agents used to convert atrial fibrillation acutely have included procainamide, quinidine, flecainide, propafenone, and amiodarone.

Preventing recurrences of atrial fibrillation after cardioversion is a daunting challenge in the management of this arrhythmia. Pharmacologic therapy has been the standard for decades, but recurrence of atrial fibrillation with these agents has been as high as 50%. Some antiarrhythmic agents, such

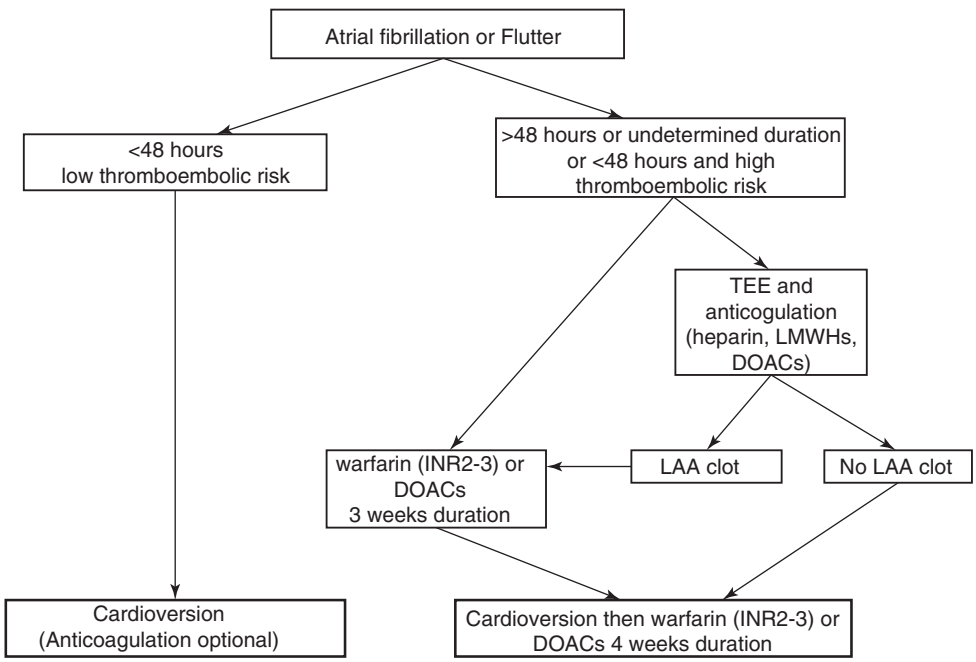

Fig. 15.4 A suggested algorithm for anticoagulation before and after cardioversion for atrial fibrillation and atrial flutter. *INR* International Normalization Ratio, *TEE* transesophageal echocardiography, *LMWH* low molecular weight heparin, *DOAC* Direct-acting oral anticoagulant, *LAA* left atrial appendage. (Adapted from Pelosi and Morady [87])

as flecainide, moricizine, and propafenone, are contraindicated in patients with structural heart disease, because of associated increased rates of mortality from drug-induced proarrhythmia [64, 65]. Certain Vaughan Williams Class III antiarrhythmics, such as amiodarone and sotalol, can be used in patients with structural heart disease and are effective in maintaining sinus rhythm [66–68]. Dofetilide is a relatively new Class III antiarrhythmic drug and has been studied in patients with structural heart disease. Although no significant increase in mortality was shown, 3% of patients experienced ventricular proarrhythmia in the first 72 h of treatment [69]. Therefore, dofetilide therapy should be initiated under inpatient telemetric monitoring.

Catheter ablation for atrial fibrillation has evolved dramatically over the last 20 years and now is the therapy of choice for symptomatic patients who have failed medical therapy. Catheter ablation of focal discharges from the pulmonary veins for the elimination of atrial fibrillation was first described by Haissaguerre et al. [14]. Today, electrical isolation of pulmonary veins remains the cornerstone of the ablation strategy for both paroxysmal and persistent atrial fibrillation [70–72]. The ablation procedure has been shown to be effective in various patient populations, including those with little or no structural heart disease, with enlarged atria, left ventricular dysfunction, and heart failure. Success rates of approximately 70–80% are expected in patients with paroxysmal atrial fibrillation whereas only 50% of patients with persistent variety maintain long-term sinus rhythm with catheter ablation alone [72, 73]. Approximately 20–30% of patients require repeat procedures for recovery of previously ablated areas or emergence of a new arrhythmogenic substrate. The risk of serious complications such as stroke or pulmonary vein stenosis at experienced centers is about 1–2% [74, 75]. The in-hospital mortality between 2000 and 2010 in the United States has been reported to be 0.46% [76]. Although radiofrequency energy has been conventionally used as the energy source for catheter ablation of atrial fibrillation, cryoballoon ablation utilizing cryothermal technology has been increasingly utilized recently with comparable arrhythmia-free outcomes [73, 77].

For patients who do not respond to the catheter based procedure or those who require cardiac surgery for another reason, the maze procedure may be considered [6, 78]. The maze procedure is a surgical technique that is performed via an open thoracotomy. The classic "cut-and-sew" procedure involves incisions in various parts of both atria with reported success rates of as high as 90% [79]. Complications of such an approach include those that are usually associated with cardiac surgery via a median sternotomy, including sinus node dysfunction that necessitates a permanent pacemaker in 4% of cases. While the classic maze procedure appears to be an effective strategy for atrial fibrillation, long-term outcomes in patients undergoing so called "mini" or "modified" maze or those performed minimally invasively are unknown. Hybrid approaches combining minimally invasive surgical ablation and catheter based endocardial ablation is an area of active research [80].

Radiofrequency ablation is an effective curative therapy for atrial flutter. The mechanism of typical atrial flutter is a single, large reentrant circuit involving a narrow band of atrial tissue between the septal leaflet of tricuspid valve and the inferior vena cava [55, 81]. This tricuspid valve *isthmus* is the target site of ablative therapy. With a catheter-based technique, a line of radiofrequency applications is formed across the isthmus until conduction across this area is completely blocked. The creation of conduction block results in a cure rate of up to 95% with a low risk of complications, eliminating the need for long-term antiarrhythmics or anticoagulants unless previously undiagnosed atrial fibrillation is detected during follow-up [82]. Increased left atrial size and atrial fibrillation inducibility with various pacing protocols during atrial flutter ablation have been implicated as risk factors for future development of atrial fibrillation post-atrial flutter ablation [82–84].

Rhythm-Control Versus Rate-Control

While much of the foregoing discussion has focused on how to achieve or maintain sinus rhythm, it is worthwhile discussing whether to pursue a rhythm-control strategy or a rate-control strategy in a given patient. The AFFIRM study reported that a strategy of rhythm-control offered no mortality benefit when compared to a rate-control strategy and anticoagulation [85]. Therefore it is reasonable to question why antiarrhythmic medications or catheter ablation procedures are offered to patients with atrial fibrillation. However, the results from AFFIRM must be analyzed with the following in mind. First, most of the patients enrolled in the trial were elderly and not very symptomatic from atrial fibrillation. Also, since less than 2/3 of the patients in the rhythm-control group were actually in sinus rhythm at 5 years, the AFFIRM trial is more of a comparison of the two strategies rather than a comparison of sinus rhythm versus atrial fibrillation. In fact, when the data are analyzed with respect to rhythm, there was a survival benefit in favor of sinus rhythm [86]. Thus, a rate-control strategy along with anticoagulation is a reasonable strategy in elderly patients with minimal symptoms, whereas a rhythm-control strategy is preferable in patients with symptomatic atrial fibrillation or those with left ventricular dysfunction attributable to the arrhythmia.

Prognosis

The overall prognosis of atrial fibrillation is favorable in the absence of other cardiac disease. In patients with structural heart disease, the presence of atrial fibrillation complicates management and is associated with increased rates of mortality. Without treatment, the risk of stroke is 4–6% per year in patients with associated risk factors. Exacerbation of congestive heart failure or the development of cardiomyopathy from chronically elevated ventricular rates can have an adverse effect on survival.

Various therapeutic agents such as anticoagulants and antiarrhythmics carry their own risks and can adversely affect survival. The rate of major bleeding associated with anticoagulation either with warfarin or DOACs is approximately 2–3% per year [42–45]. As previously mentioned, some antiarrhythmics carry the risk of potentially dangerous ventricular arrhythmias.

Follow-Up

Patients being treated for atrial fibrillation require follow-up depending on the treatment provided. In those requiring warfarin, the PT-INR should be monitored weekly in preparation for cardioversion for 3 weeks before and 4 weeks after cardioversion. Once a stable dose of warfarin is established, the PT-INR should be checked monthly. In patients taking DOACs, baseline and periodic monitoring of hemoglobin, liver function and renal function is indicated [41].

Patients taking antiarrhythmic drugs should be monitored every 4–6 months. Because of possible adverse effects, patients on amiodarone should have baseline thyroid-stimulating hormone measurements, liver function tests, and chest radiography every 4–6 months. Pulmonary function tests with assessment of diffusion capacity should be obtained at baseline and when symptoms of amiodarone pulmonary toxicity, such as dyspnea, are suspected. In patients taking sotalol or dofetilide, renal function should be assessed regularly, because elevated drug levels as a result of reduced renal clearance could lead to life-threatening proarrhythmia. With these agents, regular electrocardiograms should be obtained to assess for abnormal QT prolongation; if the corrected QT interval is greater than 500 ms, treatment drugs should be discontinued. For those taking Class IC drugs, such as flecainide or propafenone, patients should be monitored clinically, and these drugs should be stopped if structural heart disease develops or the duration of the QRS complex prolongs by more than 50% during therapy.

Practical Points

- Atrial fibrillation is the most common cardiac arrhythmia necessitating hospitalization in the United States.
- It is associated with significant morbidity, the most serious complication being stroke.
- It is most commonly associated with structural heart disease and with old age.
- The primary goals of treatment of atrial fibrillation are prevention of thromboembolic complications, control of accelerated ventricular rates, and restoration and maintenance of normal sinus rhythm.
- New understanding of the physiologic basis of atrial fibrillation facilitates the emergence of nonpharmacologic approaches to treatment.

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Ventricular Tachycardia

16

Frank Bogun and Fred Morady

Usual Causes

There are many causes of ventricular tachycardia (Table 16.1). However, ventricular tachycardia usually occurs in patients with underlying structural heart disease. This can be acquired or inherited. Myocardial disease and scarring cause abnormal cardiac impulse formation and propagation, which can lead to ventricular tachycardia. In developed countries, the most common cause of structural heart disease is coronary artery disease. In patients with coronary artery disease, ventricular fibrillation and polymorphic ventricular tachycardia usually are caused by acute ischemia, whereas sustained monomorphic ventricular tachycardia usually is caused by reentry around or within a scar from a previous myocardial infarction.

Other acquired formes of structural heart disease resulting in ventricular tachycardia include nonischemic, dilated cardiomyopathy, hypertensive heart disease, and valvular heart disease. The term arrhytmogenic cardiomyopathy has been used to describe arrhythmogenic disorders not explained by ischemic, hypertensive or valvular heart disease. The etiology may be part of a systemic disorder (sarcoidosis, amyloidosis), an apparently isolated cardiac abnormality, an infection (Chagas disease, viral myocarditis), or a genetic disorder (arrhythmogenic right ventricular cardiomyopathy [ARVC] or arrhythmogenic left ventricular cardiomyopathy [ALVC], or lamin A/C mutation) [1].

Ventricular tachycardia and fibrillation can also occur in individuals without any apparent structural heart disease. Idiopathic ventricular tachycardia most often arises in the outflow tract of the right ventricle or the left posterior fascicle in the left ventricle. A molecular abnormality of one of the cardiac membrane ion channels can also result in ventricular tachycardia. More than 600 mutations of genes have been identified as causes of congenital long QT syndrome (LQTS). Mutations of the potassium channel genes, KvLQT1 and HERG, and the sodium channel gene, SCN5A, account for >90% of cases. Each LQTS subtype has been associated with a specific T wave abnormality [2]. Criteria developed by Schwartz et al use the ECG and clinical information to indicate the probability for long QT syndrome [3]. Polymorphic ventricular tachycardia occurs in these patients as a result of early afterdepolarizations. Brugada's

Table 16.1 Causes of ventricular tachyarrhythmias

Structural causes
Acquired:
Coronary artery disease
Dilated nonischemic cardiomyopathy
Hypertensive heart disease
Valvular heart disease
Infiltrative diseases: amyloidosis
Chagas' disease
Myocarditis: Sarcoid myocarditis, viral myocarditis, Chagas myocarditis, other forms of myocarditis
Inherited:
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Congenital heart disease
Primary electrical causes
Idiopathic ventricular tachycardia
Idiopathic ventricular fibrillation
Congenital long QT syndrome
Catecholaminergic Polymorphic VT
Brugada Syndrome and J-wave syndromes
Wolf-Parkinson-White syndrome
Extrinsic causes
Drugs
Hypokalemia
Hypomagnesemia
Hypoxemia
Chest trauma
Asynchronous shock during cardioversion
Central nervous system abnormality

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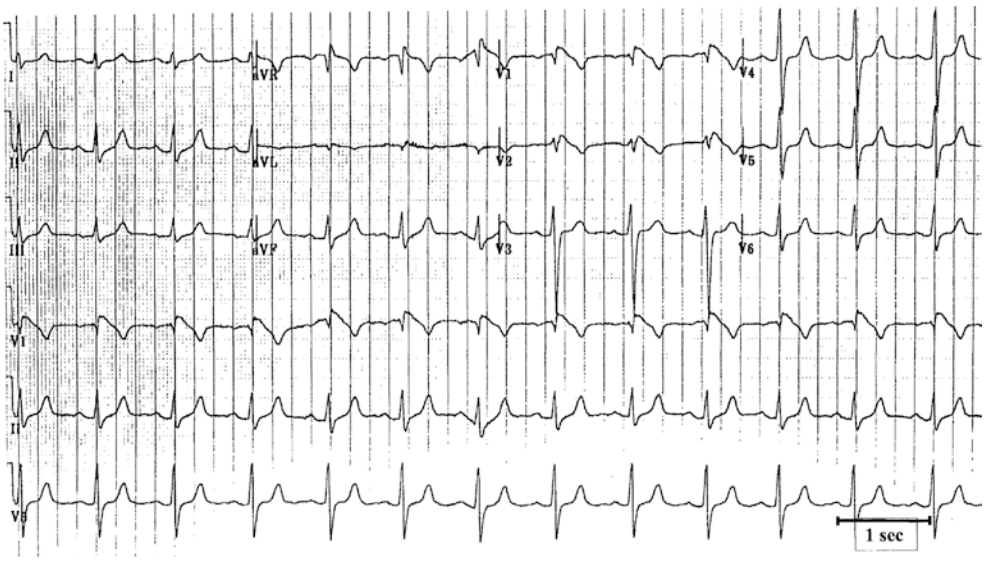

Fig. 16.1 Twelve-lead electrocardiogram of a patient with Brugada's syndrome. Note the incomplete right bundle branch block with ST segment elevation and T wave inversion in leads V_1 to V_2. Two of the patient's brothers had died suddenly

syndrome is caused by a sodium channel defect, is manifested as incomplete right bundle branch block with ST segment elevation in leads V_1 to V_3 (Fig. 16.1), and can lead to ventricular fibrillation [4]. In patients with idiopathic ventricular fibrillation early repolarization changes have been described. The Brugarda syndrome has been suggested to be be a subform of the early repolarization - or the "J-wave syndromes" that describe elevation of the J wave and slurring of the terminal part of the QRS and the ST segment in patient with idiopathic ventricular fibrillation. Early repolarization however might be completely benign and the ECG location and degree of J-wave elevation may indicate it's clinical relevance. Different subtypes of J-wave elevation have been described: in asymptomatic patients with no or low risk for ventricular arrhythmias, the J-wave elevations are often exclusively located in the lateral leads. The risk for ventricular arrhythmias may be higher if the J-wave elevation is located in the inferior and lateral leads and highest if they are located in the inferior, lateral and right precordial leads [5].

Cathecholaminergic polymorphic ventricular tachycardia is characterized by ventricular tachyarrhythmias (predominantly bidirectional VT) that occur during physical activity. This condition is caused by a mutation of calciquestrin 2 gene or the gene encoding for the ryanodine receptor which is responsible for calcium release from the sarcoplamisc reticulum. The short QT syndrome is characterized by a QT duration <300 ms [6] and is due to a gain-in-function mutation in the KCNH2, KCNQ1 or KCNJ2 gene. All of these genes have been implicated in the long QT syndrome, in which there are loss-of-function mutations.

Left ventricular noncompaction (LVNC) is a genetically determined condition characterized by excessive trabeculations in the left ventricle. It is thought to result from an arrest in the development of the compact myocardium. Abnormal trabeculations are most often located in the apical or lateral left ventricle, but the process can also involve the right or both ventricles. Deep intertrabecular recesses are often present and can result in thrombus formation. The phenotype of LVNC is heterogenous and different forms have been described ranging from a benign type with normal left ventricular size and function that is quite common in the general popultation (up to 43% in a study population in the US [7] and up to 14.8% in a cohort in the United Kingdom [8] that underwent magnetic resonance imaging) to a form with dilated cardiomyopathy or hypertrophic cardiomyopathy among others. In 30–50% of the patients, genetic disorders can be detected including mutations of genes encoding desmosomal, cytoskeletal, sarcomeric and ion channel proteins. The most severe phenotype of LVNC is seen in children with VT and atrial fibrillation being the most prevalent arrhythmias [9].

Extrinsic causes of ventricular tachycardia include drugs and electrolyte abnormalities. Many cardiac and noncardiac drugs block the potassium channel I_{Kr}. Blockade of the potassium current leads to prolongation of repolarization (Fig. 16.2) and can lead to a polymorphic ventricular tachycardia known as torsade de pointes. Commonly prescribed drugs that prolong the QT interval are listed in Table 16.2. A more complete list can be found at *www.qtdrugs.org*. Factors that predispose to torsade de pointes include female gender, bradycardia, hypokalemia, the administration of more than one QT interval–prolonging drug, and decreased drug clearance. Digitalis toxicity can cause ventricular tachycardia by causing delayed afterdepolarizations.

Presenting Symptoms and Signs

Patients who develop sustained ventricular tachycardia can present with cardiac arrest, syncope, presyncope, congestive heart failure, chest pain, or palpitations. Sudden death occurs in approximately 400,000 persons in the Unites States annually and is usually caused by ventricular fibrillation.

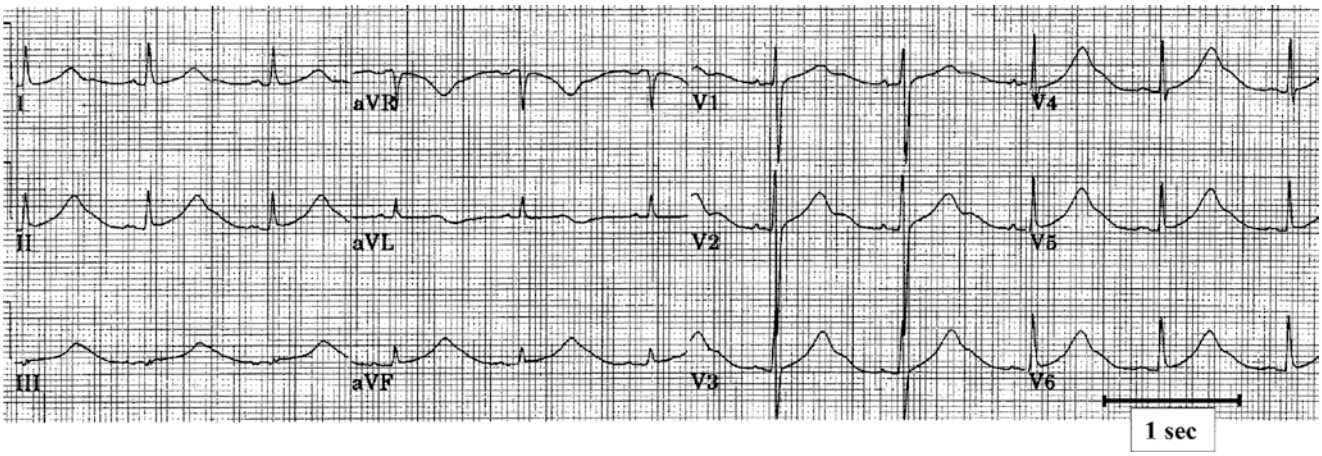

Fig. 16.2 Electrocardiogram recorded from a patient who was treated with intravenous haloperidol, showing sinus rhythm with marked prolongation of the QT interval

Table 16.2 List of commonly used medications that prolong the QT interval

Cardiac drugs
Procainamide
Quinidine
Disopyramide
Sotalol
Ibutilide
Dofetilide
Amiodarone
Probucol
Noncardiac drugs
Tricyclic antidepressants
Phenothiazines
Haloperidol
Risperidone
Halothane
Terfenadine
Astemizole
Cisapride
Pentamidine
Macrolide antibiotics

Patients with nonsustained ventricular tachycardia are usually asymptomatic but can have palpitations or syncope.

Examination of a patient who is having sustained ventricular tachycardia may reveal pulselessness, unconsciousness, pulmonary edema, or signs of shock. When ventricular tachycardia is hemodynamically tolerated, there may be signs of tachycardia and atrioventricular dissociation.

Helpful Tests

The most useful test in a patient with a sustained ventricular tachycardia is an electrocardiogram. A recording of atrial activity during a sustained wide–QRS complex tachycardia with an esophageal electrode (Fig. 16.3) can help establish the presence of atrioventricular dissociation. A recording from a temporary atrial epicardial pacing electrode is valuable in patients who have recently undergone cardiac surgery. Patients with sustained ventricular tachycardia or ventricular fibrillation must also undergo a careful physical examination, review of medications, and measurement of electrolytes and cardiac enzymes. Most patients should undergo echocardiography, coronary angiography and left ventriculography. Holter monitoring may be helpful in identifying VT and quantitating the PVC burden. Patients with frequent idiopathic PVCs (>20% of their total QRS complexes) can develop a cardiomyopathy that is reversed by catheter ablation [10]. Patients with frequent asymptomatic PVCs should have their left ventricular function assessed periodically since they are at particularly high risk to develop cardiomyopathy [11].

The prognosis of a patient with asymptomatic, nonsustained ventricular tachycardia depends on the presence or absence of ventricular dysfunction. Therefore, patients with nonsustained ventricular tachycardia should undergo testing to evaluate ventricular function and to exclude ischemia. Patients with preserved ventricular function have a good prognosis and usually do not need further testing. On the other hand, patients with significant ventricular dysfunction are at an increased risk of dying suddenly and should undergo further evaluation. Electrophysiologic testing can be done to risk-stratify patients with coronary artery disease, prior myocardial infarction, and left ventricular dysfunction who experience nonsustained ventricular tachycardia. Patients with sustained ventricular tachycardia inducible during programmed electrical stimulation are at high risk for cardiac arrest and benefit from implantation of a prophylactic cardiac defibrillator [12–14]. Electrophysiologic testing has limited value in the risk stratification of patients with a nonischemic cardiomyopathy.

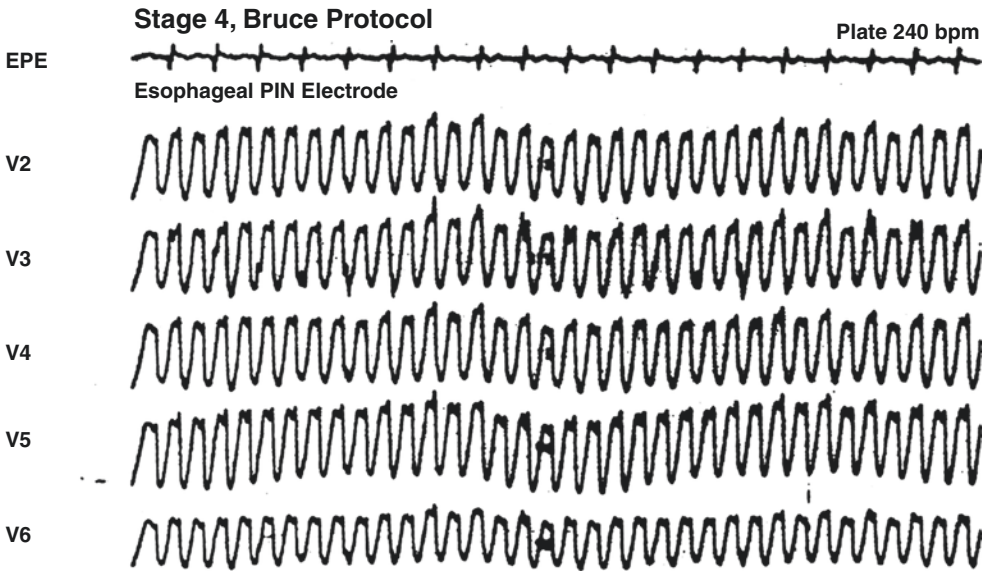

Fig. 16.3 Five-lead electrocardiogram (V2–V6) of a patient with exercise-induced wide-QRS complex tachycardia. The top tracing displays recordings from an esophageal pill electrode (EPE) reflecting the left atrial electrograms. There is 2:1 ventriculoatrial conduction, indicating that this is VT

Hyperenehnacement or delayed enhancement after gadolinium administration in cardiac magnetic resonance imaging (MRI) indicates scar tissue. The amount of hyperenhancement has been found to be of potential value for risk stratification in patients with prior myocardial infarction [15]. A prospective study that aimed to assess this value prospectively in patients with prior myocardial infarction ([DETERMINE], (http://clinicaltrials.gov NCT00487279)) was terminated prematurely due to lack of enrollment. The absence of delayed enhancement in patients with non-ischemic cardiomyopathy correlated with a more benign prognosis in 2 retrospective patient series [16, 17]. Aside from its potential as a risk stratification method, delayed enhanced MRI has also diagnostic value in patients with non-ischemic cardiomyopathy [18] and should be performed in all non-ischemic patients without contraindication for MRI prior to implantation of a cardioverter defibrillator. In case of isolated cardiac sarcoidosis, a typical pattern of delayed enhancement in the MRI can strongly suggest sarcoidosis and trigger further confirmatory tests.

Differential Diagnosis

Ventricular tachycardia is defined as three or more consecutive ventricular complexes at a rate greater than 100 beats per minute and can be categorized on the basis of the morphologic features of the QRS complexes: as monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, or ventricular fibrillation. A ventricular arrhythmia is considered sustained when it requires termination, when it results in symptoms, or when it lasts longer than 30 s.

When faced with an apparent wide–QRS complex tachycardia, it is important to first exclude electrocardiographic artifact [19]. Artifact can be recognized when portions of the baseline QRS complexes are visible within the suspected wide–QRS complex tachycardia at intervals that are similar to the cycle length of the baseline rhythm (Fig. 16.4). Other clues that suggest artifact include a disturbance of the baseline before the onset, a QRS complex that follows termination of the apparent tachycardia earlier than would be expected, and witnessed body movements during recording. Sinus tachycardia with ST segment elevation can also manifest as a pseudo–wide–QRS complex tachycardia. A 12-lead electrocardiogram identifies ST segment elevation as the cause of the apparent wide QRS complexes (Fig. 16.5).

Monomorphic Ventricular Tachycardia

Monomorphic ventricular tachycardia must be distinguished from supraventricular tachycardia with bundle branch block aberration. Other, less common causes of a regular, wide–QRS complex tachycardia include antidromic atrioventricular reentrant tachycardia that occurs through an accessory pathway and ventricular pacing. Antidromic atrioventricular reentrant tachycardia often is indistinguishable from ventricular tachycardia.

Differentiation of ventricular tachycardia from supraventricular tachycardia with aberrancy is important because of the implications for immediate and long-term treatment. Clinical and electrocardiographic factors must be considered when a wide–QRS complex tachycardia is present. An important principle is that when there is any uncertainty regarding the diagnosis, it is safest to assume that a wide–QRS complex tachycardia is ventricular tachycardia. A history of myocardial infarction or congestive heart failure has a positive predictive value of greater than 95% for ventricu-

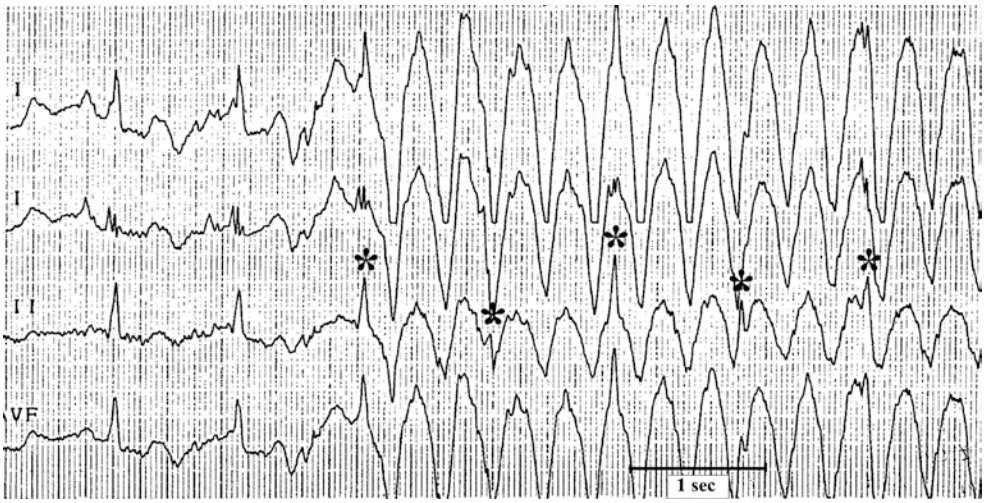

Fig. 16.4 Four-lead rhythm-strip of electrocardiographic artifact simulating monomorphic ventricular tachycardia. A diagnosis of artifact can be made on the basis of identification of portions of QRS complexes (denoted with *asterisks*) at intervals that correspond to the baseline sinus cycle length. Note the unstable baseline before the onset of the apparent tachycardia

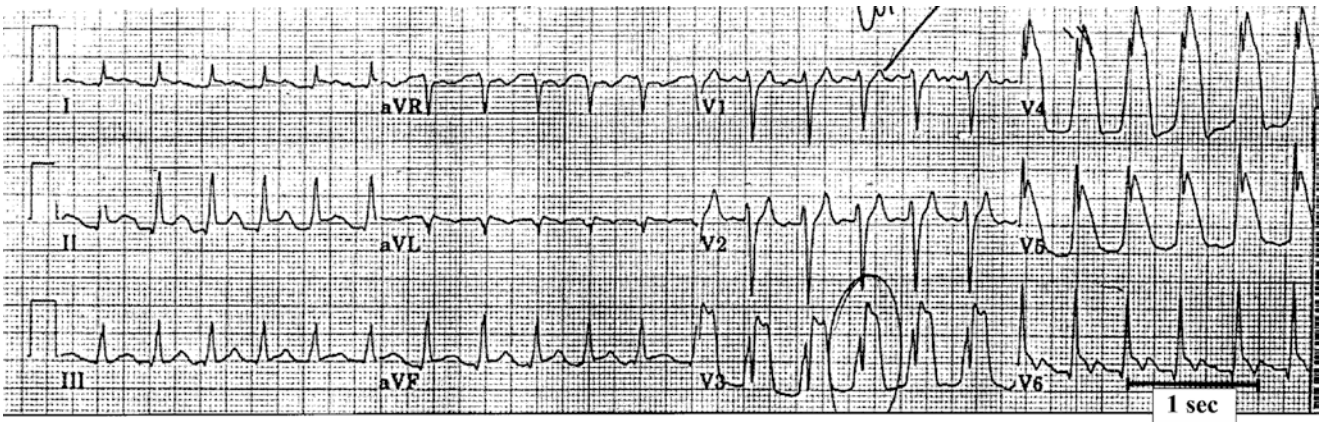

Fig. 16.5 Twelve-lead electrocardiogram recorded in a patient with an acute anterior myocardial infarction. A single, modified chest lead recording from the same patient appeared to demonstrate a wide–QRS complex tachycardia that was actually sinus tachycardia with prominent ST segment elevation

lar tachycardia [20]. The presence of hemodynamic stability and minimal symptoms should not influence the differentiation of ventricular tachycardia from supraventricular tachycardia with aberration [21].

Electrocardiographic findings that support a diagnosis of ventricular tachycardia are summarized in Table 16.3 and can be remembered by the alphabetical mnemonic: "ABCDEF." The principle of each criterion is that when the QRS morphologic pattern does not have features of a typical left or right bundle branch block pattern, the rhythm is most likely ventricular tachycardia. However, there are many exceptions to these rules. Atrioventricular dissociation ("A") is the most helpful criterion. Unfortunately, atrioventricular dissociation is not present in about one quarter of ventricular tachycardias because there is 1:1 ventriculoatrial conduction, and it is often difficult to identify unless the tachycardia rate is relatively slow. Signs of atrioventricular dissociation include P waves that are independent of the QRS complexes, capture beats, and fusion beats (Fig. 16.6). The broader ("B") the QRS complex is, the more likely it is that the rhythm is ventricular tachycardia (Fig. 16.7). A QRS duration exceeding 160 ms for left bundle branch morphologic patterns and exceeding 140 ms for right bundle branch morphologic patterns supports a diagnosis of ventricular tachycardia. An RS interval (the time from the onset of the R wave to the nadir of the S wave) in the precordial leads that exceeds 100 ms is consistent with ventricular tachycardia [22]. Concordance ("C") is defined as the presence of QRS complexes that are all upright or all inverted in the precordial leads and is a sign of ventricular tachycardia. Bundle branch block patterns do not

Table 16.3 Electrocardiographic findings that support a diagnosis of ventricular tachycardia

*A*trioventricular dissociation
*B*road
*C*oncordance
*D*eviation of axis
*E*ffect of maneuvers
*F*eatures of the QRS complex

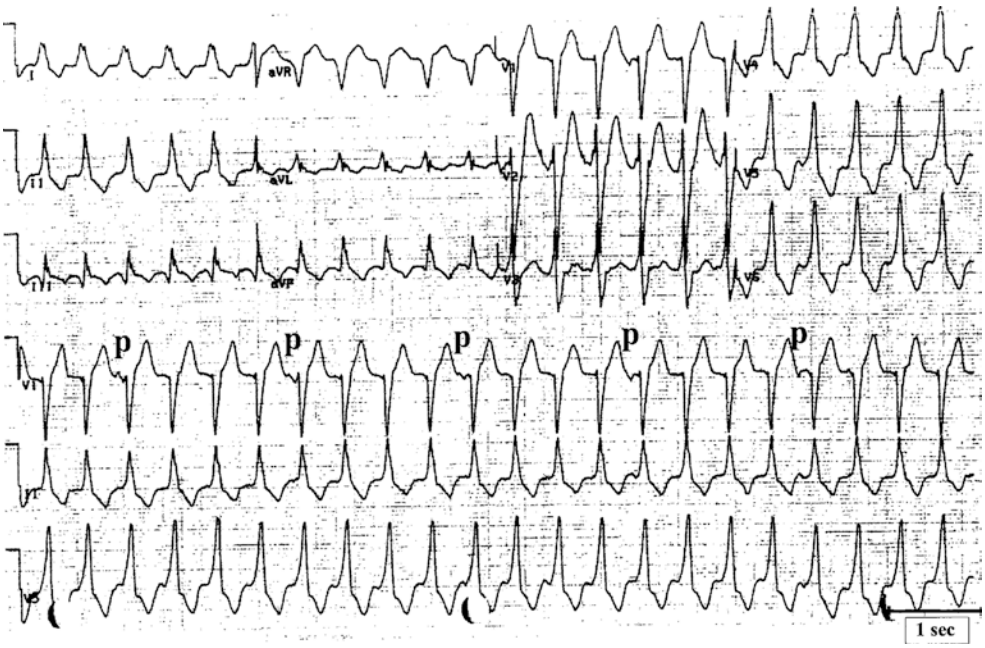

Fig. 16.6 Electrocardiogram of ventricular tachycardia arising from the ventricular septum. Although the QRS duration is relatively short, there is evidence of atrioventricular dissociation consistent with ventricular tachycardia. P waves are marked with the letter "p"

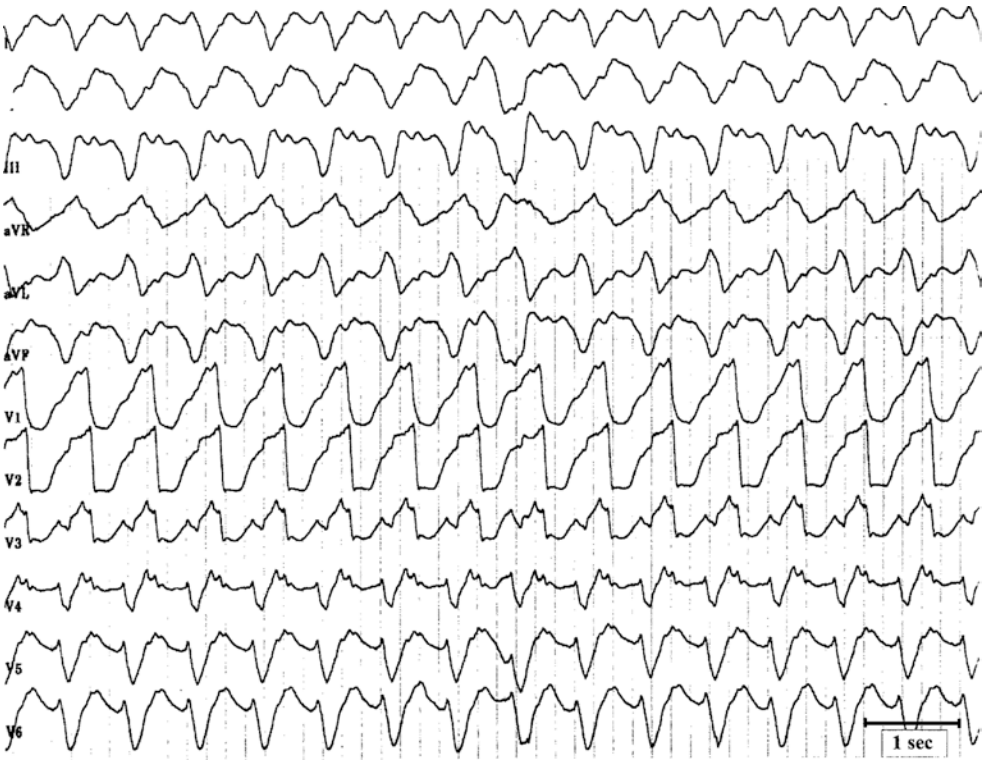

Fig. 16.7 Twelve-lead rhythm strip of ventricular tachycardia at a rate just below 100 beats per minute. The very wide QRS complex is more consistent with ventricular tachycardia than with supraventricular tachycardia with aberrancy

demonstrate concordance because they usually have at least one biphasic complex in the precordial leads. Deviation ("D") of the axis in a direction that is not typical for a bundle branch block pattern, such as right axis deviation with a left bundle branch block pattern, suggests ventricular tachycardia.

The effect ("E") of certain maneuvers can also be helpful. Vagal maneuvers or adenosine can unmask an underlying atrial tachycardia by causing transient atrioventricular block (Fig. 16.8) or can terminate an atrioventricular node–dependent supraventricular tachycardia (Fig. 16.9). Adenosine can also be helpful by inducing AV dissociation during VT (Fig 16.10) Ventricular tachycardia is probably present when the administration of adenosine has no effect or causes ventriculoatrial dissociation during tachycardia [23].

Certain morphologic features ("F") of the QRS complex are seen more commonly with ventricular tachycardia than

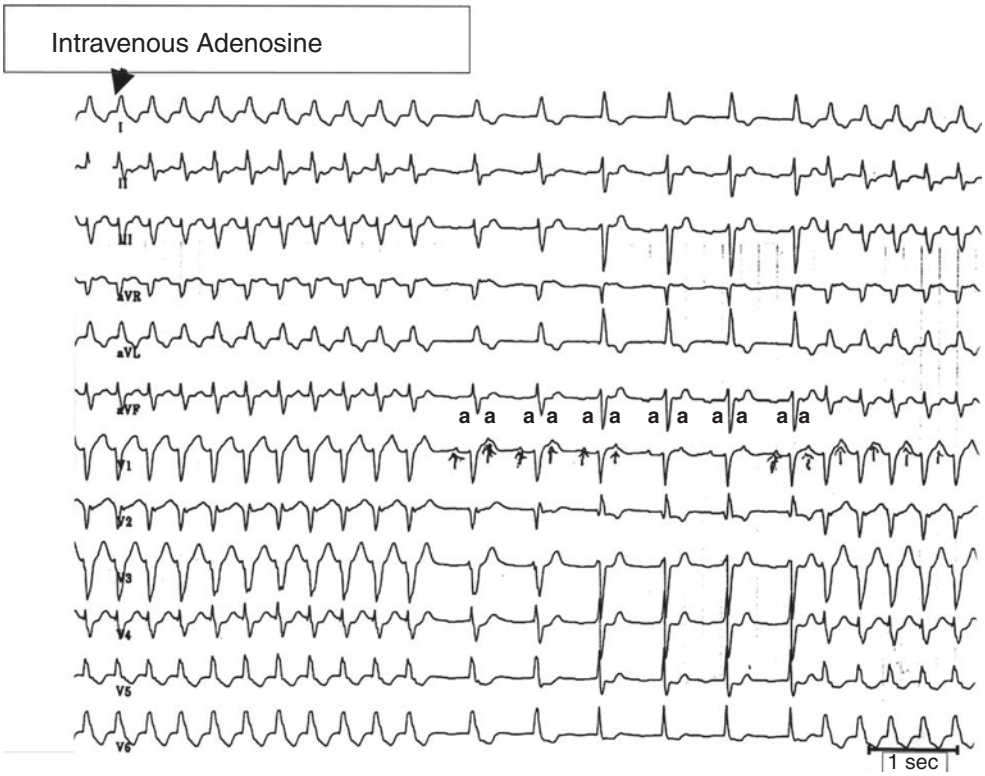

Fig. 16.8 Twelve-lead rhythm strip of a wide–QRS complex tachycardia that is caused by an atrial tachycardia with left bundle branch block aberration. Intravenous adenosine is administered during tachycardia and results in transient 2:1 atrioventricular block. During atrioventricular block, the underlying atrial tachycardia is visible (denoted with the letter "a") at the same rate as the wide–QRS complex tachycardia. The QRS complex becomes narrow when the ventricular rate slows

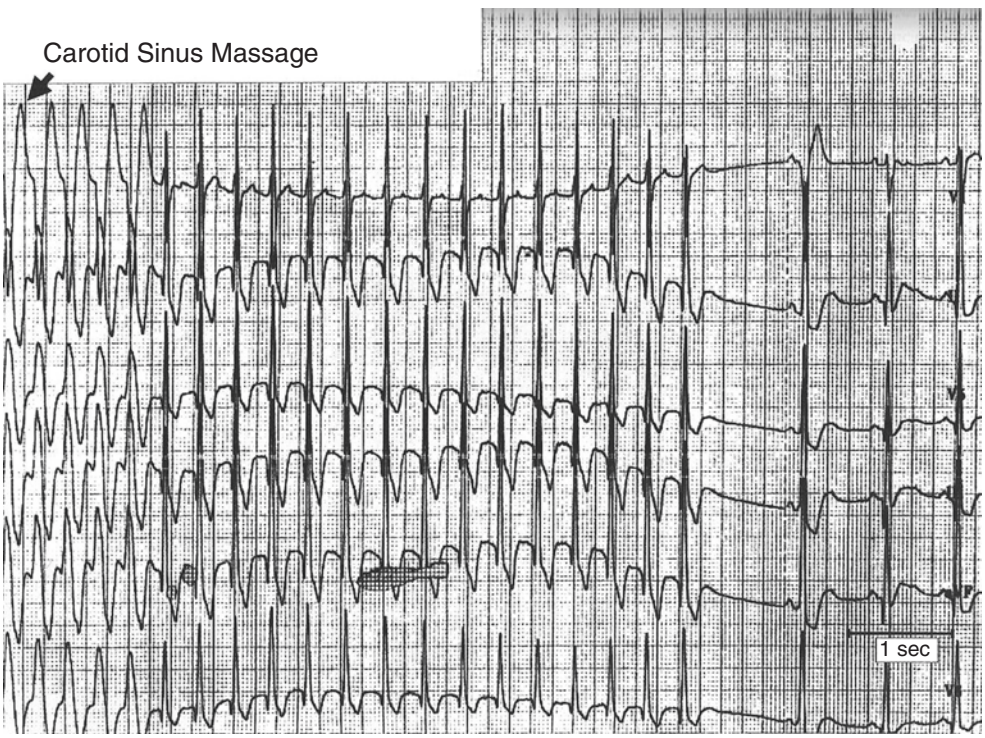

Fig. 16.9 Six-lead rhythm strip of a wide–QRS complex tachycardia that is caused by orthodromic atrioventricular reentrant tachycardia with left bundle branch block aberration. Carotid sinus massage results in slowing of the supraventricular tachycardia and resolution of the aberration. The tachycardia then terminates. The first sinus beat is associated with ventricular preexcitation

with aberrancy. For example, when the QRS complex has a right bundle branch block pattern in lead V_1, an R wave that is taller than the R′ (Fig. 16.11) or a monophasic or biphasic QRS complex suggests ventricular tachycardia. When the QRS complex has a left bundle branch block pattern in lead V_1, an R wave that is wider than 40 ms or a qS pattern favors ventricular tachycardia.

Electrocardiographic features that support a diagnosis of a supraventricular arrhythmia with aberrancy include initiation of the tachycardia by a premature atrial depolarization

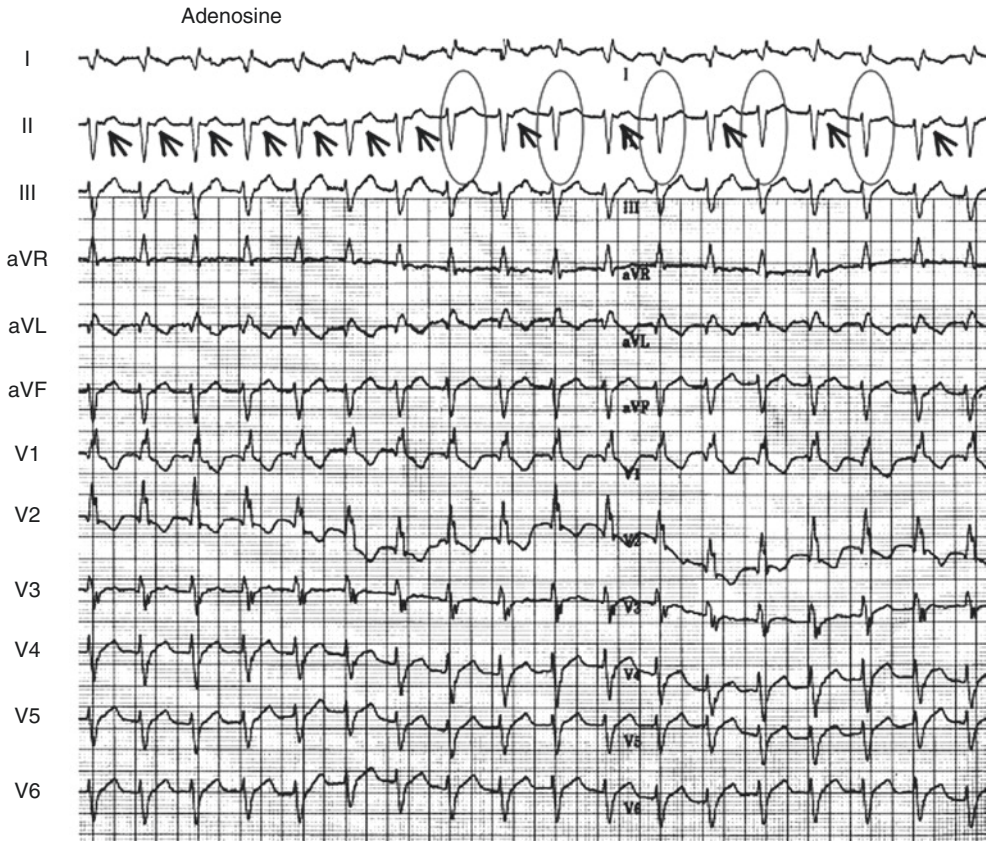

Fig. 16.10 Twelve-lead electrocardiogram of a wide-QRS complex tachycardia. Adenosine was given. The arrows in lead II indicate retrograde P waves. Oval circles surround QRS complexes where there is ventriculoatrial block due to adenosine. This indicates that the tachycardia was VT

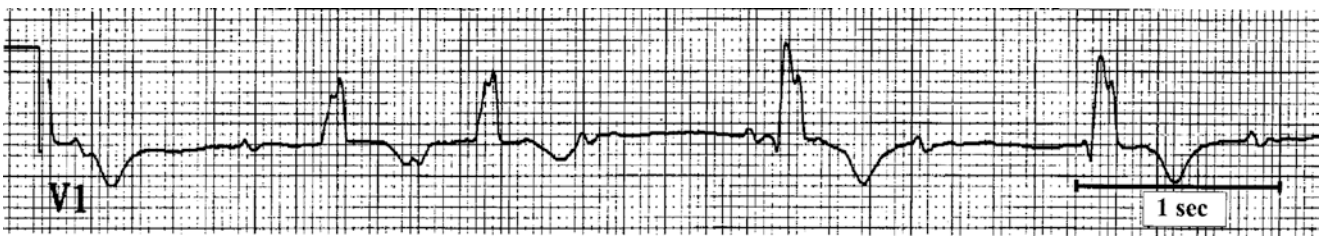

Fig. 16.11 A rhythm strip recorded from lead V_1 of sinus rhythm with right bundle branch block and first-degree atrioventricular block (first two QRS complexes), followed by complete atrioventricular block and a ventricular escape rhythm (last two QRS complexes). This recording demonstrates the morphologic differences between QRS complexes that are a result of right bundle branch block aberration (R wave smaller than R′ wave) and QRS complexes that are left ventricular in origin (R wave taller than R′ wave)

or an initiation that is associated with a long-short sequence (Ashman's phenomenon). When a patient has a documented narrow–QRS complex tachycardia that is the same rate as the wide–QRS complex tachycardia, the likelihood that the wide–QRS complex rhythm is due to aberrancy is high.

Subtypes of monomorphic ventricular tachycardia include bundle branch reentry, accelerated idioventricular rhythm, paroxysmal ventricular tachycardia, and repetitive monomorphic ventricular tachycardia. The most common type of repetitive monomorphic ventricular tachycardia arises from the right ventricular outflow tract and has a left bundle branch block, inferior axis morphologic pattern (Fig. 16.12). Ventricular flutter is a subtype of monomorphic ventricular tachycardia, occurs at a rate of 200 to 300 beats per minute, resembles a sine wave, and results in hemodynamic collapse. Pleomorphic ventricular tachycardia is characterized by multiple different monomorphic ventricular tachycardias during the same VT episode. During polymorphic VT, the morphology of the QRS complexes are constantly changing. The term *torsades de pointes* refers to polymorphic ventricular tachycardia that occurs in the setting of an abnormally long QT interval and that has a pattern of QRS complexes that appear to twist around the isoelectric line.

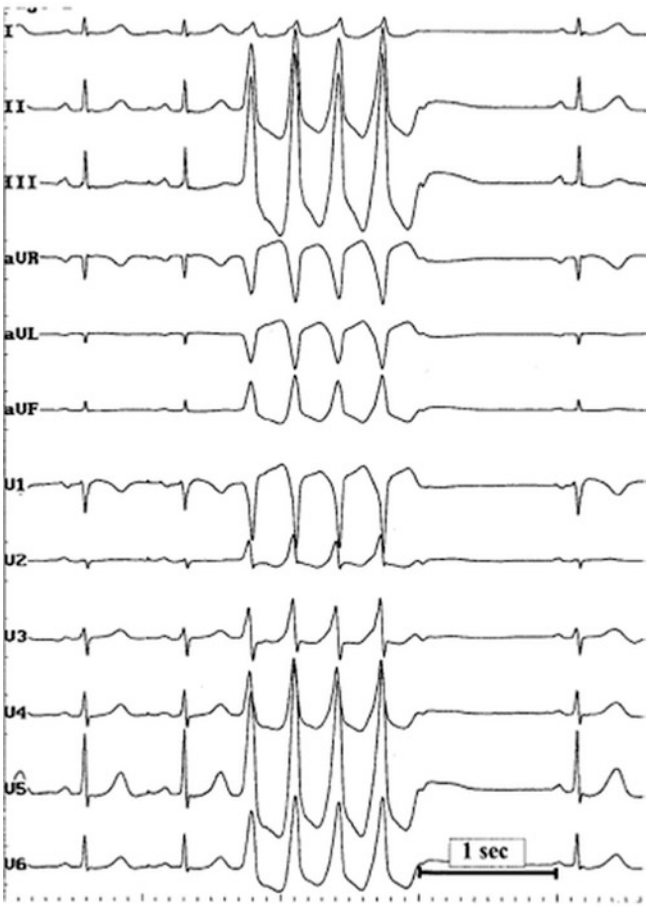

Fig. 16.12 Example of idiopathic ventricular tachycardia arising from the right ventricular outflow tract. Note the four beats of ventricular tachycardia with left bundle branch block and inferior axis morphologic pattern

Bidirectional ventricular tachycardia is an uncommon ventricular tachycardia characterized by QRS complexes that have a right bundle branch block pattern with an alternating polarity in the frontal plane (Fig. 16.13). Bidirectional ventricular tachycardia can be a result of digitalis toxicity. Bidirectional VT occurs in the Andersen syndrome and catecholaminergic polymorphic VT. Anderson syndrome, also referred to as long QT 7, is characterized by potasium-sensitive periodic paralysis, VT and dysmorphic features.

Ventricular Fibrillation

Ventricular fibrillation is present when there are irregular undulations of varying contour and amplitude (Fig. 16.14). It is important to exclude asystole when the fibrillatory waves are small in amplitude.

Complications

The complications of ventricular tachycardia are caused by insufficient cardiac output and include death, shock, loss of consciousness, and injury. There are additional complications associated with the treatment of ventricular tachycardia. Complications from antiarrhythmic drug therapy include acquired LQTS, ventricular proarrhythmia, heart block, and organ toxicity. Complications from implantation of a defibrillator include infection, pneumothorax, lead failure, inappropriate shocks for supraventricular tachycardias, premature battery depletion, and device failure [24].

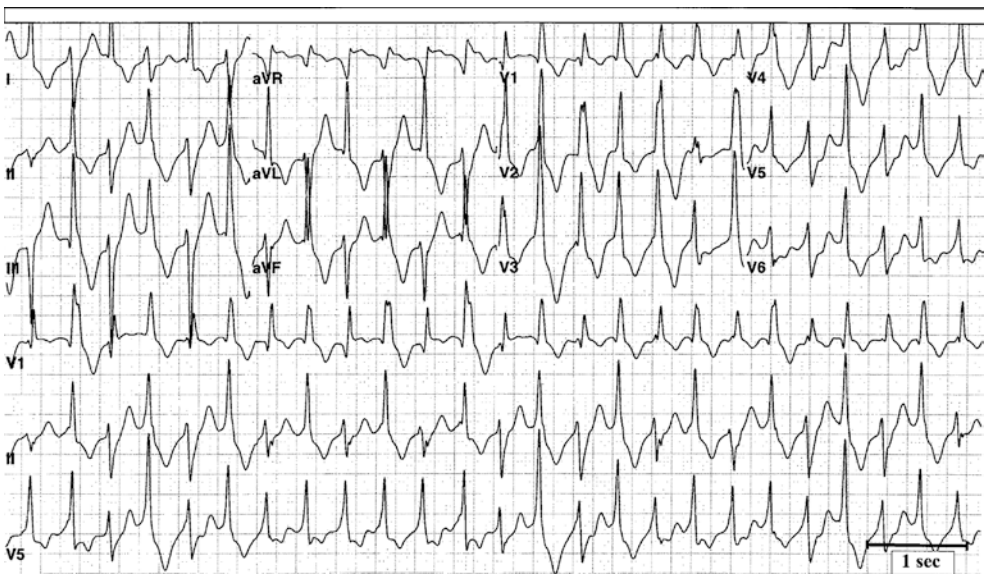

Fig. 16.13 Example of idiopathic bidirectional ventricular tachycardia. This rhythm is usually a result of digitalis toxicity. Note the right bundle branch block morphologic pattern and an alternating QRS axis in the inferior leads

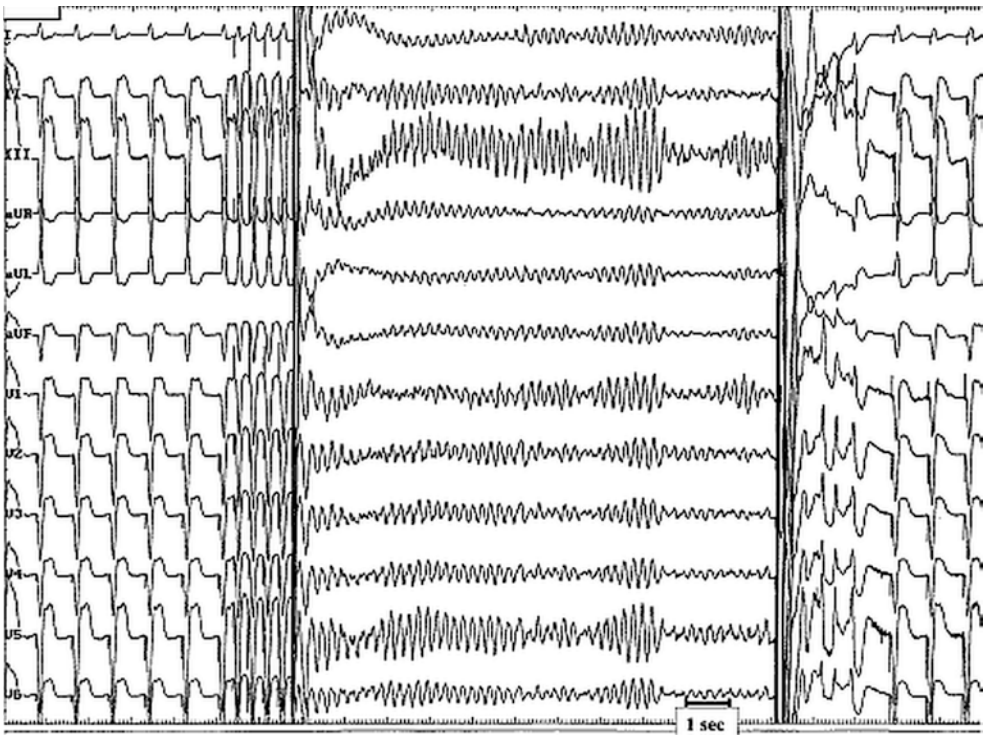

Fig. 16.14 Twelve-lead rhythm strip recorded during testing of an implantable defibrillator. The initial rhythm is atrial fibrillation with ventricular pacing. The device induces ventricular fibrillation by delivering four ventricular pacing stimuli, followed by a low-energy shock that is synchronous with the T wave. The defibrillator detects the tachycardia, charges the capacitors, and delivers a 21-joule biphasic shock. The shock successfully defibrillates the patient but is initially followed by four beats of polymorphic ventricular tachycardia

Therapy

The acute management of a patient with cardiac arrest should follow the Advanced Cardiovascular Life Support (ACLS) guidelines [25–27] The only rhythm-specific therapy proven to prolong survival is defibrillation of pulseless VT or VF. Early defibrillation preferably with a biphasic defibrillator and high quality CPR are key in the resuccitaion process. Interruptios of CPR for pulse check and defibrillations should be as brief as possible. Also if VF/pulseless VT is present for more than a few minutes initiation of CPR prior to defibrillation by unloading the volume-overloaded right ventricle might increase the likelyhood of defibrillation resulting in a perfusing rhythm. Ressucitaion efforts include perfomrance of CPR for a time period of 2 min followed by defibrillation for VF/pulseless VT. If defibrillation does not restore sinus rhythm, the ACLS protocol for pulseless VT/VF is followed which includes administration of epinephrine with the goal of improving myocardial blood flow during CPR [27]. Amiodarone is the first-line antiarrhythmic drug given since it has improved outcome in patients with cardiac arrest. It may be considered if VT/VF is refractory to CPR, defibrillation and vasopressors. IV administration of amiodarone can result in hypotension. This is due to vasoactive solvents. When given without the solvents hypotension is not more likely to occur than with lidocaine [26]. A formulation of amiodarone without these vasoactive solvents was approved in the US. Lidocaine can be given as an alternative to amiodarone. Magnesium should only be given in the presence of Torsdaes de pointes and a prolonged QT interval.

Treatment of sustained monomorphic ventricular tachycardia depends on the clinical status of the patient. If the ventricular tachycardia is not hemodynamically tolerated, immediate cardioversion is appropriate. If the patient is hemodynamically stable, intravenous pharmacologic conversion may be attempted using either amiodarone, procainamide or sotalol (not available in the US) [26]. For procainamide (10 mg/kg) the rate of administration should not exceed 50 mg/min to avoid hypotension. Endpoints for adminitration of procainamide are: VT termination, hypotension, QRS duration increasing by 50% or maximal dose of 17 mg/kg is given. Procainmaide should be avoided in the presence of QT prolongation and congestive heart failure. Amiodarone should be considered if the VT is unstable, if it is refractory to cardioversion, or if VT recurs despite other measures. Intravenous lidocaine is considered a second-line antiarrhythmic since it is less effective than amiodarone, procainamide or sotalol. Synchronized electrical cardioversion should be performed if pharmacologic attempts fail. Adequate sedation or anesthesia should precede a shock for patients who are conscious. Overdrive pacing with a temporary transvenous pacemaker can also be used to terminate sustained monomorphic ventricular tachycardia, but it is rarely indicated.

External defibrillator technology has evolved. Conventional defibrillators deliver a direct-current shock as a damped sine wave. Biphasic defibrillation waveforms that have been used in implantable defibrillators for years have been incorporated into external defibrillators. Biphasic

waveforms are more effective than a standard waveform and are able to successfully defibrillate with lower energy requirements [28]. If a clinician has access to a biphasic defibrillator, it is important to know which energy levels have efficacy equal to the doses that are recommended by ACLS guidelines. VT or VF storm is potentially life threatening and in addition to VT termination may require more specific therapy. Adrenergic blockade has been found beneficial [29] in the setting of VT storm. Also an ablation procedure can be considered if there is a trigger for VF [30] or in the case of monomorphic VTs [31, 32] causing VT storm. In case of failure of medical therapy to control VT storm, and if a patient is not a candidate for an ablation or if an ablation fails to control VT, consideration to thoracic epidural anesthesia and surgical bilateral cardiac sympathetic denveration [33, 34] should be given. For VT storm caused by Brugada syndrome administration of isoproterenol has been described to be beneficial.

Automatic external defibrillators (AED) are safe and effective and, because they are increasingly available for use by nonmedical personnel, have the potential to dramatically increase survival from cardiac arrest [35, 36]. The FDA has approved over-the-counter sales of AEDs. The wearable automatic defibrillator is a vest device that is worn continuously. It monitors the rhythm and delivers a shock if ventricular fibrillation is detected. It may be useful in patients who are at temporary high risk for sudden cardiac death, such as patients awaiting heart transplantation, or patients requiring removal of an infected ICD.

Long-Term Management

Patients who have experienced an episode of sustained ventricular tachycardia or ventricular fibrillation are at risk of having a recurrence unless there is a clear-cut and correctable cause. Patients who have had a cardiac arrest in the setting of an acute transmural myocardial infarction, severe hypokalemia, or hypoxemia are usually considered to be at relatively low risk for recurrence. However, studies have suggested that patients considered to have "reversible" causes of cardiac arrest may still carry an unacceptable risk for cardiac arrest [37]. Patients presenting with sustained VT in whom there is a mild elevation in cardiac biomarkers should be treated like patients with sustained VT and no rise biomarkers [38]. A work-up for ischemia should be performed in this situation.

Long-term management of patients with ventricular tachyarrhythmias can be divided into drug therapy, device therapy, and ablation. Occasionally, all three therapies are necessary to manage a patient with ventricular tachycardia. In general, the most effective pharmacologic therapy for secondary prevention of sustained ventricular arrhythmias is oral amiodarone. Its efficacy may be related to its ability to block sodium, potassium, and calcium channels, as well as beta-adrenergic receptors. Amiodarone appears to be less likely to cause ventricular proarrhythmia in patients with structural heart disease than pure sodium or potassium channel blockers.

Implantable defibrillators have been available since the late 1980s and are highly effective at preventing death from ventricular tachycardia or ventricular fibrillation. Several prospective, randomized, controlled trials have documented improved survival with ICD therapy as compared to antiarrhythmic drugs (primarily amiodarone) for secondary prevention of symptomatic ventricular arrhythmias [39–41]. In the Antiarrhythmic Versus Implantable Defibrillator (AVID) trial, defibrillator therapy resulted in a 31% reduction in overall mortality at 3 years of follow-up in comparison with amiodarone [39]. The Canadian Implantable Defibrillator Study (CIDS) found a 20% relative risk reduction in all-cause mortality and a 33% reduction in arrhythmic mortality with implantable cardioverter-defibrillator therapy in comparison with amiodarone [40]. In the Cardiac Arrest Study Hamburg (CASH), therapy with a defibrillator was associated with a 23% reduction of all-cause mortality when compared with treatment with amiodarone or metoprolol [41]. It is generally accepted that defibrillator implantation is first-line therapy for patients with sustained ventricular tachycardia or cardiac arrest unless a contraindication is present. Cardiac resynchronization in patients with heart failure and dyssynchhrony has been found to reduce symptoms, increase functional capacity and prolong survival [42, 43].

The American College of Cardiology and the American Heart Association have published guidelines for implantation of cardiac defibrillators. The complete guidelines were updated in 2006, 2008 and most recently in 2017; they can be accessed at *www.americanheart.org*. They are summarized in Table 16.4 [38, 44, 45].

Several prospective multicenter trials have documented improved survival with ICD therapy in high-risk patients with left ventricular dysfunction due to either prior myocardial infarction or non-ischemic cardiomyopathy [12, 14, 46–48]. Patients with nonsustained ventricular tachycardia and prior myocardial infarction represent a group at high risk for sudden death. Previously, these patients were treated with antiarrhythmic drugs to suppress ventricular ectopy in an attempt to reduce the likelihood of sustained ventricular tachycardia. However, trials such as Cardiac Arrhythmia Suppression Trial (CAST) found that pharmacologic therapy with sodium channel blockers resulted in a higher mortality rate than did placebo [34]. Empirical amiodarone for patients with an ischemic cardiomyopathy and for patients who have suffered a recent myocardial infarction may reduce the likelihood of a cardiac-related death but has not been shown to reduce overall mortality rates [35–37]. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) patients

Table 16.4 Indications and contraindications for implantable defibrillator therapy

Class I indications[a]
1. Cardiac arrest due to VF or VT not due to a transient or reversible cause
2. Spontaneous sustained VT in association with structural heart disease
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced on electrophysiologic study
4. Nonsustained VT with coronary disease, prior MI, LV dysfunction and EF≤40%, and inducible VF or sustained VT on electrophysiologic study
5. Primary prevention: A: in patients with LV dysfunction due to prior infarction who are at least 40 days post MI and have an EF of ≤ 35% and are on chronic optimal therapy having NYHA functional class II or III; B: patients with non-ischemic cardiomyopathy who have an EF of ≤35% with NYHA functional class II or III on chronic optimal medical therapy
6. Patients with prior MI, at least 40 days post MI with an EF<30% in a NYHA functional class I
7. Pateints with ARVC and sustained VT, or significant dysfunction of RV or LVEF (≤35%)
8. Patients with cardiac sarcoidosis who have an EF ≤35%
9. Patients with catecholaminergic polymorphic VT and syncope while on adequate beta blocker therapy
10. Patients with Brigada syndrome with spontaneous type I pattern who had cardiac arrest, sustained ventricular arrhythmia or syncope presumed to ventricular arrhythmia
Class II indications[b]
1. Unexplained syncope, significant LV dysfunction and nonischemic cardiomyopathy
2. Patients with hypertrophic cardiomyopathy with 1 or more risk factors for SCD
3. Patients with hypertrophic cardiomyopathy and nonsustained VT or abnormal BP response during exercise who have additional SCD risk modifiers
4. Patients with ARVC who have sustained, tolerated VT, or syncope due to a ventricular arrhythmia, or have multiple risk factors for SCD [1]
5. Patients with Long QT syndrome with syncope or VT while receiving beta blockers
6. Patients with giant cell myocarditis and VF or unstable VT
7. Patients with nonischemic cardiomyopathy and an EF ≤35% who are in NYAH functional class I
8. Patients with Long QT syndrome and risk factors for SCD
9. Syncope in patients with advanced structural heart disease in which thorough invasive and noninvasive investigation has failed to define a cause
10. Patients with LV noncompaction with non-sustained VT and reduced EF
11. Patients with Laminin A/C mutation who have ≥2 risk factors for SCD
12. Patients with cardiac sarcoidosis who have an EF of >35% and who have evidence of scar by MRI or PET study, or who have an indication for permanent pacing, or who have inducible sustained VT during an EP study
13. Patients with LVAD and sustained VT
14. Patients awaiting cardiac transplantation, who are not candidates for ICD implantation (for example: NYHA class IV)
15. Patients with repaired tetralogy of Fallot with inducible VT or VF or sustained VT
16. Patients with coronary artery spasm and cardiac arrest in whom medical therapy is ineffective or not tolerated
17. Patients with muscular dystrophy and progressive cardiac involvement
Contraindications
1. Syncope of undetermined cause in a patient without inducible VT and without structural heart disease
2. Incessant VT or VF
3. VF or VT resulting from arrhythmias amenable to surgical or catheter ablation
4. Ventricular tachyarrhythmias due to a transient or reversible disorder
5. Significant psychiatric illnesses
6. Patients without reasonable expectation of survival with acceptable functional status for at least 1 year
7. NYHA Class IV drug–refractory CHF in patients not candidates for transplantation or CRT-D

CHF congestive heart failure, *EP* electrophysiologic, *LV* left ventricular, *MI* myocardial infarction, *NYHA* New York Heart Association, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Adapted from ACC/AHA/ESC 2008 and 2017 Guidelines for device based therapy of cardiac rhythm abnormalities [44, 45]

[a]A Class I indication refers to a condition for which there is evidence that defibrillator therapy is beneficial

[b]A Class II indication refers to a condition for which there is conflicting evidence and/or a divergence of opinion

with New York Heart Association class II and III heart failure with an ejection fraction of <35% were randomized to amiodarone vs ICD implantation. In the ICD arm the mortality was 23% lower than in the amiodarone arm. Defibrillator therapy is currently recommended for patients with cardiomyopathy and heart failure, impaired ventricular function, asymptomatic nonsustained ventricular tachycardia, and sustained ventricular tachycardia that is inducible with programmed stimulation [10, 38, 48].

Defibrillator therapy should also be considered for primary prevention of sudden death in patients with congenital LQTS associated with syncope and those with hypertrophic

cardiomyopathy associated with syncope, family history of sudden death, or severe hypertrophy [44].

Primary prevention of sudden death requires efforts to reduce coronary artery disease and control hypertension, identification of high-risk patients, improved therapy for congestive heart failure, and improvements in public access to defibrillation.

Currently available implantable transvenous defibrillators are usually implanted into the pectoral position, and can deliver up to 41 Jouls within 10 s after capable of dual-chamber pacing and antitachycardia pacing, and can deliver up to a 41-joule biphasic shock within 10–15 s of the beginning of fibrillation. In patients without a pacing indication and without the need for antitachycardiac pacing, the subcutaneous defibrillator has been an alternative for ICD implantation with subcutaneous leads only [49].

Catheter ablation is a treatment option for some patients who have sustained monomorphic ventricular tachycardia. Ideal candidates for ablation are patients with idiopathic ventricular tachycardia [50] or bundle branch reentry. Catheter ablation is also effective in patients with prior myocardial infarction [51, 52] but is rarely used as sole therapy. Mapping and ablation of post-infarction VT can be performed with a high success rate, whether or not the VT is hemodynamically-tolerated, using different mapping strategies [53–57]. Ablation is useful as adjunctive therapy for patients who have experienced multiple defibrillator therapies [58]. VT ablation has not shown to reduce mortality but has been shown to reduce ICD therapy if used early on prior or at the time of ICD implantation [59, 60].

Prognosis and Follow-Up

Most patients with ventricular tachycardia have underlying structural heart disease, and their prognosis is closely related to the severity of ventricular dysfunction [61]. One study of defibrillator recipients found that the number of fixed nuclear perfusion defects was the only independent predictor of mortality [62]. Cardiac magnetic resonance imaging with delayed enhancement is a promising technique for risk stratify patients with prior myocardial infarction [49] and patients with non-ischemic cardiomyopathy [16, 17]. Identification of scar has been found to correlate with adverse outcomes in patients with non-ischmeic cardiomyopathy even in the presence of preserved ejection fraction [63]. Patients with idiopathic ventricular tachycardia generally have a good prognosis.

Patients with implantable defibrillators require careful follow-up to assess the battery status, integrity of leads, and stability of defibrillation energy requirements. Support groups are beneficial for this group of patients [64]. Patients receiving long-term amiodarone need surveillance testing to monitor for organ toxicity, including thyroid and liver function tests every 6 months and a chest radiograph every 6 to 12 months [65]. A baseline ophthalmologic examination is also recommended. More frequent assessment is indicated if symptoms develop.

Practical Points

- Ventricular tachycardia is defined as three or more consecutive ventricular complexes at a rate greater than 100 beats per minute.
- A ventricular arrhythmia is considered sustained when intervention is required for termination, when it results in symptoms, or when it lasts longer than 30 s.
- Ventricular tachycardia usually occurs in patients with underlying structural heart disease
- Patients with significant ventricular dysfunction are at increased risk of dying suddenly and should undergo further evaluation.
- The most useful test in a patient with a sustained ventricular tachycardia is an electrocardiogram.
- Electrophysiologic testing has no value in the risk stratification of patients with a nonischemic cardiomyopathy.
- The acute management of a patient with a ventricular tachyarrhythmia should follow the ACLS guidelines.
- Long-term management of patients with ventricular tachyarrhythmias includes drug therapy, device therapy, and ablation.

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Bradycardia

17

Eric D. Good and Krit Jongnarangsin

Usual Causes of Bradycardia

Bradycardia is defined as a heart rate less than 60 beats per minute (bpm). This traditional rate cutoff is arbitrary, and there are many asymptomatic people with heart rates below 60 bpm who have no cardiac abnormalities (see, "sinus bradycardia"). Pathologic causes of bradycardia are diverse and can be divided into intrinsic and extrinsic etiologies: these are listed in Table 17.1. Intrinsic causes of bradycardia may be related to conducting abnormalities of the sinus or atrioventricular (AV) nodes, HIS-purkinje system, and atrial or ventricular myocardium. Because the cardiac conduction system is composed of specialized cardiac myocytes, common myocardial diseases such as ischemia, infarction, hypertension, surgical trauma, age-related degeneration, and dilated cardiomyopathies can also result in bradycardia. Less common pathologic causes of bradycardia include infiltrative disorders, collagen vascular diseases, familial conduction system diseases, and infections such as endocarditis or Lyme disease. Because a portion of the atrioventricular conduction system is a narrow electrical corridor without redundancy, small pathologic lesions can result in profound bradycardia. Occasionally, bradycardia is caused by idiopathic degeneration of the conduction tissue. Bradycardia can also be a result of intentional or unintentional catheter ablation of the sinus node or atrioventricular junction.

Congenital heart block tends to occur in children of women with autoimmune diseases and results from transplacental transfer of maternal anti-Ro and/or anti-La antibodies. Sinus bradycardia may be associated with congenital complete heart block [1].

Table 17.1 Causes of bradycardia

Intrinsic causes
Coronary artery disease
Hypertensive heart disease
Dilated cardiomyopathy
Infiltrative diseases
Collagen vascular diseases
Surgical trauma
Catheter ablation
Infections
Genetic conduction diseases
Idiopathic degeneration
Extrinsic causes
Drugs
Neurocardiogenic syncope
Increased vagal tone
Carotid sinus hypersensitivity
Hypothyroidism
Neurologic disorders
Hyperkalemia

Extrinsic causes of bradycardia include hypervagotonia, drugs, hypoxemia, central nervous system disease, thyroid disease, and electrolyte abnormalities. Sleep is normally accompanied by marked bradycardia, especially in young patients. Complex partial seizures have also been included among the long list of functional causes of bradycardia [2].

An abnormal increase in vagal tone is responsible for the bradycardia seen during vasodepressor syncope, carotid sinus hypersensitivity, and cough and micturition syncope, although adrenergic withdrawal can also be a factor. Careful identification of reversible causes can lead to prevention of unnecessary therapy. For example, tracheostomy can correct the bradycardia associated with sleep apnea [3].

Presenting Symptoms and Signs

Patients with bradycardia have a broad spectrum of signs and symptoms. Because symptoms are usually nonspecific, it is important to be as certain as possible that the symptoms are

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secondary to bradycardia. Patients with persistent bradycardia can present with symptoms that progress gradually, such as fatigue, dizziness or exercise intolerance, or can present with symptoms that occur suddenly, such as syncope, congestive heart failure, or cardiac arrest. Patients with paroxysmal bradycardia usually present with palpitations, dizzy spells, presyncope, syncope, or seizures, depending on the escape rhythm and the degree of cerebral perfusion during the bradycardia. Many patients with bradycardia are asymptomatic.

Bradycardia is often accompanied by a bounding pulse and a large pulse pressure. When complete heart block is present, the physical examination can reveal signs of atrioventricular dissociation such as cannon A waves in the neck veins and variable atrioventricular valve closure sounds. In affected elderly patients, confusion is occasionally the sole manifestation of bradycardia.

Helpful Tests

Proper characterization of a bradycardia often helps identify the cause. For example, transient atrioventricular block that occurs at the same time as transient sinus slowing is diagnostic of a vagal cause and does not require further evaluation. However, when an intrinsic cause is suspected, further testing is usually warranted, to exclude underlying structural heart disease.

An electrocardiographic recording is necessary to establish a diagnosis of bradycardia. Simple palpation of the pulse can lead to an erroneous diagnosis of bradycardia in the setting of atrial or ventricular bigeminy. A 12-lead electrocardiogram should be obtained for all patients with symptoms suggestive of bradycardia.

For patients with daily symptoms suggestive of bradycardia, an ambulatory Holter monitor can be helpful for characterizing the rhythm. For patients with less frequent symptoms, a continuous-loop recorder collects data better than does a Holter monitor. Continuous-loop recorders can be worn for several weeks and can be used to transmit a rhythm strip over the phone after a patient has symptoms [4]. An implantable loop recorder is also available for patients who have infrequent symptoms but is usually reserved for patients with recurrent, unexplained syncope [5].

A formal exercise treadmill test can be helpful in establishing a diagnosis of chronotropic incompetence. However, a simple recording of the cardiac rhythm before and immediately after a short walk or stair climbing is often sufficient and saves the expense of formal exercise testing.

Maneuvers or medications that increase the sinus rate, such as ambulation or atropine, are useful tests in the setting of second-degree atrioventricular block. If the atrioventricular block worsens when the sinus rate increases, the conduction block is usually pathologic and related to an intrinsic abnormality of the His-Purkinje system.

Electrophysiologic testing can be useful in the evaluation of patients with symptoms suggestive of bradycardia [6]. Measurement of the sinus node recovery time—the time between cessation of rapid atrial pacing and the first spontaneous atrial depolarization from sinus node—is a useful test of sinus node function. Intracardiac recordings are valuable in patients with atrioventricular block when the surface electrocardiogram is not sufficient to determine the level of block. Intracardiac His bundle recordings can reveal whether atrioventricular block is at or below the level of the atrioventricular node. If the level of atrioventricular block is below the atrioventricular node, placement of a pacemaker is often indicated. Early studies suggested that electrophysiologic testing should be performed in patients with bundle branch block to determine whether the patient is at risk for developing higher degree atrioventricular block [7]. However, the predictive value in this setting is low. Therefore, electrophysiologic testing is currently not indicated for the evaluation of asymptomatic patients with isolated bundle branch block.

Patients with unexplained syncope and bundle branch block should undergo electrophysiologic testing to exclude inducible ventricular tachycardia before paroxysmal bradycardia is assumed to be the cause of syncope, especially in the setting of left ventricular dysfunction [8].

Differential Diagnosis

Bradyarrhythmias can be categorized as those caused by dysfunction of the sinus node and those caused by dysfunction of the atrioventricular conduction system. The characteristics of each bradyarrhythmia are described in the following sections. Proper characterization of the bradyarrhythmia is important because it helps determine the cause, prognosis, and treatment.

Tissues that constitute the cardiac conduction system have the ability to depolarize spontaneously. The intrinsic spontaneous rate of depolarization usually decreases in the anatomic direction of normal impulse propagation. The dominant pacemaker normally arises from within the sinus node complex and suppresses spontaneous depolarization of the distal conduction tissue. During bradycardia, these latent pacemaker cells are unmasked and give rise to the dominant rhythm. Escape beats and rhythms are also described hereafter.

Sinus Node Dysfunction

Abnormal sinus node function can result from abnormal automaticity or from sinus node exit block, and it manifests as sinus bradycardia, sinus pauses, or chronotropic incompetence. Sinus node dysfunction is often referred to as sick sinus syndrome and is the most common indication for pace-

maker implantation. Patients with sinus node dysfunction often have concomitant atrial disease, which results in atrial tachyarrhythmias. This common association is referred to as the *tachycardia-bradycardia syndrome.*

Sinus Bradycardia

Sinus bradycardia is defined as a sinus rhythm with a rate less than 60 beats per minute (bpm) (Figs. 17.1 and 17.2). Some authors have argued that sinus rhythm rates as low as 46 bpm in men and 51 in women should be considered normal [9]. Young patients and trained athletes often have even more marked sinus bradycardia because of elevated vagal tone. Sinus bradycardia is also observed normally during sleep.

Sinus Pause

A sinus pause is present when the length of a pause is not a multiple of the baseline sinus cycle length (Fig. 17.3). In contrast, sinoatrial (SA) exit block is diagnosed when there is a pause and the length of the pause is equal to a multiple of the baseline sinus cycle length. As with atrioventricular blocks, SA block can be categorized as first-, second-, or third-degree block. First-degree SA block is caused by a delay in transmission of SA depolarization to the atrial tissue and can be diagnosed only with specialized intracardiac recordings. Second-degree SA block is manifested as a sinus pause and results from intermittent failure of conduction from the sinus node to the surrounding atrial muscle. Second-degree SA block can be categorized in the Wenckebach classification system as type I or type II. Type I SA block is manifested as gradual shortening of the sinus cycle length followed by a pause that is not equal to the preceding PP interval (Fig. 17.4). Type II SA block is characterized by a constant sinus cycle length followed by a sinus pause that is equal to the preceding PP interval. High-grade SA block is present when the pause is equal to a multiple of the preceding PP interval.

An excessively long pause is often called *sinus arrest* and can be caused by third-degree SA exit block or decreased automaticity (Fig. 17.5).

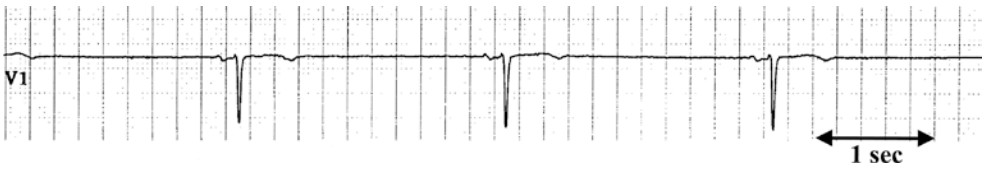

Fig. 17.1 Rhythm strip from lead V_1, showing marked sinus bradycardia. The sinus rate is 27 beats per minute

Fig. 17.2 Sinus bradycardia competing with a junctional escape

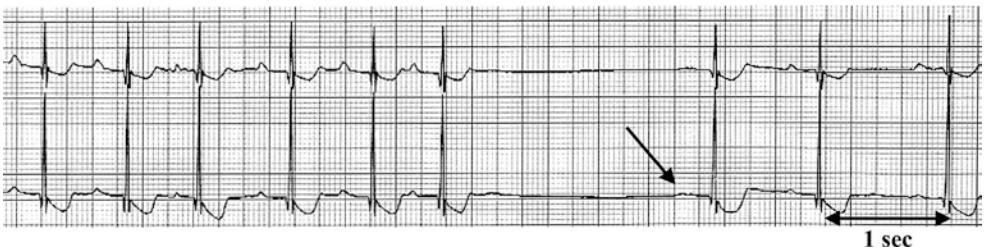

Fig. 17.3 Two-lead rhythm strip of a sinus pause with an atrial escape beat. Note that the morphologic pattern of the first P wave after the sinus pause differs from the sinus P waves (*arrow*)

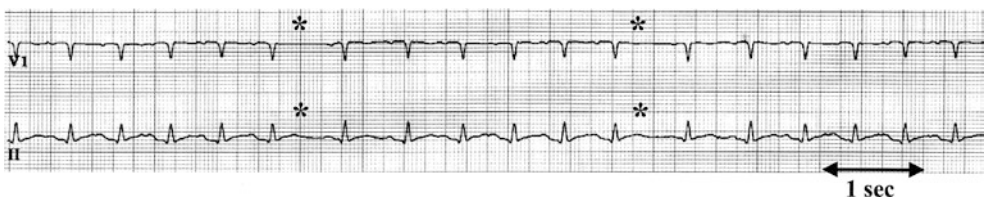

Fig. 17.4 Rhythm strip from leads V_1 and II of second-degree, type I sinoatrial exit block. Note the progressive shortening in the PP interval, followed by a sinus pause (*asterisk*). The duration of the sinus pause is less than twice the sinus cycle length. The pattern repeats itself

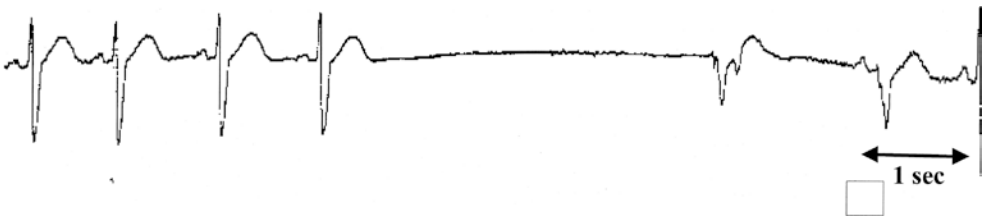

Fig. 17.5 Sinus arrest. There is a ventricular escape beat before the sinus rhythm recovers

Chronotropic Incompetence

A rate of increase in sinus node firing that is inappropriately slow relative to the level of exertion indicates a condition termed, *chronotropic incompetence*; this is considered to be a relative bradycardia. There are several proposed definitions for chronotropic incompetence, including failure to reach a heart rate that is either 85% of, or two standard deviations below, the age-predicted maximum heart rate (220 bpm minus years of age). However, patients who have clinically relevant chronotropic incompetence usually demonstrate an obvious inability to increase the heart rate appropriately with activity.

Atrioventricular Conduction Disturbances

Atrioventricular block can occur at the level of the atria, AV node, within the His bundle, or within the purkinje system distal to the His bundle. Atrioventricular block caused by intraatrial conduction block results when the sinus node impulse does not reach the atrioventricular node, but this is rare. Causes include atrial myopathies, cardiac surgery, heart transplant and ablation procedures. Atrioventricular block is categorized as first-, second-, or third-degree. Identification of the level and type of block is important, because they are related to the prognosis and therapy.

The atrioventricular conduction system serves to prevent rapid atrial rhythms from conducting to the ventricle on a 1:1 basis. Therefore, pathologic atrioventricular block must be distinguished from atrioventricular block that results from normal refractoriness (Fig. 17.6).

First-Degree Atrioventricular Block

First-degree atrioventricular block itself does not result in bradycardia but is often associated with other bradycardic rhythms and may be a precursor of higher degree atrioventricular block. First-degree atrioventricular block is caused by conduction delay from the atrium to the ventricle and is manifested as a prolonged PR interval (more than 200 ms in the adult). The level of conduction delay is usually within the atrioventricular node but can be due to delay within the atrial or lower in the conduction system. An associated bundle branch block suggests that the first-degree atrioventricular block is caused by conduction delay below the atrioventricular node. In rare instances, patients with dual atrioventricular nodal pathways can have a prolonged PR interval when atrioventricular conduction occurs preferentially over the "slow" atrioventricular nodal pathway (Fig. 17.7).

Second-Degree Atrioventricular Block

Second-degree atrioventricular block is present when there is intermittent failure of atrioventricular conduction, and can be categorized as Mobitz type I (Wenckebach) or Mobitz type II atrioventricular block. The names Mobitz and Wenckebach continue to be used to describe the types of second-degree atrioventricular block. Karel Frederik Wenckebach, using arterial and jugular venous pressure recordings, first described type I atrioventricular block in 1899 [10]. John Hay, also using pressure recordings, reported a patient with type II atrioventricular block in 1906 [11]. Woldemar Mobitz used electrocardiographic recordings to classify the two types of atrioventricular block [12].

During sinus rhythm with type I atrioventricular block, there is progressive prolongation of the PR interval before atrioventricular block (Fig. 17.8). Although the PR interval gradually lengthens with each sinus beat, the amount by which the PR interval lengthens with each sinus beat actually decreases. Therefore, in classic Wenckebach atrioventricular block, the RR interval progressively decreases before atrioventricular block. This pattern often repeats itself and results in so-called *grouped beating*. However, this classic atrioventricular Wenckebach pattern is present in fewer than half of Wenckebach atrioventricular blocks. In the absence of progressive prolongation of the PR interval, a diagnosis of Wenckebach atrioventricular block can be made when the PR interval of the first conducted beat is shorter than the PR interval of the last conducted beat before the block. During type II atrioventricular block, the PR interval remains constant before and after atrioventricular block (Fig. 17.9).

Type I atrioventricular block is a more benign conduction disturbance than is type II and usually does not necessitate pacemaker therapy. Wenckebach atrioventricular block is usually caused by block in the atrioventricular node secondary to increased vagal tone, but in rare instances, it can occur

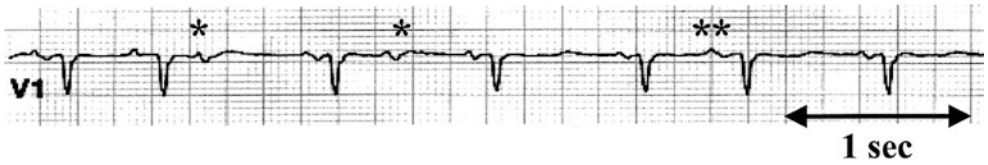

Fig. 17.6 Sinus rhythm with premature atrial depolarizations that result in atrioventricular block when the coupling interval is short (*asterisk*) but are conducted to the ventricle when the coupling interval is longer (*double asterisk*). This is an example of functional, nonpathologic atrioventricular block

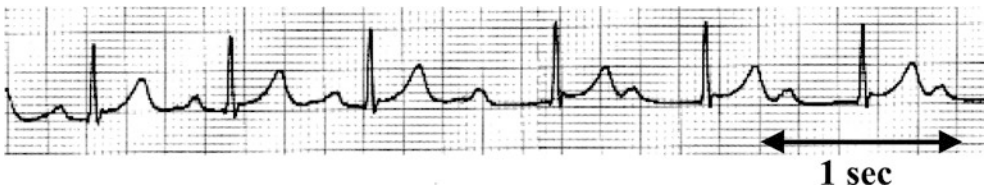

Fig. 17.7 Rhythm strip obtained from a patient who had just been laid supine from a sitting position. The first three PR intervals are normal. Then the PR interval increases to approximately 400 ms. This tracing can be explained by the presence of dual atrioventricular nodal pathways

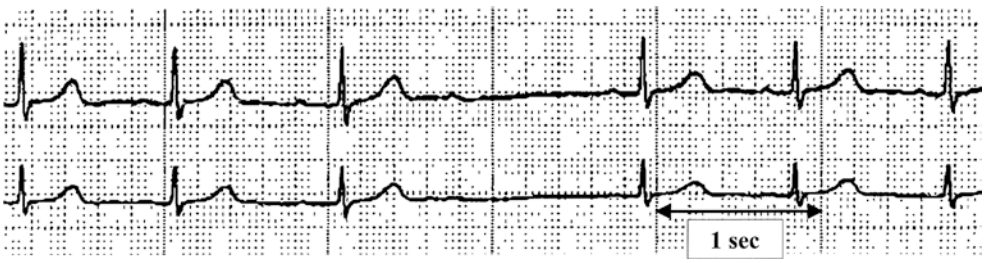

Fig. 17.8 Mobitz type I (Wenckebach) second-degree atrioventricular block

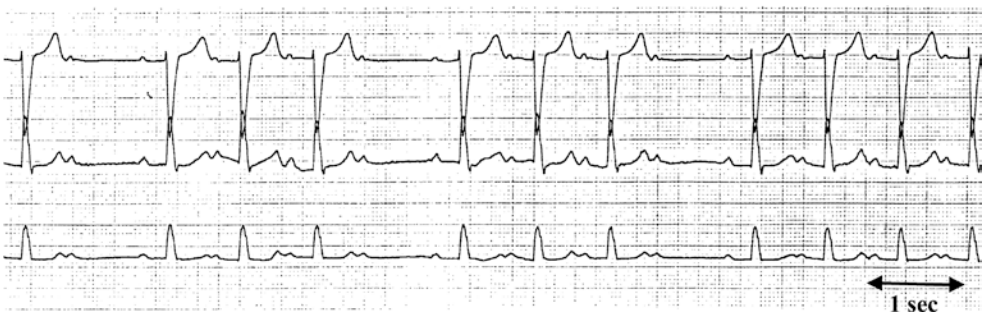

Fig. 17.9 Three-lead rhythm strip of Mobitz type II, second-degree atrioventricular block. There is a constant PR interval before the block sinus beats. The PR interval is prolonged with the conducted beats, and there is an intraventricular conduction delay

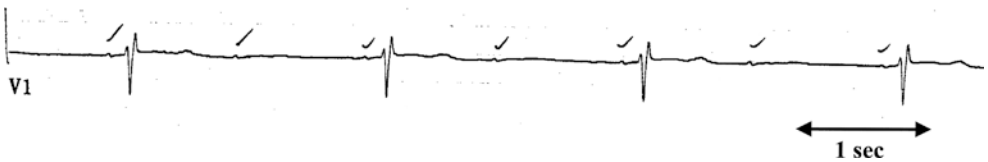

Fig. 17.10 Rhythm strip from lead V_1 showing 2:1 atrioventricular block. The slow sinus rate and narrow QRS complex suggest that the level of atrioventricular block is within the atrioventricular node

in the His-Purkinje system. Because type II atrioventricular block is usually associated with conduction system disease, it tends to be progressive and to eventually necessitate pacemaker therapy. The presence of a bundle branch block is suggestive of type II atrioventricular block. Type I atrioventricular block occurs more commonly during inferior myocardial infarction, is transient, and does not require temporary pacing; whereas type II atrioventricular block occurs more commonly during anterior myocardial infarction, necessitates pacing, and is associated with higher mortality.

When 2:1 atrioventricular block is present, two consecutive PR intervals are not available for comparison (Figs. 17.10

and 17.11). Distinguishing atrioventricular nodal block from His-Purkinje block may not be straightforward in this situation. Clues that suggest that the level of block is in the atrioventricular node include a narrow QRS complex and prolonged PR interval during the conducted beats, slowing of the sinus rate during atrioventricular block, and documented Wenckebach block when lower degree atrioventricular block is present (Figs. 17.12 and 17.13). When two or more consecutive P waves fail to be conducted to the ventricle, high-grade atrioventricular block is present. The same clues during 2:1 atrioventricular block can help determine the level of block during high-grade atrioventricular block.

Complete Atrioventricular Block

Third-degree, or complete atrioventricular block occurs when no atrial activity is conducted to the ventricles. During complete heart block, atrioventricular dissociation is present and a ventricular *escape rhythm* occurs at a slower rate than the atrial rhythm (Figs. 17.14 and 17.15). Isorhythmic atrioventricular dissociation is a rare arrhythmia that occurs when two independent atrial and ventricular foci discharge at similar rates; it is characterized by a P wave that migrates in and out of the QRS complexes with successive beats (Fig. 17.16). Either slowing of the dominant atrial pacemaker or accelera-

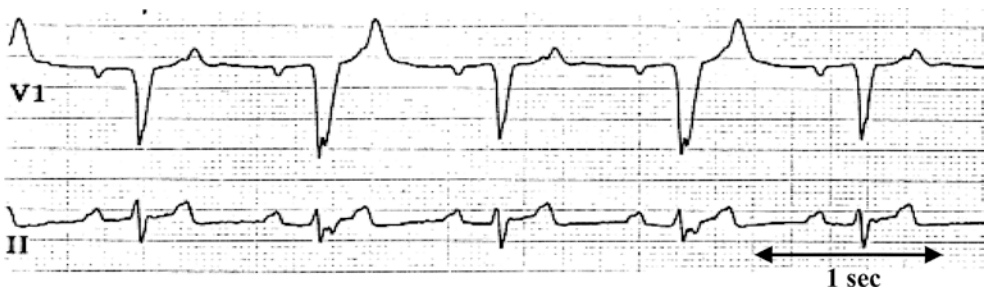

Fig. 17.11 Rhythm strip from lead V_1 showing 2:1 atrioventricular block. The alternating QRS morphologic pattern is consistent with alternating degrees of left bundle branch block and suggests that the level of atrioventricular block is within the His-Purkinje conduction system

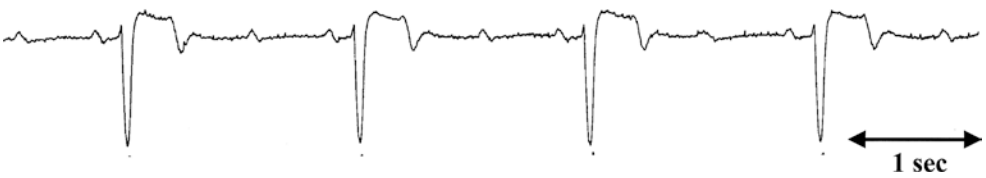

Fig. 17.12 High-grade atrioventricular block with a 3:1 conduction ratio

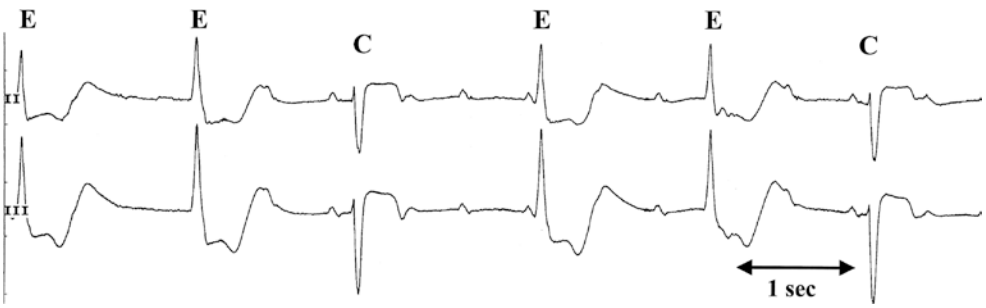

Fig. 17.13 Sinus tachycardia and high-grade atrioventricular block. The morphologic pattern of the conducted beats (C) differs from that of the ventricular escape beats (E)

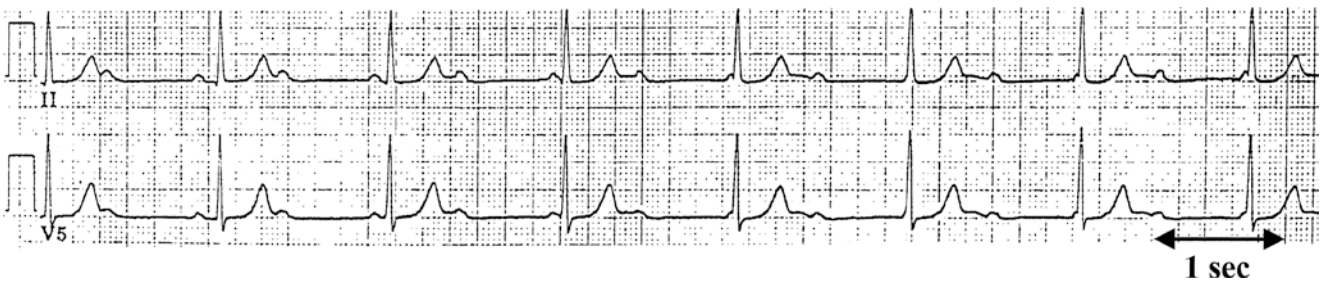

Fig. 17.14 Rhythm strip from leads II and V_5 showing third-degree atrioventricular block with a junctional escape. There is atrioventricular dissociation

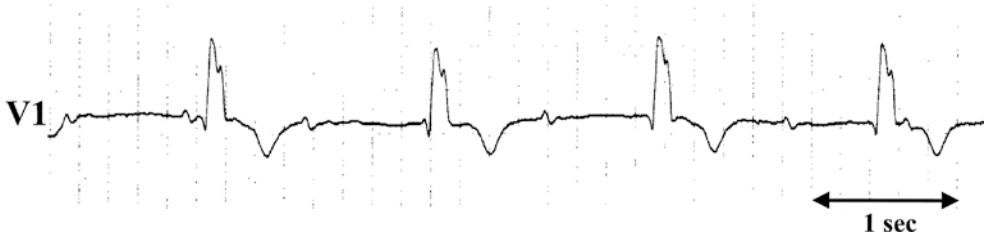

Fig. 17.15 Third-degree atrioventricular block with a ventricular escape. There is atrioventricular dissociation

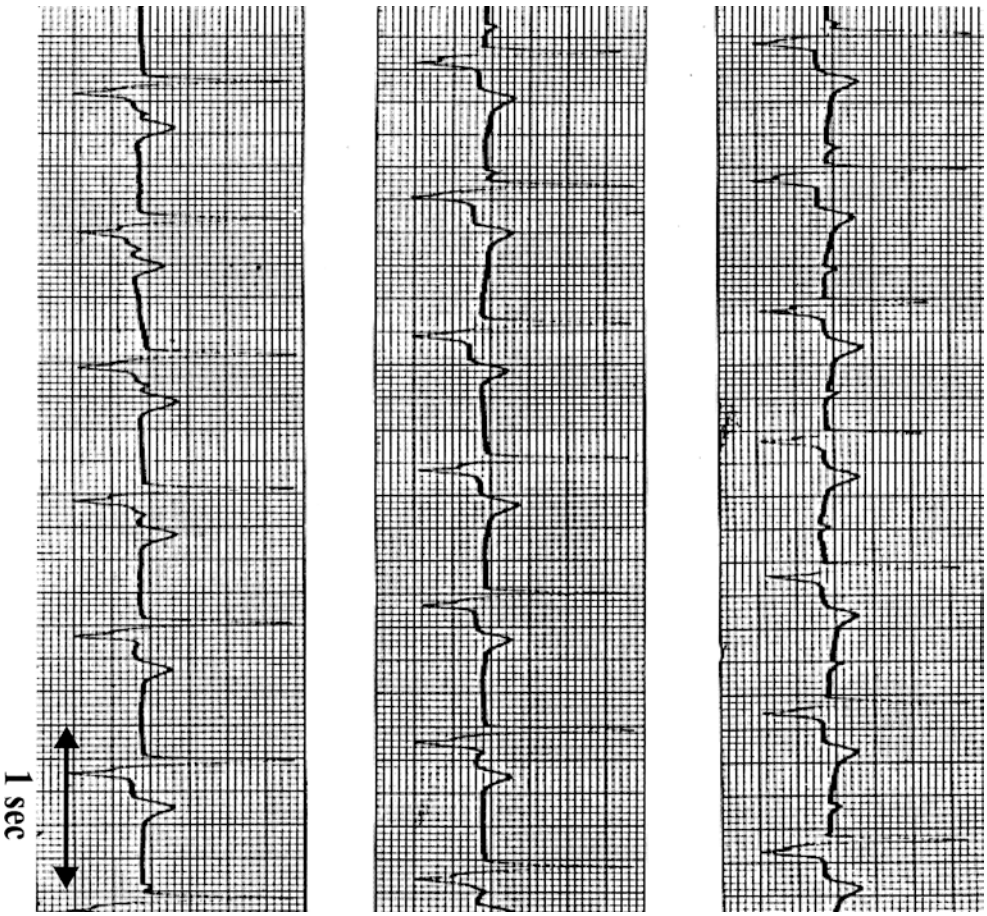

Fig. 17.16 Continuous rhythm strip showing isorhythmic atrioventricular dissociation. The atrial rate is slightly variable and competing with a fixed junctional rhythm. The result is a P wave that migrates in and out of the QRS complexes with successive beats. Atrioventricular conduction is probably intact because the third RR interval is approximately 40 ms shorter than the other RR intervals

tion of a subsidiary junctional or ventricular pacemaker results in this rhythm. Common causes include increased vagal tone and medications. It may be difficult to determine whether atrioventricular conduction is intact.

Escape Rhythms

Escape beats and rhythms that are associated with bradycardias arise from the atrium (Fig. 17.3), the atrioventricular junction (Figs. 17.2 and 17.14), and the His-Purkinje system within the ventricles (Figs. 17.5, 17.13, and 17.15). The escape rhythm usually arises from conduction tissue just below the level of block. The morphology of ventricular escape rhythms associated with block below the level of the AV node is dependent on the anatomic origin of pacemaker cells within the HIS-purkinje system: proximal sites (e.g. junction) produce narrower QRS complexes and faster rates (>40 bpm); while more distal sites (e.g. fascicles or ventricles) result in broad QRS complexes and slower escape rates. The latter tend to be less reliable than the former and should raise more immediate concern about progression to asystole. Occasionally, no escape rhythm is present and asystole is the first manifestation of complete AV block.

Complications

Complications associated with bradycardia include syncope, physical injury, cardiac arrest, bradycardia-dependent ventricular tachycardia, and complications from pacemaker therapy. Early pacemaker complications include bleeding, pneumothorax, cardiac perforation, and brachial plexus injury. Long-term complications related to pacing therapy

include infection, venous thrombosis, skin erosion, device migration, and lead failure. The weakest link in the pacing system is the leads, because they are susceptible to insulation failure and conductor fracture. Pacemaker generator failure is rare, but premature battery depletion does occur.

Therapy

The management of bradycardia can be divided into acute and long-term management.

Acute Management

When patients present with bradycardia that is associated with serious signs and symptoms, the acute management should follow the Advanced Cardiovascular Life Support (ACLS) guidelines (Fig. 17.17) [13]. Atropine at a dose of 0.5–1.0 mg can be administered safely in most cases. However, in some situations, atropine may worsen the bradycardia. When there is intermittent atrioventricular block below the atrioventricular node, atropine can increase the sinus rate and result in higher-grade atrioventricular block and, therefore, a slower ventricular rate. Dopamine and epinephrine can be used in refractory cases of symptomatic bradycardia associated with hypotension. Isoproterenol is a strong positive chronotropic agent but is no longer included in the ACLS algorithm because of its potential for causing cardiac ischemia. It still might prove useful in instances where coronary artery status is known. Reversible causes of bradycardia should be identified and corrected.

A temporary transvenous pacemaker should be inserted as soon as possible in patients with bradycardia who continue to be symptomatic despite pharmacologic therapy. Transcutaneous pacing has the advantage of being applied quickly at the bedside, in comparison with transvenous pac-

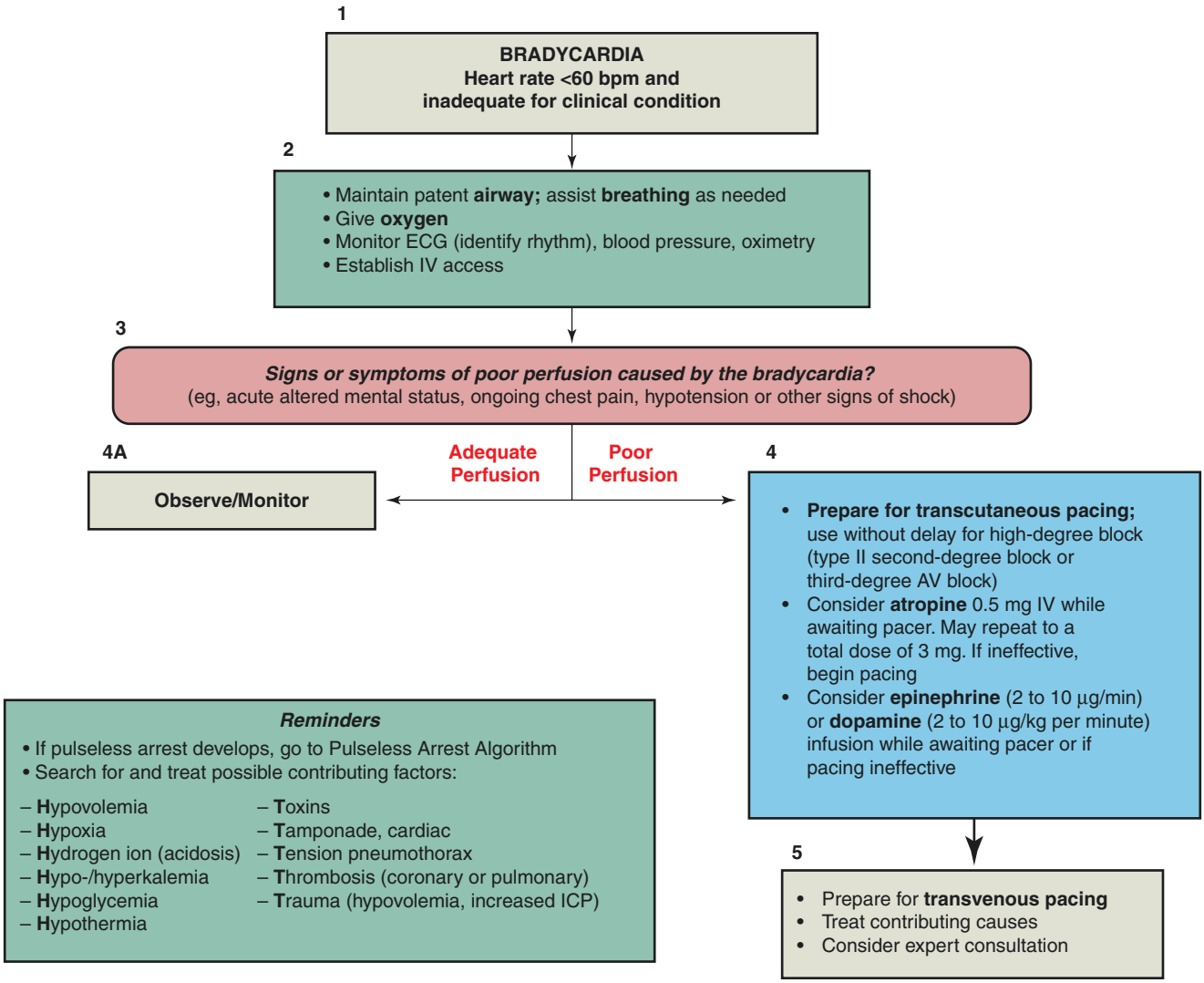

Fig. 17.17 Advanced Cardiovascular Life Support (ACLS) algorithm for the acute management of bradycardia

ing, and is available in most external defibrillators. However, external pacing does not always result in ventricular capture, is often poorly tolerated by the patient, and should be used only to stabilize the patient while a transvenous pacer is being inserted.

Long-Term Management

Because there is no well-tolerated, effective, long-term pharmacologic therapy for bradycardia, most patients with persistent symptomatic bradycardia require implantation of a permanent pacemaker.

The American College of Cardiology and the American Heart Association have published guidelines for implantation of cardiac pacemakers [14]. A Class I indication refers to a condition for which there is evidence that pacing is beneficial, and a Class II indication refers to a condition for which there is conflicting evidence and/or a divergence of opinion which is either in favor of the usefulness/efficacy (IIa) or less well established by evidence/opinion (IIb). A Class III indication refers to a condition for which a procedure/treatment is not useful/effective and in some cases may be harmful. The summary of indications is listed in Table 17.2. These indications focus on the presence or absence of symptoms. In general, patients with symptoms caused by an inadequate heart rate due to either sinus bradycardia or atrioventricular nodal block should undergo pacemaker implantation (Class I).

Patients who do not have symptoms from bradycardia but have complete heart block or are likely to develop complete heart block should undergo prophylactic pacemaker implantation. These situations include documented Mobitz II atrioventricular block or a HV interval exceeding 100 ms at electrophysiologic study in association with chronic bifascicular block. In addition, patients with sustained pause-dependent ventricular tachycardia or long-QT syndrome can benefit from pacemaker therapy to prevent the occurrence of ventricular tachyarrhythmia. However, the long-term benefit on risk of sudden cardiac death remains to be determined. Biventricular should be considered in patients who have congestive heart failure and a wide QRS complex. It has been demonstrated in several multicenter studies that biventricular pacing improved hemodynamics and symptoms of congestive heart failure. Although previous studies demonstrated that dual-chamber pacing decreased LV outflow gradient and improved symptom in some patients with hypertrophic obstructive cardiomyopathy, there is currently no consensus of opinion that pacing improves survival or quality of life.

It is important to understand pacemaker nomenclature. Pacing modes are described using the NBG code (North American Society of Pacing and Electrophysiology; British Pacing and Electrophysiology Group). The first letter in the code refers to the chamber that is paced (A, artrium; V, ventricle; D, dual), the second letter refers to the chamber sensed (A, atrium; V, ventricle; D, dual; or O, none), and the third letter refers to the response to sensing (T, triggered; I, inhibit; D, dual; or O, none). The letter R is added as a fourth letter in the code if the mode is rate responsive. Common pacing modes include VVI for ventricular demand pacing; AAI for atrial demand pacing; DDD for dual-chamber, demand, atrial-tracking, pacing; and VOO for asynchronous ventricular pacing.

In general, most patients who need a pacemaker should undergo implantation of a dual-chamber device, unless chronic atrial fibrillation or atrial flutter is present. Because the additional atrial lead required for physiologic pacing is

Table 17.2 Indications for permanent pacemaker implantation

Class I
• Third-degree or advance second-degree AV block associated with symptoms of bradycardia, asystole ≥3.0 s or escape rate ≤40 bpm, neuromuscular diseases, or after catheter ablation or cardiac surgery
• Bifascicular block with intermittent third-degree AV block, type II second-degree AV block or alternating bundle branch block
• Symptomatic sinus node dysfunction
• Sustained pause-dependent VT
• Recurrent syncope caused by carotid sinus hypersensitivity
Class IIa
• Asymptomatic third-degree AV block with awake ventricular rates ≥40 bpm
• Asymptomatic type II second-degree AV block with a narrow QRS complex
• Asymptomatic type I second-degree AV block at intra- or infra-His levels
• First- or second-degree AV block with symptoms similar to those of pacemaker syndrome
• Bifascicular block with markedly prolonged HV interval (≥100 ms) or inducible infra-His block
• Sinus node dysfunction without a clear etiology of syncope or association between symptoms consistent with bradycardia and documented bradycardia
• High-risk patients with congenital long-QT syndrome
• Recurrent neurocardiogenic syncope associated with documented bradycardia
Class IIb
• Marked first-degree AV block in patients with LV dysfunction and symptoms of congestive heart failure
• Neuromuscular disease with any degree of AV block
• Minimally symptomatic sinus node dysfunction
• Medically refractory, symptomatic hypertrophic cardiomyopathy with significant resting or provoked LV outflow obstruction
Class III
• Asymptomatic first-degree AV block, type I second-degree AV block at supra-His level, bifascicular block with first-degree AV block or sinus node dysfunction
• Reversible AV block
• Asymptomatic carotid hypersensitivity
• Patients with hypertrophic cardiomyopathy who are asymptomatic or without LV outflow obstruction

associated with additional costs and perioperative complications, studies have been conducted to quantify the benefit of physiologic pacing. A prospective, randomized clinical trial found that physiologic pacing reduced the incidence of atrial fibrillation but did not significantly reduce rates of stroke, mortality, or hospitalization for heart failure in comparison with ventricular pacing [15]. This study may have underestimated the benefit of physiologic pacing, because the follow-up period was only 3 years. Other studies have found the incidence of pacemaker syndrome, characterized by palpitations, fatigue, presyncope, and syncope in patients with a ventricular pacemaker, to be as high as 26% [16].

Studies have also shown that ventricular pacing can be associated with higher rates of death or hospitalization for heart failure, especially in patients with underlying ventricular dysfunction [17, 18]. A single-chamber, rate-responsive atrial pacemaker is a reasonable option for patients with sinus node dysfunction and normal atrioventricular conduction. The risk of development of atrioventricular block in these patients is low. If a dual-chamber device is implanted in patients with intact atrioventricular conduction, attempts should be made to minimize ventricular pacing.

Patients with sinus node dysfunction or with persistent atrial fibrillation and atrioventricular block are usually treated with a rate-responsive pacemaker. Most rate-responsive pacemakers use sensors that detect body movement and increase the pacing rate accordingly. Sensors that are based on minute ventilation are more physiologic and have been combined with motion sensors to maximize the benefits of rate-responsive pacing.

Pacemaker technology has dramatically improved over the past few decades. Advances include atrial preference pacing algorhythms, improved sensor technology, automatic gain control, improved diagnostics, automatic assurance of capture, dynamic adjustment of pacing intervals and refractory periods, and the ability to automatically switch to a nonatrial tracking mode in response to intermittent atrial tachyarrhythmias to prevent unnecessary rapid ventricular pacing. Improved pacemaker lead technology has led to high-impedance and steroid-eluting leads that result in lower capture thresholds and therefore increased battery longevity. Future leads will also be isodiametric, to allow for easier extraction.

Prognosis and Follow-Up

The prognosis opatient with bradycardia depends largely on the nature of the bradycardia and the presence of structural heart disease. Patients with second-degree atrioventricular block are less likely to progress to complete heart block if the level of block is nodal rather than infranodal. Patients with reversible causes and no structural heart disease have an overall good prognosis.

Pacemaker therapy can significantly improve quality of life. However, pacemakers do not prolong survival, except for pacemaker-dependent patients. In one study, the 5- and 10-year survival rates among pacemaker recipients older than 65 years with heart block and coexisting heart disease were 31% and 11%, respectively [19]. In evaluating patients who are candidates for pacing therapy, it is important to remember that many have severe underlying structural heart disease. Implantation of a prophylactic defibrillator with pacing capabilities rather than a pacemaker alone may reduce mortality among pacemaker recipients who are at high risk for sudden death [20].

Patients treated with a permanent pacemaker need careful follow-up. Patients should be seen in clinic every 4–6 months to determine battery status, check lead sensing, impedence and pacing thresholds, and to identify any associated clinical problems. Transtelephonic (TTM) monitoring can be used to supplement clinic visits to confirm adequate battery status and ventricular capture. TTM patients apply a magnet to the pacemaker, which results in asynchronous pacing at a model-specific rate that relates to the battery status. Newer devices with home monitoring capability provide more complete remote diagnostics, including transmission of intracardiac electrograms and linking to wireless blood pressure and weight monitors. Transmission can be automated so that these devices have the advantage of providing alerts for device malfunction or high-rate events. Battery longevity ranges from 7 to 10 years and can be improved by minimizing the pacing output and avoiding unnecessary stimulation. Stored diagnostic tests, including histograms, are often useful when patients have symptoms suggestive of pacemaker malfunction or arrhythmias.

Practical Points

- Bradycardia is associated with a wide spectrum of symptoms ranging from syncope to fatigue and exercise intolerance.
- Documentation and characterization of the rhythm during bradycardia are helpful in determining the origin, prognosis, and therapy.
- A continuous-loop recorder is a better test than a Holter monitor for evaluating a patient with infrequent symptoms suggestive of bradycardia.
- An implantable loop recorder is currently available as an alternative to prolonged monitoring with an external loop recorder.
- Causes of bradycardia can be divided into sinus node dysfunction or atrioventricular conduction disturbances.

- Atrioventricular block that is associated with slowing of the sinus rate is caused by an increase in vagal tone and usually does not indicate a need for pacing.
- The ACLS guidelines are useful during the acute management of symptomatic bradycardia.
- Long-term management of symptomatic bradycardia requires implantation of a permanent pacemaker.
- The American College of Cardiology/American Heart Association guidelines provide accepted indications for pacemaker implantation.
- Implantation of a prophylactic defibrillator with pacing capabilities rather than a pacemaker alone should be considered for patients who require pacing and who are at high risk for sudden cardiac death.

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Infective Endocarditis

18

Ragavendra R. Baliga and Sunil K. Das

Definition

Infective endocarditis (IE) is defined as infection of the vascular endocardium typically involving heart valves (Fig. 18.1) and congenital heart defects. Other arterial vascular beds may also be involved. The hallmark of the infection is known as vegetation, which may vary in size ranging from millimeter to centimeters consisting mainly of a fibrin-platelet matrix infiltrated by abundant microorganisms. The disease may occur in an acute (or a fulminating form) or in a chronic insidious form known as subacute bacterial endocarditis.

Acute IF is associated with a severe rapid and destructive process often caused by *Staphylococcus aureas*. Both normal and damaged valves may be affected by the organism. In the subacute form viridian streptococcus is often the cause of the endocarditis. It usually affects previously damaged heart valves and certain congenital defects.

It is estimated that nearly 40,000 to 50,000 new cases of IE are diagnosed yearly in the US [1]. This number continues to rise. The 1-year mortality associated with IE has not improved over two decades, despite trends toward earlier diagnosis and surgical intervention. Men appear to be more prone than women to develop IE with a male-female case ratio greater than 2:1 [2]. The estimated annual incidence of IE is 3 to 9.3 cases per 100,000 in 1998 to 15 per 100,000 in 2011 and this incidence is greater in urban areas, 11.6 cases versus 5 cases per 100,000 person years in semi-urban regions [3, 4]. A follow-up study from the same semi urban region spanning three decades showed that the incidence has remained remarkably unchanged [5]. Older individuals (>60 years) seem to be more susceptible to the disease [6].

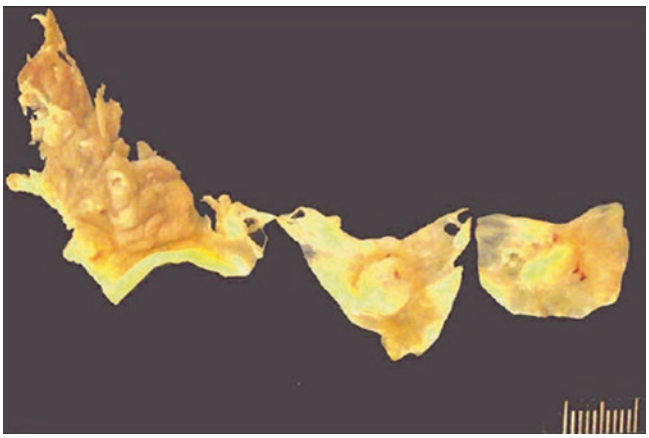

Fig. 18.1 Gross photograph of excised three cusp aortic valve with infective endocarditis. The left cusp has adherent infected thrombus (vegetation). The middle cusp has a small non-ruptured acquired aneurysm (windsock lesion) related to the infection. Ruler = 1 cm. (From Venoit [18]; with permission)

Health care-acquired IE now accounts for 34% of all cases; hemodialysis, non-hemodialysis intravascular catheters, prosthetic heart valves (Fig. 18.2), cardiac implantable electrophysiological devices (CIEDs) and invasive procedures are commonly associated with infection. Community-associated infective endocarditis accounts for nearly 70% of the cases and is typically associated with oral, gastrointestinal or cutaneous bacterial organisms.

A normal cardiac valve is usually resistant to endocarditis. However under certain circumstances such as when a virulent organism is involved or when the host is immunocompromised as in an injection drug user, a normal valve may become infected. In most cases of IE underlying valvular or congenital heart defects are present. Blood flow turbulence induced by lesions such as valvular insufficiency causes further trauma to the endothelial surface promoting the aggregation and deposition of platelet-fibrin matrix over the damaged surface. These aggregates can become secondarily infected from bacteremia from various sources resulting in typical vegetations containing abundant microorganisms.

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Fig. 18.2 Infection of a biologic prosthetic valve with multiple vegetations on valve leaflets and cusps. (From Wang and Cabell [19]; with permission)

Usual Causes

Nearly 50% of individuals who develop native valve endocarditis (NVE) appear to have some predisposing structural cardiac abnormalities. These include rheumatic heart disease mainly mitral valve involvement, congenital defects mainly ventricular septal defect, patent ductus arteriosus, bicuspid aortic valves and coarctation of aorta. Other conditions such as mitral valve prolapse with mitral regurgitation, degenerative valvular disease and hypertrophic obstructive cardiomyopathy are also considered risk factors for IE. Patients with prior prosthetic cardiac valves, including transcatheter aortic valve replacement (TAVR), are considered at high risk for IE (PVE). Injection drug users are particularly susceptible to both right and left sided endocarditis. Infective endocarditis associated with IV drug abuse has increased in the US from 7% of the hospitalizations in 2000 to 12% in 2013. Another study reported that in parallel with the opioid epidemic in the United States IV drug abuse associated infective endocarditis increased from 14% of the infective endocarditis hospitalizations in 2009 to 56% in 2014. Nosocomial source of infection from medical intervention such as use of intravenous catheters, pacemakers, dialysis shunts, and prosthetic vascular grafts should not be overlooked as contributors to risk of IE in susceptible individuals. Currently principal risk factors include immunosuppression hemodialysis, venous catheters, prosthetic valve replacement and IV drug abuse.

Almost any microorganism can cause IE but the three most common bacteria incriminated include Staphylococcus aureus, Streptococcus viridans, and Enterococcus faecalis. *Staphylococcus aureus* is now the most common organism, accounting for approximately 40% of cases in the US. It is also the most common cause of prosthetic valve IE, often requiring redo-surgery and has mortality rates of ~50% in some centers. The most common organism in patients who have undergone TAVR is *Enterococcus* (34.4%) with *S. aureus* accounting for only 6.2% of all organisms. The risk factors for developing infective endocarditis in TAVR patients include male gender, younger age, diabetes mellitus and moderate to severe aortic regurgitation. *S. aureus* can cause both acute and subacute endocarditis. It is the commonest offending micro-organism among injection drug users (IDU). Based on the International Collaboration on Endocarditis-Prospective Cohort Study there appears to be a variation in the risk characteristics of patients who developed S. aureus endocarditis in the different countries [7]. Thus cases in the United States were more likely to be hemodialysis dependent, a diabetic, and likely to have intravascular devices, pacemakers and central venous catheters. A nosocomial mode of infection seemed more likely than the community acquired source. Coagulase-negative staphylococci account for approximately 10% of cases and are often the causative organism in native valve endocarditis and prosthetic valve endocarditis occurring in the first year after initial surgery. Coagulase negative staphylococci are important organisms related to prosthetic valve and cardiac devices. These coagulase negative bacteria are often resistant to methicillin therapy and in the case of *Staphylococcus lugdunensis* they cause highly destructive lesions of the valve and perivalvular structures. Oral streptococci—S. viridians, an alpha-hemolytic streptococcus is responsible for approximately 20% of cases. These bacteria are normal commensals of the pharynx and upper respiratory tract. Other streptococci approximately 10%; and HACEK (*Hemophilus, Aggregati bacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella species*) organisms, zoonoses, and fungi collectively account for <5%. Approximately 10–20% of patients have negative blood cultures suggesting that either the patient was exposed to antibiotics before the diagnosis of IE or the IE is caused by fastidious organisms. In 60% of the latter cases the pathogen is identified by techniques such as blood or valve polymerase-chain reaction (PCR), serologic testing or other specialized microbiologic techniques for diagnosis—the most frequent being brucella, bartonella, *Coxiella burnetti*, HACEK organisms and *Tropheryma whipplei*. Coagulase negative staphylococci (*S. epidermidis*), fungi (Histoplasma, Candida, Aspergillus), and Brucella species are organisms that commonly cause infection in patients with prosthetic valves, intravenous drug abusers, and alcoholic persons. Since *E. faecalis* is found in the perineal region and feces, genitourinary procedures, pelvic surgery, pelvic infections, and prostatic disease in older men are predisposing factors for this infection. *Streptococcus bovis* present in

the bowel often causes IE in the elderly. There appears to be striking relationship between this organism and colonic abnormalities including adenoma and carcinoma. *C. burnetii* is a rickettsia that is widespread in both domestic and farm animals. It spreads to humans through aerosols, dust, and unpasteurized milk. HACEK an acronym for a group of fastidious organism (Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus (Haemophilus) actinomycetemcomitans, Cardiobacterium hominis, Eikenella species, and Kingella species, may account for 5–10% of cases of IE.

Other causative bacteria include *Streptococcus pyogenes* and Neisseri and Pseudomonas. The blood culture may occasionally be negative after 7 days usually termed culture negative endocarditis. Prior antibiotic use or involvement of fastidious bacteria or fungi may account for this phenomenon (Table 18.1). When blood cultures have initially tested negative a systematic approach that includes serological studies, polymerase chain reaction (PCR) of the heart valves and histopathology have increased the diagnostic yield.

Table 18.1 Epidemiological clues that may be helpful in defining the etiological diagnosis of culture-negative endocarditis

Epidemiological feature	Common microorganism
IDU	S aureus, including community-acquired cocacillin-resistant strains
	Coagulase-negative staphylococci
	β-Hemolytic streptococci
	Fungi
	Aerobic Gram-negative bacilli, including
	Pseudomonas aeruginosa
	Polymicrobial
Indwelling cardiovascular medical devices	S aureus
Coagulase-negative staphylococci	
	Fungi
Aerobic Gram-negative bacilli	
	Corynebacterium sp.
Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion	Enterococcus sp.
	Group B streptococci (S agalactiae)
	Listeria monocytogenes
	Aerobic Gram-negative bacilli
	Meisseria gonorrhoeae
Chronic skin disorders, including recurrent infections	Saureus
	β-Hemolytic streptococci
Poordental health, dental procedures	VGS
	Nutritionally variant streptococci
	Abiotrophia defectiva
	Granuiicatella sp.
	Gemella sp.
	HACEK organisms
Alcoholism, cirrhosis	Bartonella sp.
	Aeromonas sp.
	Listeria sp.
	S pneumoniae
	β-Hemolytic streptococci
Burn	S aureus
	Aerobic Gram-negative bacilli, including
	P aeruginosa
	Fungi
Diabetes mellitus	S aureus
	β-Hemolytic streptococci
	S pneumoniae
Early (≤years) prosthetic valve placement	Coagulase-negative staphylococci
	S aureus
	Aerobic Gram-negative bacilli
	Fungi
	Corynebacterium sp.
	Legionella sp.

(continued)

Types of Endocarditis

Acute Endocarditis

The onset usually dates to a preceding suppurative infection or to intravenous drug abuse. Persistent fever, new heart murmurs, vasculitis, hemorrhagic petechiae, embolic phenomena and metastatic abscesses, and development of heart failure are suggestive of acute endocarditis. The clinical presentation of fevers, rigors and systemic complication s is not distinguishable from other causes of sepsis of sepsis except when there is a new onset heart murmur. *S. aureus* is usually implicated in acute endocarditis.

Subacute Endocarditis

The onset of illness is insidious, and the date of onset is usually unclear. Patients present with systemic symptoms such as fever, malaise, anorexia, weight loss, rigors, arthralgia, symptoms of heart failure, or embolism. Heart failure results from destruction of valve or rupture of chordae, and in these cases, the onset may be more fulminant. Embolic phenomena include stroke, pulseless limbs, pulmonary infarctions, or renal infarctions. Thus, a combination of heart murmur, anemia, hematuria, and renal failure should raise the suspicion of subacute endocarditis.

Prosthetic Valve Endocarditis

There are two modes of onset in PVE. The first has an early onset, develops soon after surgery, and is caused by bacterial contamination of the prosthesis at the time of surgery or

Table 18.1 (continued)

Epidemiological feature	Common microorganism
Late (>1 years) prosthetic valve placement	Coagulase-negative staphylococci
	S aureus
	Viridans group streptococci
	Enterococcus species
	Fungi
	Corynebacterium sp.
Dog or cat exposure	Bartonella sp.
	Pasteurella sp.
	Capoccytophaga sp.
Contact with contaminated milk or infected farm animals	8 rucella sp.
	Coxiella burnetii
	Erysipelothrix sp.
Homeless, body lice AIDS	Bartonella sp.
	Salmonella sp.
	S pneumoniae
	S aureus
Pneumonia, meningitis	S pneumoniae
Solid organ transplantation	S aureus
	Aspergillus fumigatus
	Enterococcus sp.
	Candida sp.
Gastrointestinal lesions	S gallolyticus (bevis)
	Enterococcus sp.
	Glostridium septicum

Adapted from Baddour et al. [14]
HAC BK indicates Haemophilus species, Aggregatibacter species, Cardiobacterium nomiris, Ellenella cornodens, and Kingella species, *IDU*, injection drug use, and *VGS* viridans group streptococci

during the perioperative due to septicemia. The second has a late onset and is caused by infection of the valve as a result of persistent bacteremia. Infection of the valve ring occurs in both types, vegetations can interfere with valve function and myocardial abscesses can interfere with cardiac conduction system.

Clinical Features of Infective Endocarditis

Symptoms

The symptoms and signs and their frequencies are shown in Table 18.2. Nonspecific symptoms of inflammation, including intermittent fever, malaise, anorexia, weight loss, and rigors, may occur. Fever may be absent in moribund or immunocompromised individuals. Some patients also complain of myalgia and arthralgia. Endocarditis must always be suspected in a patient with a heart murmur and fever. Progressive cardiac failure is another presenting feature, and the onset of heart failure can be dramatic when there is destruction of a valve. Emboli from vegetations can result in a pulseless limb, stroke, renal infarction, or pulmonary infarction. Loin pain and arthralgia may occur due to immune complex deposition. Low lumbar back pain is a fairly typical complaint although this has to be elicited by gentle pressure on the lower back. The cause of the pain is unclear.

Table 18.2 Clinical features of infective endocarditis

Symptoms	Percentage	Signs	Percentage
Fever	80–85	Fever	80–90
Chills	42–75	Murmur	80–85
Sweats	25	Changing/new murmur	10–40
Anorexia	25–55		
Weight loss	25–35	Neurologic abnormalities[b]	30–40
Malaise	25–30		
Dyspnea	20–40	Embolic event	20–40
Cough	25	Splenomegaly	15–50
Stroke	13–20	Clubbing	10–20
Headache	15–40	Peripheral manifestation	
Nausea/vomiting	15–20		
Myalgia/ arthralgia	15–30	Osler nodes	7–16
Chest pain[a]	8–35	Splinter hemorrhage	5–15
Abdominal pain	5–15		
Back pain	7–10	Petechiae	10–40
Confusion	10–20	Janeway lesion	6–10
		Retinal lesion/Roth spots	4–10

[a]More common in intravenous drug abusers
[b]Central nervous system

Signs

Cardiac: a change in the character of an existing murmur or the development of a new systolic murmur must raise the suspicion of infective endocarditis. In some instances, the only finding may be a "trivial" aortic regurgitation. In right-sided endocarditis, murmurs are not usually present.

Vascular lesions: Such lesions include petechiae, Roth's spots (Fig. 18.3), Janeway's lesions, subungual splinter hemorrhages, and Osler's nodes. Petechial or mucosal hemorrhages are caused by vasculitis and are typically small and red with a pale center. They are seen on the conjunctiva or pharyngeal mucosa. Those seen on the retina are called Roth's spots Janeway's lesions are flat, small, erythematous macules that are not tender and seen mainly on the hypothenar and thenar eminences. These lesions blanch with pressure. Osler's nodes are painful, tender, hard, subcutaneous swellings that occur in the palms, soles, toes, and fingers.

Clubbing of fingers: Clubbing of fingers typically occurs in persons with subacute bacterial endocarditis. This is, however, a late manifestation and is rarely seen nowadays.

Splenomegaly: Splenomegaly is a feature of subacute endocarditis, and usually the spleen is mildly enlarged.

Renal manifestations: Microscopic hematuria is almost always present. Frank hematuria is suggestive of renal infarction caused by emboli. Acute glomerulonephritis and renal abscesses are other manifestations.

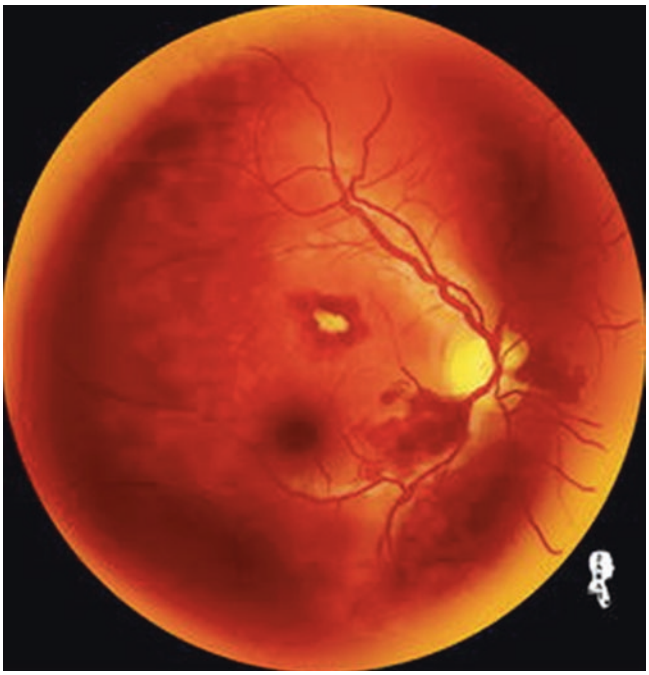

Fig. 18.3 Roth's spots. (From Al-Tubaikh [20]; with permission)

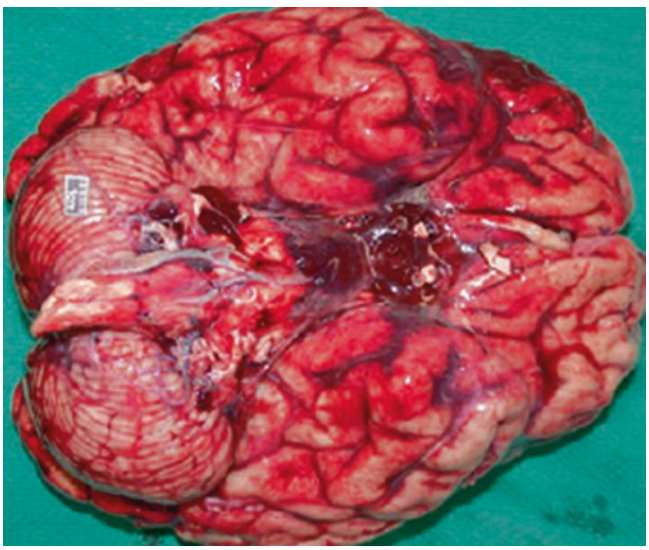

Fig. 18.4 Gross photograph of the base of the brain with adherent blood clot. Subarachnoid hemorrhage occurred due to a ruptured mycotic cerebral artery aneurysm. The mitral valve was infected with bacteria. Ruler = 1 cm. (From Venoit [18]; with permission)

Arthritis: Arthritis of major joints has been reported frequently.

Embolic phenomena: Stroke can be caused by emboli to the middle cerebral artery and its branches. Vegetations can embolize and result in infarction of a limb, pulmonary infarction, and coronary infarctions. Mycotic aneurysms can occur anywhere on the vascular tree; when cerebral vessels are affected, there may be cerebral hemorrhage (Fig. 18.4). Extracranial mycotic aneurysms are usually asymptomatic until they rupture or leak. These can occur in intrathoracic or intraabdominal vessels.

Helpful Tests

Laboratory Tests: Typically, affected patients have normocytic normochromic anemia. There usually is an increase in neutrophils with mild thrombocytopenia. Markers of inflammation, including the erythrocyte sedimentation rate and C-reactive protein, are increased. There may be hemolysis with paraprosthetic leaks.

Liver function tests: There may be mild derangement of liver function test results, particularly a raised alkaline phosphatase level.

Immunoglobulin: There is an increase in serum immunoglobulin levels.

Complement: Both total complement and C3 complement levels are decreased as a result of immune complex formation.

Urine: Microscopic hematuria is an almost constant phenomenon, and proteinuria may occur.

Blood cultures: Blood cultures are positive in about 90% of cases permitting identification of the suspected pathogen and determination of susceptibility of the organism to antimicrobial agents. At least three separate sets of cultures, 1 h apart from separate venipuncture samplings, with at least 20 mL of blood from each venipuncture should be taken. Each set equals one aerobic bottle and one anaerobic bottle. Special cultures may be required for HACEK organisms and Bartonella, Legionella, Brucella, and Histoplasma species. The administration of antibiotics before obtaining blood cultures may reduce the yield of isolated pathogens by 35 or 40%. Polymerase chain reaction testing on blood is useful when the suspected pathogens are *Tropheryma whippleii* or Bartonella species.

Serologic tests: serologic tests may be required when uncommon organisms, including Coxiella, Chlamydia, Candida, Bartonella, and Brucella species, are suspected.

Chest radiograph: Chest radiography is useful for documenting pulmonary septic emboli in right-sided endocarditis or for confirming evidence of cardiac failure.

Electrocardiogram: electrocardiography may show defects in cardiac conduction or, in rare cases myocardial infarction caused by emboli.

Echocardiography: Fig. 18.5 and Tables 18.3 and 18.4 show the recommendations for the use of echocardiography in the diagnosis of IE.

Transthoracic echocardiography: four major echocardiographic features of infective endocarditis are typical vegetations, abscesses, new prosthetic valve dehiscence, or new regurgitation, which must be interpreted in combination

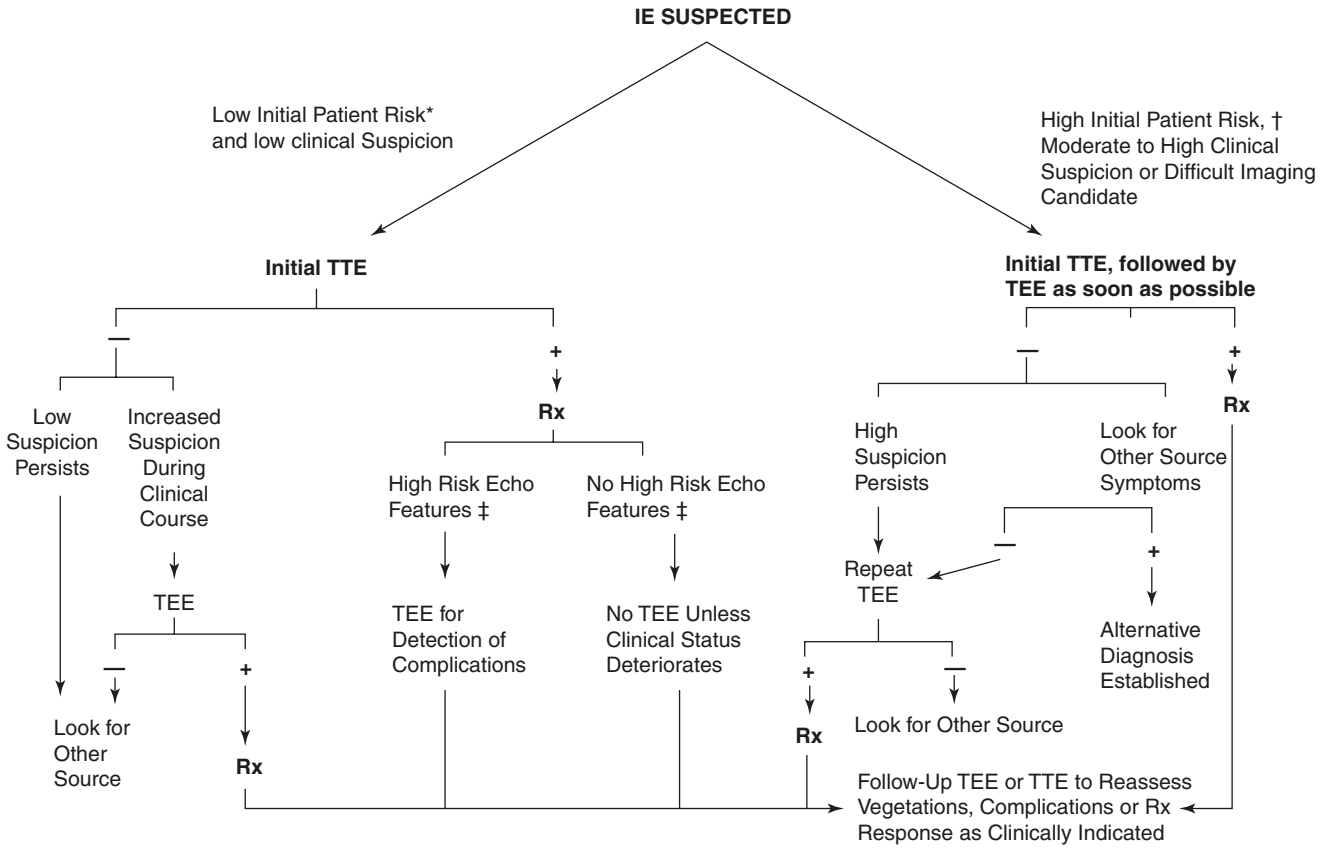

Fig. 18.5 An approach to the diagnostic use of echocardiography (echo). Rx indicates prescription; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography. ∗For example, a patient with fever and a previously known heart murmur and no other stigmata of infective endocarditis (IE). †High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. ‡High-risk echocardiographic features include large or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction (see text). (Adapted from Baddour et al. [14])

Table 18.3 2015 AHA recommendations for echocardiography in infective endocarditis

Early
Echocardiography as soon as possible (<12 h after initial evaluation)
TEE preferred; obtain TTE views of any abnormal findings for later comparison
TTE if TEE is not immediately available
TTE may be sufficient in small children
Repeat echocardiography
TEE after positive TTE as soon as possible in patients at high risk for complications
TEE 3–5 days after initial TEE if suspicion exists without diagnosis of IE or with worrisome clinical course during early treatment of IE
Intraoperative
Prepump
Identification of vegetations, mechanism of regurgitation, abscesses, fistulas, and pseudoaneurysms
Post pump
Confirmation of successful repair of abnormal findings
Assessment of residual valve dysfunction
Elevated afterload if necessary to avoid underestimating valve insufficiency or presence of residual abnormal flow
Completion of therapy
Establish new baseline for valve function and morphology and ventricular size and function
TTE usually adequate; TEE or review of intraoperative TEE may be needed for complex anatomy to establish new baseline

TEE indicates transesophageal echocardiography, and *TTE*, transthoracic echocardiography

Table 18.4 Echocardiographic features that suggest potential need for surgical intervention

Vegetation
Persistent vegetation after systemic embolization
Anterior mitral leaflet vegetation, particularly with size >10 mm[a]
≥1 embolic events during first 2 weeks of antimicrobial therapy[a]
Increase in vegetation size despite appropriate antimicrobial therapy[a,b]
Valvular dysfunction
Acute aortic or mitral insufficiency with signs of ventricular failure[b]
Heart failure unresponsive to medical therapy[b]
Valve perforation or rupture[b]
Perivalvular extension
Valvular dehiscence, rupture, or fistula[b]
New heart block[b,c]
Large abscess or extension of abscess despite appropriate antimicrobial therapy[b]

See text for more complete discussion of indications for surgery based on vegetation characterizations

[a]Surgery may be required because of risk of embolization

[b]Surgery may be required because of heart failure or failure of medical therapy

[c]Echocardiography should not be the primary modality used to detect or monitor heart block

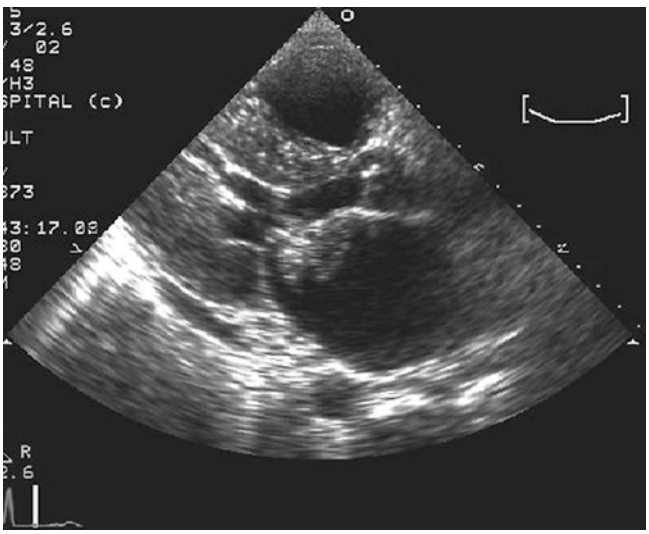

Fig. 18.6 Two-dimensional echocardiogram showing vegetation on the mitral valve

with other clinical features [8] (Fig. 18.6). Transthoracic echocardiography cannot exclude the diagnosis of infective endocarditis, and in a fifth of the cases, vegetations may not be detected because of obesity, chest wall abnormalities, or chronic obstructive pulmonary disease. For native valve vegetations, this procedure has better specificity (~90%), but sensitivity is only 50–90% [9–11] and for prosthetic valve endocarditis the sensitivity is lower ~40 to 70% because of its relatively low resolution. The procedure is useful in detecting vegetations larger than 2 mm in diameter,

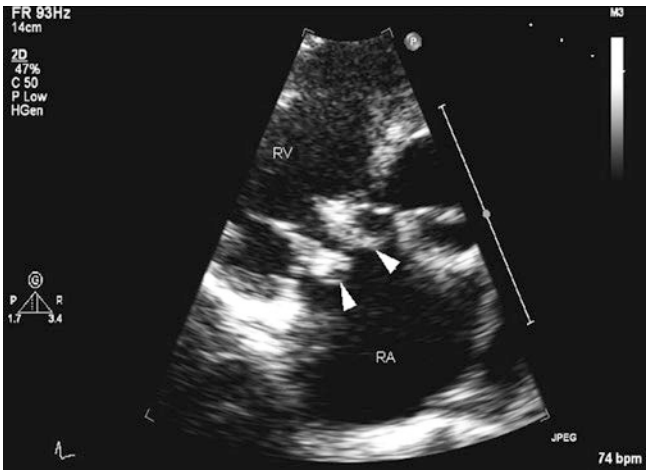

Fig. 18.7 2D echocardiogram showing vegetation involving tricuspid valve vegetation (arrows) in an injection drug user

particularly on right-sided valves that are close to the anterior portion of the chest (Fig. 18.7) [12]. It is not useful in excluding prosthetic valve endocarditis, perforation of leaflets, fistulae, or periannular abscess [11, 13]; therefore, a negative study result in a suspected case does not rule out endocarditis. The other limitation is that a positive study result does not rule out major complications. Since all patients with IE are at risk of recurrent infection, obtaining a new baseline after therapy is recommended particularly to determine the presence of vegetations and valvular insufficiency. Also post-treatment TTE can guide both medical management and the discussion of the appropriate timing of surgical interventions [14].

Transesophageal echocardiography: this procedure is the investigation of choice and more accurately identifies infective endocarditis (Figs. 18.8 and 18.9). Transesophageal echocardiography is particularly suitable for investigating PVE. The sensitivity is 86–94% and specificity is 88–100%. Abscesses of the aortic root, a serious complication, are only reliably excluded by this procedure. Because of the low sensitivity of transthoracic echocardiography for intracardiac abscesses, a surgically correctable condition, transesophageal echocardiography should be performed in all causes of suspected abscess. It has a specificity of 94% and sensitivity varies from 76 to 100% for perivalvular infection because the esophageal transducer allows examination of the root of the aorta and basal part of the ventricular septum, where most such complications occur. However, the technique is not 100% sensitive for other infection, and in such situations, the diagnosis may have to be made on clinical grounds. False-negative findings result from prior embolization of vegetations, small size of vegetations, or inadequate views to detect small abscesses. Another limitation is that prosthetic valve shadows may not allow complete visualization; therefore, multiple views and planes must be studied in order to

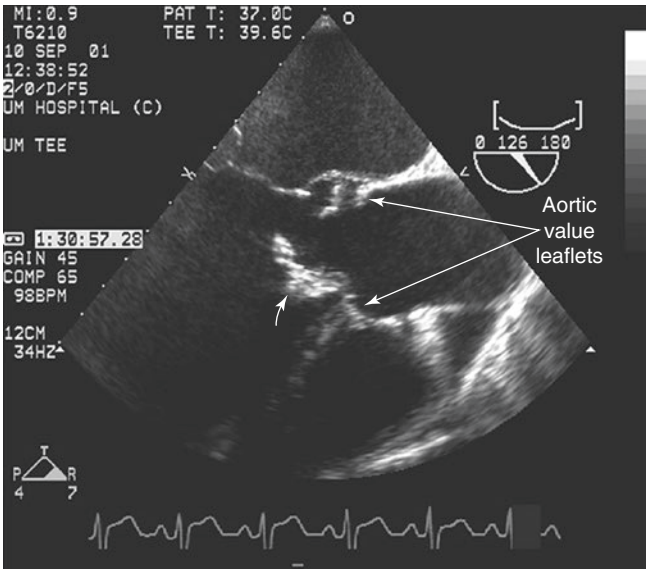

Fig. 18.8 Transesophageal echocardiogram in a patient with aortic valve endocarditis and vegetations. Vegetations attached to the aortic valve leaflets (*arrows)* can be identified; their presence was subsequently confirmed by surgery. *LA* left atrium, *LV* left ventricle

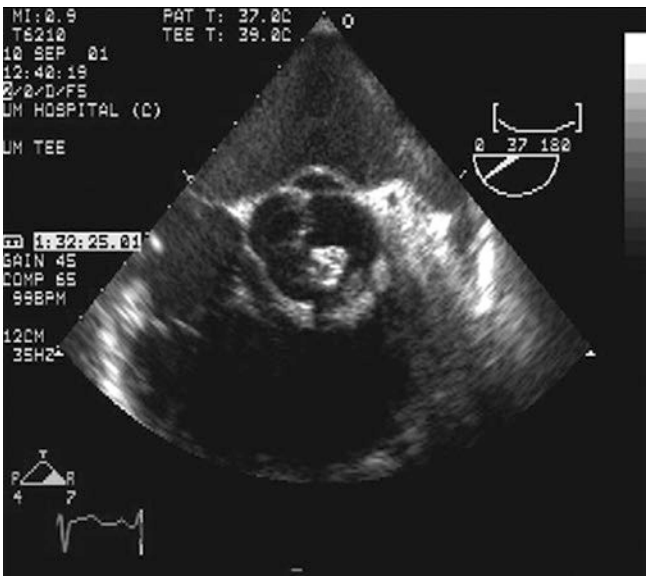

Fig. 18.9 Aortic valve endocarditis

decrease the number of false-negative findings. Also, a combination of transthoracic and transesophageal techniques may have to be used to obtain accurate images; when both studies yield negative results, the negative predictive value approaches 95%. The American Heart Association (AHA) 2015 Scientific Statement recommends [14] that when clinical suspicion of infective endocarditis is high and the transesophageal study result is negative, a repeat study should be considered within 3–5 days or sooner to demonstrate previously undetected vegetations or abscesses. After a course of therapy, vegetations may persist in nearly 60% of the patients, and this does not correlate with subsequent complications; however, any increase in the size of the vegetations with therapy heralds late complications, despite absence of persistent bacteremia or clinical features of ongoing infection [15, 16]. The 2015 AHA IE Scientific Statement recommends that repeat TEE should be done after an initially positive TEE if clinical features suggest a new development of intracardiac complications [14]. Transesophageal echocardiography is preferred to transthoracic echocardiography in suspected CIED infections because it allows visualization of the extracardiac portion of the leads.

3-D Echocardiography: Remains an investigation tool because of limited temporal and lateral resolution resulting in over-estimation of vegetation size [14].

Cardiac CT: now has a class II, Level of Evidence B recommendation for use in infective endocarditis and may be useful particularly when anatomy is not well delineated by echocardiography. It is possibly superior to TEE to delineate paravalvular anatomy and complications such as paravalvular abscesses and mycotic organisms. Combined CT imaging with metabolic imaging by PET is currently an investigational tool and can be helpful with detection of peripheral emboli and cardiac and extra-cardiac sites of infection. It is useful in suspected CIED endocarditis when transesophageal echocardiography is equivocal or negative.

Diagnosis

Unexplained fever lasting more than 48 h in a patient with predisposing factors for IE including underlying valvular, congenital heart disease, prior cardiac prosthetic valve placement, patients on hemodialysis, immunosuppressive states, history of injection drug abuse and prior history of endocarditis should strongly suggest endocarditis. Approximately 50% of subjects who develop NVE seem to have some risk factors. Recent dental, gastrointestinal, urologic or gynecologic manipulation inducing transient bacteremia may be incriminated as a cause of the infection. A positive blood culture together with typical echocardiographic changes constitutes a strong diagnosis of IE. The Duke Criteria has been utilized to facilitate diagnosis: definite, possible or rejected diagnosis of infective endocarditis (Tables 18.5 and 18.6). A definite diagnosis requires isolation of the causative microorganism, a histologic diagnosis of the vegetation, or the presence of clinical criteria. Clinical criteria are defined specifically in Table 18.6; a definite diagnosis of infective endocarditis requires the presence of two major criteria, one major and three minor criteria, or five minor criteria. A possible diagnosis includes findings that fall short of definite but not "rejected." The diagnosis is rejected when there is a firm alternative diagnosis for the clinical manifestations, when

Table 18.5 Definition of infective endocarditis according to the proposed Modified Duke Criteria[a]

Definite infective endocarditis
Pathological criteria
1. Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
2. Pathological lesions; vegetation, or intracardiac abscess confirmed by histological examination showing active endocarditis
Clinical criteria
1. 2 major criteria, or
2. 1 major criterion and 3 minor criteria; or
3. 5 minor criteria
Possible infective endocarditis
1. **1 major criterion and 1 minor criterion;** or
2. **3 minor criteria**
Rejected
1. Firm alternate diagnosis explaining evidence of infective endocarditis; or
2. Resolution of infective endocarditis syndrome with antibiotic therapy for less than 4 days; or
3. No pathological evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for less than 4 days; or
4. Does not meet criteria for possible infective endocarditis, as noted above

From Li et al. [21]; with permission
[a]Modifications are shown in bold type. Reprinted with permission from Li JS, Sexton DJ. Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000:30:633–8(722)

clinical manifestations resolve with a 4-day course of antibiotic therapy, or when pathologic evidence of infective endocarditis is absent at surgery or autopsy, after a 4-day course of antibiotic therapy. Major criteria include positive blood cultures and documentation of endocardial vegetations by echocardiography. Minor criteria include predisposing heart conditions or intravenous drug use, temperature of 38.0 °C, major arterial emboli, septic pulmonary infarctions, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions, glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor (see Table 18.6).

Therapy

The management of a patient with infective endocarditis is a multidisciplinary approach with the involvement of the cardiologist, an Infective disease specialist, and a cardiothoracic surgeon.

Pharmacologic Therapy

Bactericidal antibiotics, selected on the basis of blood culture results and sensitivity, should be administered for at least 4–6 weeks. In febrile patients with suspected endocarditis,

Table 18.6 Definition of terms used in the proposed Modified Duke Criteria for the diagnosis of infective endocarditis[a]

Major criteria
Blood culture positive for IE
Typical microorganisms consistent with IE from two separate blood cultures:
Viridans *streptococci, Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, or Community-acquired *enterococci* in the absence of a primary focus, or
Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
At least two positive cultures of blood samples drawn more than 12 h apart; or
All of three or a majority of greater than four separate cultures of blood (with first and last sample drawn at least 1 h apart)
Single positive blood culture for *Coxiella burnetti* or anti-phase 1 IgG antibody titer greater than 1:900
Evidence of endocardial involvement
Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" try clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
Abscess; or
New partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition, or injection drug use
Fever, temperature greater than 38 °C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
Immunologic phenomena; glomerulonephritis. Osler's nodes, Roth's spots, and rheumatoid factor
Microbiological evidence: positive blood culture but does not meet a major criterion[b] or serological evidence of active infection with organism consistent with IE
Echocardiographic minor criteria eliminated

From Li et al. [21]; with permission
IE indicates infective endocarditis, *TEE* transesophageal echocardiography, and *TTE* transthoracic echocardiography
[a]Modifcations are shown in bold type
[b]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis. Reprinted with permission from Li JS. Sexton DJ. Mick N. et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000:30:633–8 (722)

immediate antibiotic treatment is not necessary (unless there are signs of toxicity); a delay of 48–72 h will allow efforts to identify the organism. When the infecting organism is not isolated, patients may be treated empirically keeping in mind that the pathogen might be resistant to standard therapy. With subsequent identification of the pathogen therapy may be modified.

In acute endocarditis, the antibiotics included should cover for Staphylococcus species; in subacute endocarditis, they should cover for S. viridans. In most instances, a broad-

Table 18.7 Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci (VGS) and Streptococcus gallolyticus (bovis)

Regimen	Dose[a] and route	Duration, weeks	Strength of recommendation	Comments
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 4 or 6 equally divided doses	4	*Class IIa; Level of Evidence B*	Preferred in most patents >65 years or patents with impairment of eighth cranial nerve function or renal function
Or				Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	4	*Class IIa; Level of Evidence B*	
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 6 equally divided doses	2	*Class IIa; Level of Evidence B*	2-weeks regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired eighth cranial nerve function, or Abiotpophia, Granulicatella, or Genella spp. infection; gentamicin does should be adjusted to achieve peak serum concentration of 3–4 μg/mL and tough serum concentration of <1 μg/mL when 3 divided doses are used; there are no optimal drug concentrations for single daily dosing[b]
Or				
Ceftriaxone sodium	2 g/24 h IV or IM in 1 dose	2	*Class IIa; Level of Evidence B*	
Plus				
Gentamicin sulfate[c]	3 mg/kg per 24 h IV or IM in 1 dose	2		
Vancomycin hydrocholoride[d]	30 mg/kg per 24 h IV in 2 equally divided	4	*Class IIa; Level of Evidence B*	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dose should be adjusted to a trough concentration range of 10–15 μg/mL

IM indicates intramuscular, *IV* intravenous, *NVE* native valve infective endocarditis, and *VGS* viridans group streptococci. Minimum inhibitory concentration is ≤0.12 μg/mL. The subdivisions differ from Clinical and Laboratory Standards Institute-recommended break point that are used to define penicillin susceptibly

[a]Doses recommended are for patients with normal renal function

[b]Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist

[c]Other potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses

[d]Vancomycin dosages should be infused during the course of at least 1 h to reduce the risk of histamine-release "red man" syndrome

spectrum combination of gentamicin and penicillin is used, and the choice of antibiotics is adjusted when patients do not respond. Specific antibiotic therapy guidelines as recommended by the ACC/AHA are shown in Tables 18.7, 18.8, 18.9, 18.10, 18.11, 18.12, 18.13, 18.14, 18.15, and 18.16.

Surgical Therapy (Table 18.17): Recommendations for surgical therapy is predominantly based on observational data.

Surgery is indicated in the following situations

- Progressive heart failure.
- Worsening renal function.
- Embolization.
- Failure of medical treatment to control infective process (possible abscess formation), indicated by continuing fever for more than 10 days, rising C-reactive protein concentration, and worsening nephritis.
- Indicators of abscess formation, such as conduction abnormalities, cavity on echocardiography, or prosthetic valve dehiscence.
- Hemodynamic deterioration; for example, pulmonary edema or increasing cardiomegaly.
- Infection by organisms that are difficult to eradicate, such as S. aureus, Candida species, and Aspergillus species.
- Infection of a prosthetic valve or of a prosthetic material.
- Recurrent embolization or enlarging, large vegetations while patient is on effective antimicrobial therapy.

Once the need for surgery is established, early surgery is preferable. Early surgery is associated with lower mortality.

Prognosis: Infective endocarditis has a poor prognosis with in-hospital mortality of 20% and a 6-month mortality of about 30%. And despite advances in care this mortality rate has not improved over the last 20 years because of multiple factors including changing natural history of this condition;

Table 18.8 Therapy of native valve endocarditis caused by strains of viridans group Streptococci and *Streptococcus gallolyticus (bovis)* relatively resistant to penicillin

Regimen	Dose[a] and route	Duration, weeks	Strength of recommendation	Comments
Aqueous crystalline penicillin G sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	4	*Class IIa; Level of Evidence B*	It is reasonable to treat patients with IE caused penicillin-resistant (MIC ≥0.5 μg/mL) VGS strains with a combination of ampicillin or penicillin plus gentamicin as done for enterococci IE with infectious diseases consultation (*Class IIa; Level Evidence C*). Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists
Plus				
Gentamicin sulfate[b]	3 mg/kg per 24 h IV or IM in 1 dose	2		Ceftriaxone may be a reasonable alternative treatment option for VGS isolates that are susceptible to ceftriaxone (*Class IIa; Level of Evidence C*)
Vancomycin hydrochloride[c]	30 mg/kg per 24 h IV in 2 equally divided doses	4	*Class IIa; Level of Evidence C*	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone therapy

IE indicates infective endocarditis, *IM* intramuscular, *IV* Intravenous, *MIC* minimum inhibitory concentration, *NVE* native valve infective endocarditis, end VGS, viridans group streptococci. MIC is >0.12 to <0.5 μg/mL for penicillin. The subdivisions differ from Clinical and Laboratory Standards Institute-recommended break points that are used to define penicillin susceptibility

[a]Doses recommended are for patients with normal renal function

[b]See Table 18.9 for appropriate dose of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses

[c]See Table 18.9 for appropriate dosage of vancomycin

Table 18.9 Therapy for native valve or other prosthetic material caused by VGS and Streptococcus gallolyticus (bovis)

Regimen	Dose[a] and route	Duration, weeks	Strength of recommendation	Comments
Penicillin-susceptible strain (≤0.12 μg/mL)				
Aqueous crystalline penicillin G sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	*Class IIa; Level of Evidence B*	Penicillin or ceftriaxone together with gentamicin has not demonstrated superior cure rates compared with monotherapy with penicillin or ceftriaxone for patients with nighty susceptible strain; gentamicin therapy should not be administered to patients with creatinine clearance <30 mL/min
Or				
Ceftriaxone	2 g/24 h IV or IM in 1 dose	6	*Class IIa; Level of Evidence B*	
With or without Gentamicin sulfate[b]	3 mg/kg per 24 h IV or IM in 1 dose	2		Apicillin 2 g IV every 4 h is a reasonable alternatives to penicilllin if a penicillin shortage exists
Vancomycin hydrochloride[c]	30 mg/kg per 24 h IV in 2 equality divided doses	6	*Class IIa; Level of Evidence B*	Vancomycin is reasonable only for patients unable to tolerate penicillin or ceftriaxone
Penicillin relatively or fully resistant strain (MIC >0.12 μg/mL)				
Aqueous crystalline penicillin sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	*Class IIa; Level of Evidence B*	Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists
Or				
Ceftriaxone	2 g/24 h IV/IM in 1 dose	6	*Class IIa; Level of Evidence B*	
Plus				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 1 dose	6		
Vancomycin hydrochloride	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIa; Level of Evidence B*	Vancomycin is reasonable only for patients unable to tolerate penicillin or ceftriaxone

IM indicates intramuscular, *IV* intravenous, *MIC* indicated minimum inhibitory concentration, and *VGS* viridans group streptococci

[a]Doses recommended are for patients with normal renal function

[b]See Table 18.9 for appropriate dose of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis resulting from VGS, as a second option, gentamicin can be administered daily in 3 equally divided doses

[c]See text and Table 18.9 for appropriate dose of vancomycin

Table 18.10 Therapy for native valve endocarditis caused by Staphylococci

Regimen	Dose[a] and route	Duration, weeks	Strength of recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 4–6 equally divided doses	6	*Class I; Level of Evidence C*	For complicated right-sided ID and for left-sided IE; for uncomplicated right-sided IE, 2 weeks (see text)
For penicillin-allergic (non anaphylactoid type) patients				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin
Cefazolin[a]	6 g/24 h IV in 3 equally divided doses	6	*Class I; Level of Evidence B*	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases
Oxacillin-resistant strains				
Vancomycin[b]	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class I; Level of Evidence C*	Adjust vancomycin dose to achieve trough concentration of 10–20 μg/mL (see text for vancomycin alternatives)
Daptomycin	≥8 mg/kg/dose	6	*Class IIb; Level of Evidence B*	Await additional study data to define optimal dosing

IE indicates infective endocarditis, *IV* intravenous, and *NVE* native valve infective endocarditis
[a]Doses recommended are for patients with normal renal function
[b]For specific dosing adjustment and issues concerning vancomycin, see Table 18.9 footnotes

Table 18.11 Therapy for endocarditis involving a prosthetic valve or other prosthetic material caused by Staphylococci

Regimen	Dose[a] and route	Duration, weeks	Strength of recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV 6 equally divided doses	≥6	*Class I; Level of Evidence B*	Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 18.6 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non-immediate-type hypersensitivity reactions to penicillins
Plus				
Rifampin	900 mg per 25 h IV or orally in 3 equally divided doses	≥6		
Plus				
Gentamicin[b]	3 mg/kg per 24 h IV or IM in 2 or 3 equally divided doses	2		
Oxacillin-resistant strains				
Vancomycin	30 mg/kg 24 h in 2 equally divided doses	≥6	*Class I; Level of Evidence B*	Adjust vancomycin to a trough concentration of 10–20 μg/mL (see text for gentamicin alternatives)
Plus				
Rifampin	900 mg/24 h IV/PO in 3 equally divided doses	≥6		
Plus				
Gentamicin	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	2		

IM indicates intramuscular, and *IV* intravenous
[a]Doses recommended are for patients with normal renal function
[b]Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 18.9 for appropriate dose of gentamicin

Table 18.12 Therapy for endocarditis involving a native or prosthetic valve or other prosthetic material resulting from Enterococcus species caused by strains susceptible to penicillin and gentamicin in patients who can tolerate **β**-lactam therapy[a]

Regimen	Dose[b] and route	Duration, weeks	Strength of recommendation	Comments
Either				
Ampicillin sodium	2 g IV every 4 h	4–6	*Class IIa; Level of Evidence B*	Native valve: 4-weeks therapy recommended for patients with symptoms of illness <3 months; 6-weeks therapy recommended for native valve symptoms >3 months and for patients with prosthetic valve or prosthetic material. Recommended for patients with creatinine clearance >50 mL/min
Or		4–6	*Class IIa; Level of Evidence B*	
Aqueous penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses	4–6		
Plus				
Gentamicin sulfate[c]	3 mg/kg ideal body weight in 2–3 equally divided doses			
Or				
Double β-lactam Ampicillin	2 g IV every 4 h	6	*Class IIa; Level of Evidence B*	Recommended for patients with initial creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during therapy with gentamicin-containing regimen
Plus				
Ceftriaxone	2 g IV every 12 h	6		

IV indicates intravenous
[a]For patients unable to tolerate a β-lactam, see Table 18.19
[b]Doses recommended are for patients with normal renal and hepatic function
[c]Dose of gentamicin should be adjusted to achieve a peak serum concentration of 3–4 μg/mL and a trough concentration of <1 μg/mL

Table 18.13 Therapy for endocarditis involving a native or prosthetic valve or other prosthetic material resulting from enterococcus species caused by a strain susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate **β**-lactam therapy[a]

Regimen	Dose[b] and route	Duration, weeks	Strength of recommendation	Comments
Double β-lactam				
Ampicillin	2 g IV every 4 h	6	*Class IIa; Level of Evidence B*	Double β-lactam is reasonable for patient with normal or impaired renal function abnormal cranial nerve VIII function or if the laboratory is unable to provide rapid results of streptomycin serum concentration; native valve infection with symptoms of infection <3-months duration may be treated for 4 weeks with the streptomycin-containing regimen. PVE, NVE with symptoms >3 months, or treatment with a double β-lactam regimen require a minimum of 6 weeks of therapy
Plus				
Ceftriaxone	2 g IV every 12 h			
Alternative for streptomycin susceptible/ gentamicin resistant				

(continued)

Table 18.13 (continued)

Regimen	Dose[b] and route	Duration, weeks	Strength of recommendation	Comments
Either Ampicillin sodium	2 g IV every 4 h	4–6	*Class IIa; Level of Evidence B*	Use is reasonable only for patients with availability of rapid streptomycin serum concentrations. Patients with creatinine clearance <50 mL/min during treatment should be treated with double-β-lactam regimen. Patients with abnormal cranial nerve VII function should be treated with double-β-lactam regimen
Or				
Aqueous penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses			
Plus				
Streptomycin sulfate[c]	15 mg/kg ideal body weight per 24 h IV or IM in 2 equally divided doses			

IM indicates intramuscular, *IV* intravenous, *NVE* native valve infective endocarditis, and *PVE* prosthetic valve infective endocarditis
[a]For patients unable to tolerate a β-lactam, see Table 18.19
[b]Doses recommended for patients with normal renal and hepatic function
[c]Streptomycin dose should be adjusted to obtain a serum peak concentration of 20–35 μg/mL and a trough concentration of <10 μg/mL

Table 18.14 Vancomycin-containing regimens for vancomycin- and aminoglycoside-susceptible penicillin-resistant enterococcus species for native or prosthetic valve (or other prosthetic material) ie in patients unable to tolerate **β**-lactam

Regimen	Dose[a] and route	Duration, weeks	Strength of recommendation	Comments
Unable to tolerate β-lactams vancomycin[b]	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIa; Level of Evidence B*	
Plus				
Gentamicin[c]	3 mg/kg per 24 h IV or IM in 3 equally divided doses	6		
Penicillin resistance; intrinsic or β-lactamase producer Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIb; Level of Evidence C*	For β-lactamase–producing strain, if able to tolerate a β-lactam antibiotic, ampicillin-sulbactam[d] plus aminoglycoside therapy may be used
Plus Gentamicin[c]	3 mg/kg per 24 h IV or IM in 3 equally divided doses	6		

IE indicates infective endocarditis, *IM* intramuscular, and *IV* intravenous
[a]Doses recommended are for adults with normal renal function
[b]Dose of vancomycin should be adjusted to obtain a serum trough concentration of 10–20 μg/mL
[c]Dose of gentamicin should be adjusted to obtain serum peak and trough concentrations of 3–4 and <1 μg/mL, respectively
[d]Ampicillin-sulbactam dosing is 3 g/6 h IV

Table 18.15 Therapy for endocarditis involving a native or prosthetic valve or other prosthetic material resulting from enterococcus species caused by strains resistant to penicillin, aminoglycosides, and vancomycin

Regimen	Dose[a] and route	Duration, weeks	Strength of recommendation	Comments
Linezolid or daptomycin	600 mg IV or orally every 12 h	>6	*Class IIb; Level of Evidence C*	Linezolid use may be associated with potentially severe bone marrow suppression, neuropathy, and numerous drug interactions. Patients with IE caused by these strains should be treated by a care team including specialists in infectious diseases, cardiology, cardiac surgery, clinical pharmacy, and in children, pediatrics. Cardiac value replacement may be necessary for cure
	10–12 mg/kg per dose	>6	*Class IIb; Level of Evidence C*	

IE indicates infective endocarditis, and *IV* intravenous
[a]Doses recommended are for patients with normal renal and hepatic function

Table 18.16 Therapy for native valve, prosthetic valve or other prosthetic material endocarditis caused by HACEK[a] microorganisms

Regimen	Dose and route	Duration, weeks	Strength of recommendation	Comments
Ceftriaxone sodium[a]	2 g/24 h IV or IM in 1 dose	4, NVE; 6, NVE	*Class IIa; Level of Evidence B*	Preferred therapy: ceforaxime or another third- or fourth-generation cephalosporin may be substituted
or				
Ampicillin sodium	2 g IV every 4 h		*Class IIa; Level of Evidence B*	Ampicillin sodium may be option if the growth of the isolate is sufficient to permit in vitro susceptibility results
or				
Ciprofloxacin[b]	1000 mg/24 h orally or 800 mg/24 h IV in 2 equally divided doses		*Class IIb; Level of Evidence C*	Fluoroquinolone therapy[c] may be considered for patients un able to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted; fluoroquinolones generally is not recommended for patients <18 years old. Treatment for 6 weeks is reasonable in patients with PVE (*Class IIa; Level of Evidence C*)

HACEK indicates Haemophilus species, Aggregatibacter species, Cartiobacterium hominis, Eikenella corrodens, and Kingella species, *IM* intramuscular, *IV* intravenous, *NVE* native valve infective endocarditis, and *PVE* prosthetic valve infective endocarditis

[a]Patients should be informed that intramuscular injection of ceftriaxone is painful

[b]Dose recommended for patients with normal renal function

[c]Fluoroquinolones are hightly active in vitro against HACEK microorganisms. Published data on the use of fluoroquinolones for endocarditis caused by HACEK are minimal

patients more likely to be older, pathogens are more likely to be resistant to antibiotics and increased prevalence of host factors such as TAVR, hemodialysis, CIEDs. Also patients with infective endocarditis are more likely to have strokes, myocardial infarctions, re-hospitalizations for heart failure and sudden death or ventricular arrhythmia.

Poor prognostic factors include the following:

- Age: In older patients, endocarditis is typically more difficult to treat: elderly patients are poor candidates for surgery, frequently have comorbid conditions, and are more likely develop renal insufficiency.
- Comorbid conditions, including chronic renal or liver disease and immunocompromised states such as acquired immunodeficiency syndrome.
- Prosthetic valve infection, in contrast to native valve infection.
- Right-sided endocarditis.
- Complications such as cardiac failure, embolic phenomena, or persistent pyrexia.

Echocardiographic predictors of poor prognosis including the following:

- Larger vegetations: The increased size is associated with increased risk of emboli and, consequently, need for surgery. It is not associated with increased mortality.
- Destruction or dehiscence of the valve.
- Abscesses of valve ring.
- Fistulae.

Microbiologic predictors of prognosis including the following:

- Low morbidity: infection with S. viridans
- High morbidity: Staphylococcus fungi, and nosocomial infection.

Clinical situations constituting high risk for complications for infective endocarditis include the following:

- Prosthetic cardiac valves.
- Left-sided infective endocarditis.
- S. aureus caused infective endocarditis.
- Fungal infective endocarditis.
- Previous infective endocarditis.
- Prolonged clinical symptoms (3 months or longer).
- Cyanotic or complex congenital heart disease.
- Presence of systemic-to-pulmonary shunts.
- Poor clinical response to antimicrobial therapy.

Prophylaxis

The ACC/AHA guidelines recommend antibiotic prophylaxis in patients with cardiac conditions whose risk of infective endocarditis is judge to be significantly higher than that of the general population [17] and particularly in individuals with a substantially higher rate of morbidity and mortality as a consequence of the infection. These car-

Table 18.17 Indications for surgery in AHA and ESC guidelines

	AHA guidelines 2015 (89)	Class, level of evidence	ESC guidelines 2015 (68)	Class, level of evidence	Timing[a]
Heart failure	Early surgery[b] is indicated in patients with IE who present with valve dysfunction resulting in symptoms or signs of HF	I, B	Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary edema or cardiogenic shock	I, B	Emergency
	Early surgery[b] is indicated in patients with PVE with symptoms or signs of HF resulting from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction	I, B	Aortic or mitral NVE or PVE with severe regurgitation or obstruct ion causing symptoms of HF, or echocardiographic signs of poor hemodynamic tolerance	I, B	Urgent
Uncontrolled infection	Early surgery[b] is indicated in patients when IE is complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	I, B	Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	I, B	Urgent
	Early surgery[b] is reasonable for patients with relapsing PVE	IIa, C			
	Early surgery[b] should be considered, particularly in patients with IE caused by fungi or highly resistant organisms (e.g. VRE, multidrug-resistant gram-negative bacilli)	I, B	Infection caused by fungi or multiresistant organisms	I, C	Urgent/ elective
	Early surgery[b] is indicated for evidence of persistent infection (manifested by persistent bacteremia or fever lasting >5–7 days, and provided that other sites of infection and fever have been excluded) after the start of appropriate antimicrobial therapy	I, B	Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	IIa, B	Urgent
			PVE caused by staphylococci or non-HACEK gram-negative bacteria	IIa, B	Urgent/ elective
Prevention of embolism	Early surgery[b] is reasonable in patients who present with recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy	IIa, B	Aortic or mitral NVE, or PVE with persistent vegetations >10 mm after >1 embolic episode despite appropriate antibiotic therapy	I, B	Urgent
	Early surgery[b] is reasonable in patients with severe valve regurgitation and mobile vegetations >10 mm	IIa, B	Aortic or mitral NVE, with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	IIa, B	Urgent
	Early surgery[b] may be considered in patients with mobile vegetations >10 mm, particularly when involving the anterior leaflet of the mitral valve and associated with other relative indications for surgery	IIb, C	Aortic or mitral NVE. or PVE with isolated very large vegetations (>30 mm)	IIa, B	Urgent
			Aortic or mitral NVE. or PVE with isolated large vegetations (>15 mm) and no other indication for surgery	IIb, C	Urgent

HACEK—*Haemophilus* species, *Aggregatibacter* species, *Cardiobocterium hominis, Eilonells carrodens,* and Jingella species, *HF* heart failure, *NVE* native valve infective endocarditis, *PVE* prosthetic valve infective endocarditis, *VRE* vancomycin-resistant Enterococcus; other abbreviations as in Tables 18.1 and 18.2

From Cahill et al. [22]; with permission

[a]Defined as: emergency surgery—performed within 24 h; urgent surgery—within a few days; elective surgery—after at least 1–2 weeks of antibiotic therapy

[b]Defined as "during initial hospitalization and before completion of a full course of antibiotics"

diac conditions are stratified as high, moderate and negligible risk (Table 18.18).

High-risk conditions include the presence of, (a) prosthetic heart valves including transcatheter-implanted prostheses and homografts, (b) complex cyanotic congenital heart diseases, (c) history of previous endocarditis, even in the absence of other cardiac disease, (d) surgically constructed systemic pulmonary shunts and conduits, (e) prosthetic material used in heart valve repair, such as annuloplasty rings and cords.

Moderate-risk conditions include, (a) uncorrected congenital conditions, such as ventricular septal defect, ostium primum atrial septal defect, patent ductus arteriosus, bicuspid aortic valve, and coarctation of the aorta, (b) acquired

Table 18.18 ACC/AHA and ESC guidelines on use of antibiotic prophylaxis for the prevention of IE

	ACC/AHA	Class, level of evidence	ESC	Class, level of evidence
Dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa[a]	1. Patients with prosthetic cardiac valves 2. Patients with previous IE 3. Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve 4. Patients with CHD, including (a) Unrepaired cyanotic CHD, including palliative shunts and conduits; (b) Completely repaired CHD repaired with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 months after the procedure; or (c) Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device	IIa, B	1. Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair 2. Patients with previous IE 3. Patients with CHD, including (a) Any type of cyanotic CHD (b) Any type of CHD repaired with a prosthetic material, whether placed surgically or by using percutaneous techniques, up to 6 months after the procedure, or lifelong if residual shunt or valvular regurgitation remains	IIa, C
Vaginal delivery[b]	1. Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair[c] 2. Patients with unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits[c]	IIa, C	Not recommended. "During delivery the indication for prophylaxis has been controversial and, given the lack of convincing evidence that infective endocarditis is related to either vaginal or caesarean delivery, antibiotic prophylaxis is not recommended" (145)	III, C

CHD congenital heart disease, *IE* infective endocarditis
From Cahill et al. [22]; with permission
[a]ACC/AHA guidelines on valvular heart disease 2014 and ESC guidelines on infective endocarditis 2015
[b]ACC/AHA management of adults with congenital heart disease 2008 (146); and ESC management of cardiovascular diseases in pregnancy 2011 (145)
[c]Infective endocarditis prophylaxis at the time of vaginal delivery is controversial and not included as an indication in the ACC/AHA guidelines on valvular heart disease 2014 or the main ESC 2015 guidelines

conditions, such as valvular heart disease due to rheumatic heart disease, (c) mitral valve prolapse with regurgitation, (d) hypertrophic obstructive cardiomyopathy.

Negligible risk conditions in which prophylaxis is generally not indicated include, (a) patients with secundum atrial septal defect, (b) those who have undergone pervious coronary artery bypass grafting, (c) those with mitral valve prolapse without regurgitation, (d) those with physiologic or functional heart murmur, (e) those with previous rheumatic fever without valvular dysfunction.

Antibiotic prophylaxis is recommended for procedures (including dental and oral procedures and respiratory, gastrointestinal, and genitourinary procedures) know to induce bacteremias and endocarditis. The new ACC/AHA guidelines specifically identify procedures in which antibiotic prophylaxis is required and those in which it is not (Table 18.19). The choice of antibiotic for dental procedures is outlined (Table 18.20) and antibiotic prophylaxis is limited to high and moderate-risk cardiac conditions. Antibiotic prophylaxis is also recommended in surgical procedures involving infected tissues that may result in bacteremia. Patients undergoing elective cardiac surgery should undergo dental evaluation to reduce the risk of late postoperative endocarditis. Finally, physicians should exercise their own clinical judgement in the choice of antibiotic and the number of doses that are to be administered in any given point.

Table 18.19 AHA/ACC statement on endocarditis prophylaxis for nondental procedures

We concluded that bacteremia resulting from dally activities is much more likely to cause IE than bacteremia associated with a dental procedure
We concluded that only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis even if prophylaxis is 100% effective
Antibiotic prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of IE
Limit recommendations for IE prophylaxis only to those conditions listed in Tables 18.3 and 18.4
Antibiotic prophylaxis is no longer recommended for any other form of CHD, except for the conditions listed in Tables 18.3 and 18.4
Antibiotic prophylaxis is reasonable for all dental procedures that involve manipulation of gingival tissues or periapical region of teeth or perforation o oral mucosa only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Tables 18.3 and 18.4)
Antibiotic prophylaxis is reasonable for procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissue only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Tables 18.3 and 18.4)
Antibiotic prophylaxis solely to prevent IE Is not recommended for GU or GI tract procedures
Although these guidelines recommend changes in indications for IE prophylaxis with regard to selected dental procedures (see text), the writing group reaffirms that those medical procedures listed as not requiring IE prophylaxis in the 1997 statement remain unchanged and extends this view to vaginal delivery, hysterectomy, and tattooing. Additionally, the committee advises against body piercing for patients with conditions listed in Tables 18.3 and 18.4 because of the possibility of bacteremia, while recognizing that there are minimal published data regarding the risk of bacteremia or endocarditis associated with body piercing

Table 18.20 Endocarditis prophylaxis regimens for dental procedures

		Regimen: single dose 30–60 min Before procedure	
Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin[a,b]	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin	Cefazolin or ceftriaxone[b]	1 g IM or IV	50 mg/kg IM or IV
and unable to take oral medication	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

IM indicates intramuscular, *IV* intravenous

[a]Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage

[b]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillins or ampicillin

Practical Points

- Infective endocarditis is usually cause by bacteria, and the three most common bacteria are S. viridans, S. aureus, and E. faecalis.
- The management of a patient with infective endocarditis is a multidisciplinary approach with the involvement of a cardiologist, an Infective disease specialist, and a cardiothoracic surgeon.
- Persistent fever, new heart murmurs, vasculitis, hemorrhagic petechiae, embolic phenomena and metastatic abscesses, and development of heart failure are suggestive of acute endocarditis. S. *aureus* is usually implicated in acute endocarditis.
- The ACC/AHA guidelines recommend antibiotic prophylaxis in patients with cardiac conditions whose risk of infective endocarditis is significantly higher than that of the general population.
- Fever may be absent in moribund or immunocompromised individuals.
- The change in the character of an existing murmur or the development of a new murmur or the development of a new murmur must raise the suspicion of infective endocarditis. In some instances, the only finding may be a "trival" aortic regurgitation. In right-sides endocarditis, murmurs are not present.

- Antibiotic prophylaxis with dental procedures, (and procedures on respiratory tract or infected skin or musculoskeletal tissue) is recommended only for patients with the following cardiac conditions:
  (a) Prosthetic cardiac valve
  (b) Previous infective endocarditis
  (c) Congenital heart disease, limited to un-repaired cyanotic lesions (including palliative shunts and conduits), completely repaired defects for a period of 6 months after the repair procedure, repaired defects with residual defects at or near the location of prosthetic material
  (d) Cardiac transplantation recipients with a cardiac valvulopathy
- Dental procedures for which appropriate patients should receive antibiotics include all procedures that involve manipulation of gingival tissue or the periapical region of teeth, or of the oral mucosa. This does not include routine anesthetic injection through non-infected tissue.
- Antibiotic prophylaxis should consist of amoxicillin 2 g PO prior to the dental procedure. In the setting of an allergy to penicillin, other oral regimens are cephalexin 2 g *or* clindamycin 600 mg *or* azithromycin or clarithromycin 500 mg.
- Antibiotic prophylaxis solely to prevent infective endocarditis is not recommended for GI tract or GU tract procedures.

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Mitral Regurgitation

19

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Usual Causes

The mitral apparatus is a complex structure including the anterior and posterior mitral leaflets, the left atrium and mitral valve annulus, the subvalvular chordae tendineae and papillary muscles, and, because of its potential effect on mitral valve function, the left ventricle [1]. Disease or geometric change involving any of these structures can result in mitral regurgitation. In general, the causes of mitral regurgitation can be divided into two categories: primary and secondary. Primary or organic mitral regurgitation is caused by abnormal anatomy of the mitral leaflets, papillary muscles, or chordae, whereby mitral regurgitation can be attributed to a mechanical abnormality that precludes valve competency. In contrast, secondary or functional mitral regurgitation is caused by changes in the size or geometry of either the left ventricle or the left atrium and mitral annulus. Left ventricular dilatation often leads to displacement of the papillary muscles and mitral leaflet tethering, which results in mitral regurgitation from incomplete coaptation of usually anatomically normal or nearly normal leaflets.

Chronic Mitral Regurgitation

Chronic mitral regurgitation caused by anatomic abnormalities of the mitral leaflets can be caused by myxomatous degeneration, rheumatic disease, infective endocarditis, connective tissue diseases, congenital disease, or annular calcification (Table 19.1). Myxomatous degeneration of the mitral valve occurs in the setting of mitral valve prolapse syndromes (Barlow's syndrome and fibroelastic insufficiency), in which redundant leaflet tissue and elongation of chordae tendineae are associated with premature valve degeneration and chordal rupture. In mitral valve prolapse, mitral regurgitation can be caused by complete or partial leaflet flail or by pathologic prolapse without flail. Barlow's syndrome refers to myxomatous degeneration involving most or all segments of both mitral leaflets, whereas fibroelastic insufficiency refers to limited degeneration of only a limited region—most commonly the middle cusp of the posterior leaflet.

Table 19.1 Causes of mitral regurgitation

Chronic mitral regurgitation, primary or organic
Myxomatous degeneration
Rheumatic
Infective endocarditis
Connective tissue diseases
Congenital
Radiation
Annular calcification
Prosthetic valve dysfunction
Chronic mitral regurgitation, secondary or functional
Dilated cardiomyopathy
Coronary artery disease
Acute mitral regurgitation
Infective endocarditis
Myxomatous degeneration with chordal rupture
Acute myocardial infarction with papillary muscle rupture
Acute myocardial infarction with infarct expansion
Prosthetic valve dysfunction

The mitral valve is the most commonly affected valve in rheumatic heart disease, with thickening and sclerosis of leaflet and subvalvular tissue, resulting in stenosis, regurgitation, or both. Mitral regurgitation caused by infective endocarditis can occur because of direct interference of a vegetation with leaflet coaptation or because of tissue destruction with leaflet erosion, perforation, or chordal rupture with complete or partial leaflet flail. Connective tissue diseases associated with mitral regurgitation include systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, and scleroderma. Valvular involvement in connective tissue diseases is variable. About half of patients with systemic lupus erythematosus have some mitral regurgitation, and approximately one fourth have significant

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regurgitation. Congenitally cleft anterior leaflet usually occurs as part of an endocardial cushion defect, with accompanying primum atrial septal defect, paramembranous ventricular septal defect, and abnormalities of the tricuspid valve. Finally, mitral annular calcification is common among elderly patients as well as among patients with diseases associated with dystrophic calcification, including chronic kidney disease. Although mitral regurgitation is commonly seen in association with mitral annular calcification, it is not usually severe. Although mitral regurgitation has been described in association with anorectic drug use, this association is not supported by case-controlled studies.

Secondary mitral regurgitation is caused by alteration of left ventricular size or geometry or, less commonly, alteration of mitral annular geometry that results in restriction of mitral leaflet motion and incomplete mitral leaflet coaptation. As such, significant functional mitral regurgitation occurs in the setting of normal or nearly normal leaflet anatomy. Functional mitral regurgitation can occur in the setting of nonischemic or ischemic cardiomyopathy, or from dynamic displacement of the mitral leaflets due to systolic anterior motion in patients with hypertrophic obstructive cardiomyopathy.

Ischemic mitral regurgitation is secondary mitral regurgitation that results from underlying coronary artery disease (Fig. 19.1). Ischemic mitral regurgitation can be caused by mechanical disruption of the mitral apparatus, such as papillary muscle rupture complicating acute myocardial infarction. More commonly, ischemic mitral regurgitation is functional mitral regurgitation that occurs in the setting of a temporally remote myocardial infarction with unfavorable left ventricular remodeling or left ventricular dilation that causes incomplete mitral leaflet coaptation. Even a relatively small inferior or posterolateral myocardial infarction can result in restrictive mitral leaflet motion with incomplete leaflet coaptation and significant regurgitation. Ischemic mitral regurgitation can be dynamic, varying in severity with varying left ventricular loading conditions which cause dynamic changes in left ventricular size and geometry. In addition, transient ischemia involving a papillary muscle with an adjacent region of the left ventricle also can cause dynamic ischemic mitral regurgitation.

Finally, mitral regurgitation can occur as a result of mechanical or bioprosthetic valve dysfunction. Mild transvalvular regurgitation is normal and an anticipated finding with many mechanical prostheses, as well as with some constructed pericardial bioprostheses. In addition, small amounts of paraprosthetic regurgitation are common with any mitral valve prosthesis. Larger paraprosthetic leaks can cause significant regurgitation, which is of potential clinical importance either because of hemodynamic significance or because of associated hemolysis. Pathologic transvalvular prosthetic regurgitation can occur in association with either mechanical or tissue prostheses. Significant valvular regurgitation with a mechanical valve is suggestive of entrapment or dysfunction of the occluder; significant regurgitation in association with a bioprosthesis is suggestive of leaflet fracture.

Acute Mitral Regurgitation

Acute severe mitral regurgitation is caused by infective endocarditis, myxomatous disease with chordal rupture, acute myocardial infarction with either papillary muscle rupture or infarct expansion and leaflet restriction, or prosthetic valve dysfunction.

Presenting Symptoms and Signs

Symptoms

Mitral regurgitation results in left ventricular volume overload with ejection of left ventricular volume into both the high-impedance aorta and the compliant, low-impedance left atrium. In chronic mitral regurgitation, left atrial dilation maintains low left atrial and pulmonary venous pressures. Compensatory left ventricular dilation results in increases in left ventricular end-diastolic volume, ejection fraction, and stroke volume, thereby maintaining forward cardiac output [2]. Patients typically remain asymptomatic during this phase of compensated mitral regurgitation, which may last for years. Prolonged left ventricular volume overload eventually leads to left ventricular systolic dysfunction and pulmonary congestion, with an increase in left ventricular end-systolic volume and decreases in ejection fraction and forward cardiac output. Because left ventricular emptying does not rely on overcoming high aortic pressure, left ventricular stroke volume remains elevated, and ejection fraction can remain within the normal range despite progressive left ventricular systolic dysfunction [3–6]. Late in the course of disease, the left ventricular ejection fraction falls below normal. At some time during the course of chronic severe mitral regurgitation, patients develop symptoms of fatigue and exertional dyspnea, followed by more overt symptoms of congestive heart failure. However, symptoms typically are insidious in onset, and patients often fail to recognize the gradual fatigue and subtle exercise limitations associated with chronic severe mitral regurgitation.

In acute severe mitral regurgitation, limited left atrial distensibility results in an acute increase in left atrial and pulmonary venous pressures with resulting pulmonary edema. Although increased preload associated with acute severe

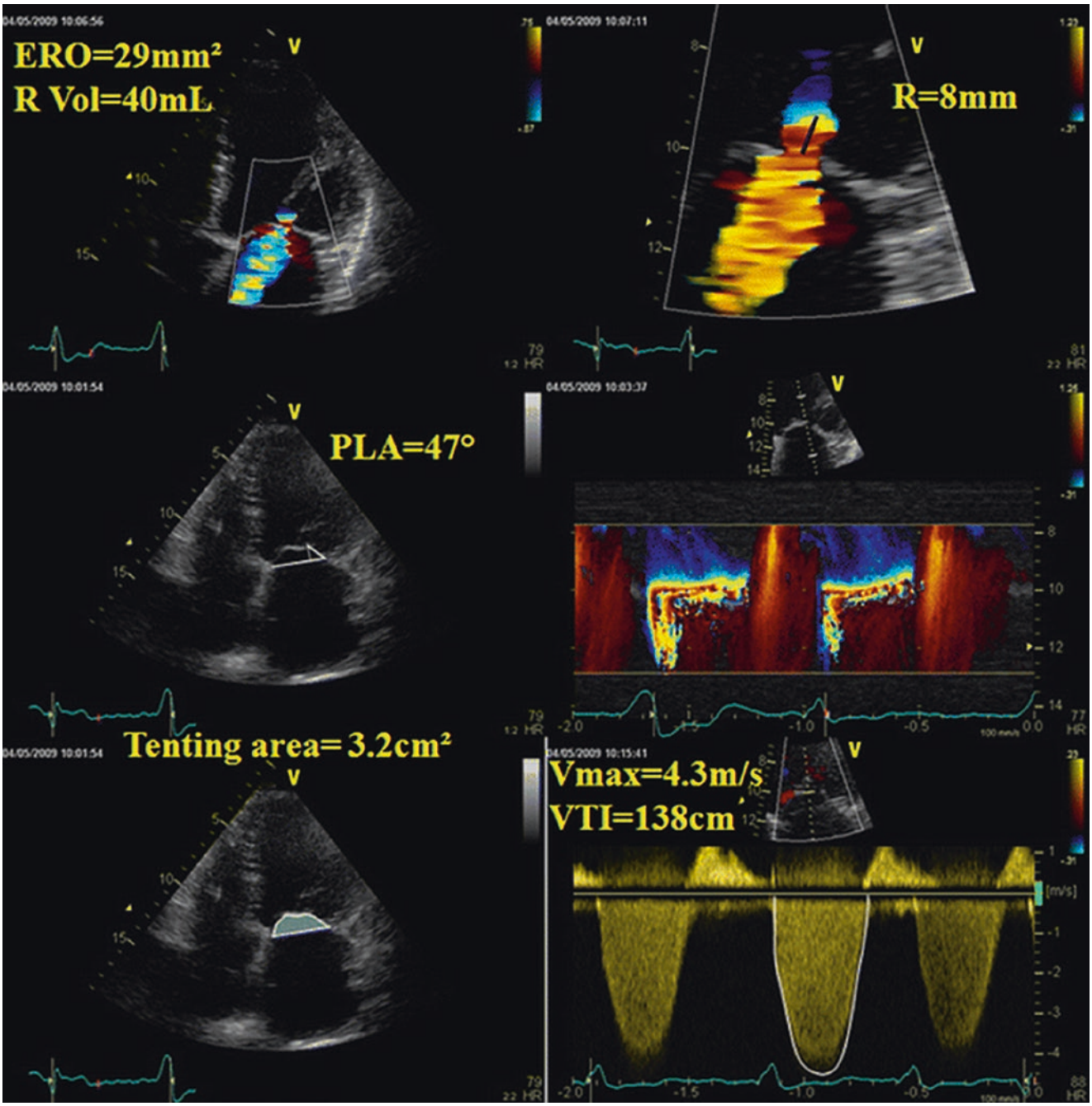

Fig. 19.1 Example of a 68-year-old patient presenting severe ischemic mitral regurgitation. There is marked tethering of the mitral valve resulting in high posterior leaflet angle (PLA) and in the presence of "seagull" sign on the anterior leaflet. *ERO* effective regurgitant orifice area, *R* proximal isovelocity surface area radius, *R Vol* regurgitant volume, *Vmax* peak mitral regurgitation velocity, *VTI* velocity-time integral. (From Unger et al. [66]; with permission)

mitral regurgitation results in a modest increase in total left ventricular stroke volume [5], the absence of compensatory left ventricular dilation results in reduced forward stroke volume. Compensatory tachycardia typically is insufficient to maintain forward cardiac output. In this setting, patients with acute severe mitral regurgitation are almost always symptomatic, with fulminant symptoms of pulmonary edema.

Signs

Physical examination of patients with chronic severe mitral regurgitation may reveal a hyperactive precordium and lateral displacement of the left ventricular apical impulse because of ventricular enlargement. A late systolic left parasternal lift caused by left atrial expansion may be present;

this, in conjunction with an apical heave, results in a rocking motion of the precordium. An apical systolic thrill may be evident. The first heart sound is usually normal, although it may be encompassed by the systolic murmur and difficult to appreciate. An S3 often is present because of the large regurgitant volume reentering the left ventricle across a fixed mitral orifice and is not necessarily indicative of ventricular failure. The classic murmur of mitral regurgitation is a loud, blowing holosystolic murmur that may obliterate S1 and S2. The murmur usually is loudest at the apex with radiation to the axilla or the back, although it is often audible throughout the precordium. Mitral regurgitation caused by leaflet flail is usually eccentric, and the murmur associated with posterior leaflet flail radiates anteriorly to the left sternal border. Because of the proximity of the ascending aorta immediately anterior to the roof of the left atrium, the murmur of an anteriorly directed mitral regurgitation jet can be transmitted to the carotid arteries. The large volume of blood crossing the mitral valve in diastole causes turbulent flow in patients with severe regurgitation, sometimes causing a diastolic rumble, despite the absence of mitral stenosis. In contrast, the systolic murmur in patients with acute severe mitral regurgitation may be decrescendo rather than holosystolic because of early equilibration of left atrial and left ventricular pressures. In acute severe mitral regurgitation, the apical left ventricular impulse is not displaced, and an S3 and S4 are common.

Mitral Valve Prolapse Syndrome

Mitral valve prolapse syndrome can occur without associated mitral regurgitation, although progression of mitral regurgitation is common over the course of the disease. Patients with mitral valve prolapse syndrome may have symptoms of palpitations or atypical chest pain [7, 8]. Physical examination reveals a characteristic midsystolic nonejection click that moves later in systole with maneuvers such as squatting that increase left ventricular preload. In patients with mitral valve prolapse without leaflet flail, mitral regurgitation, if present, occurs late in systole, and the accompanying murmur occurs only in the portion of systole after the midsystolic click.

Helpful Tests

In general, echocardiography with Doppler imaging is an ideal modality for the assessment of the presence, etiology, severity, and impact of mitral regurgitation (Table 19.2). Transthoracic imaging usually allows for sufficient assessment of mitral valve anatomy and the severity of mitral regurgitation, as well as assessment of left atrial and left ventricular size and systolic function. Anterior and posterior mitral leaflet anatomy and the submitral apparatus are usually well visualized on transthoracic imaging. Left ventricular size and overall left ventricular systolic function can be assessed and quantified, and left ventricular wall motion abnormalities associated with coronary artery disease may be evident. The determination of mitral regurgitation severity by echocardiography involves an integration of several qualitative, semiquantitative, and quantitative parameters [9]. Color flow Doppler imaging allows semiquantitative assessment of mitral regurgitation severity [9], as well as assessment of jet characteristics that may help with determination of the cause of regurgitation [10]. Highly eccentric jets are usually indicative of leaflet flail, although an eccentric jet also can be seen with leaflet restriction in the setting of ischemic mitral regurgitation [11]. Evidence of concomitant valve disease or pulmonary hypertension also may be visible. Quantitative methods, including vena conracta, regurgitant volume, and effective regurgitant orifice area, should be performed to classify mitral regurgitation severity [9]. However, each method has its own accuracy pitfalls and can be limited by poor reproducibility [12, 13].

Transesophageal echocardiography provides superb visualization of mitral valve anatomy, including the mitral leaflets and subvalvular apparatus [14]. Transesophageal echocardiographic imaging essentially always allows visualization of mitral anatomy sufficient to define the cause of regurgitation and is instrumental in the assessment of mitral anatomy in anticipation of possible mitral valve repair. In addition, transesophageal echocardiography is indicated in order to evaluate suspected prosthetic mitral regurgitation [15], which can be underestimated on transthoracic imaging. Three-dimensional transthoracic and transesophageal

Table 19.2 Echocardiographic imaging in mitral regurgitation

Transthoracic echocardiography
Baseline evaluation to quantify mitral regurgitation
Baseline evaluation to quantify left ventricular size and systolic function, right ventricular and left atrial size
Delineation of mechanism of mitral regurgitation
Annual or semiannual surveillance of left ventricular systolic function
Establish cardiac status after change in symptoms
Evaluation after mitral valve replacement or repair
Exercise echocardiography/Doppler
Assess exercise tolerance and effects of exercise on MR severity and right ventricular systolic pressure in asymptomatic patients
Transesophageal echocardiography
Evaluation of mitral regurgitation in patients with nondiagnostic transthoracic echocardiogram
Preoperative assessment of feasibility of mitral valve repair
Intraoperative assessment of mitral valve repair
Assessment of suspected prosthesis dysfunction

Adapted from Nishimura et al. [29]

echocardiography are gaining in popularity for the preoperative assessment of mitral leaflet anatomy; three-dimensional echocardiography provides unique multi-dimensional imaging compared to two-dimensional echocardiography, but has lower temporal and spatial resolution, and currently should be considered as an adjunct to and not a replacement for two-dimensional imaging. Intraoperative transesophageal echocardiography is used to evaluate the suitability for and results after surgical mitral valve repair.

Other tests that may be useful in patients with mitral regurgitation include electrocardiogram (ECG), chest radiograph, cardiac catheterization, stress testing, cardiac magnetic resonance (CMR) [16] imaging, and cardiac computed tomography (CT) [17]. The ECG and chest radiograph may reveal evidence of left atrial or left ventricular enlargement in patients with chronic mitral regurgitation. Later, the ECG may disclose atrial arrhythmias, including atrial fibrillation. Although cardiac catheterization with left ventriculography allows assessment of left ventricular ejection fraction and semiquantitative assessment of mitral regurgitation severity, both are usually available with noninvasive imaging. Coronary angiography is useful for assessment of coronary anatomy in patients at risk for coronary disease who are undergoing mitral valve surgery, and in patients in whom an ischemic cause of mitral regurgitation is suspected. Among asymptomatic patients with severe mitral regurgitation, exercise stress testing is useful for objectively defining exercise tolerance. Inasmuch as symptoms in chronic mitral regurgitation are slowly progressive, many patients do not recognize the insidious decrease in exercise tolerance that occurs over years. Exercise stress echocardiography with Doppler is useful to determine the effects of exercise on right ventricular systolic pressure. In addition, Doppler studies during exercise can sometimes disclose worsening of mitral regurgitation that is less significant at rest [18]. CMR has emerged as an invaluable tool in cardiac imaging and has become the gold standard for chamber volume and ejection fraction measurements [19]. While mitral regurgitation can be assessed by several techniques using CMR, quantification of regurgitant volume and fraction is the recommended technique [9]. CMR assessment of mitral regurgitation has been shown to have excellent reproducibility, but among the few studies comparing it to echocardiography, there is only modest concordance between the two modalities [16]. Cardiac CT also allows for quantification of mitral regurgitation with good agreement of regurgitant volume and regurgitant fraction with CMR and echocardiography [17]. However, cardiac CT is limited by lower temporal resolution and higher radiation exposure and is thus considered a last resort for mitral regurgitation quantification in patients with poor echocardiogram windows or contraindication to CMR [20].

Differential Diagnosis

Symptoms of fatigue and exertional dyspnea are nonspecific and potentially referable to a long list of cardiac and noncardiac causes. The murmur of mitral regurgitation can be differentiated from that of aortic stenosis by its holosystolic nature and by its blowing, rather than harsh, quality. The murmur of tricuspid insufficiency is usually loudest at the lower left sternal border and should be augmented with inspiration. Echocardiographic imaging should be diagnostic, although mitral regurgitation can be dynamic and therefore can vary in severity during different conditions of loading [21]. In some instances, functional mitral regurgitation can appear less significant on left ventriculography if the patient has taken nothing by mouth for several hours, as is customary before invasive testing, or if loading conditions are altered during invasive testing with the use of nitroglycerin. Finally, catheter-induced mitral regurgitation can occur if the left ventricular catheter interferes with otherwise normal mitral valve function, typically caused by catheter entanglement in the chordae tendineae.

Myxomatous degeneration of the mitral valve can be expressed in one of three ways: billowing, prolapse, or flail. Mitral valve *billowing* implies that the body of the valve extends above the plane of the annulus in systole, but the zone of leaflet coaptation is preserved, and there is usually no associated regurgitation. Mitral valve *prolapse* occurs when the free edge of a leaflet extends above the plane of the annulus in systole, usually with associated regurgitation. Partial or complete leaflet *flail* is loss of continuity between the leaflet and one or more chordae, usually with significant associated regurgitation. Finally, the diagnosis of mitral valve prolapse on echocardiography should be distinguished from normal variants that can occur in the setting of dehydration and a hypercontractile left ventricle [22]. In addition, significant enlargement of the right ventricle can affect the shape of the mitral valve annulus and cause an appearance of mitral valve prolapse in the absence of any myxomatous tissue degeneration.

Complications

Chronic severe mitral regurgitation results in left ventricular dilation and eventually in progressive systolic dysfunction with resulting congestive heart failure. Atrial arrhythmias, including atrial fibrillation, occur more often over time among patients with untreated mitral regurgitation. By one estimate, the linearized rates of acquired chronic atrial fibrillation or congestive heart failure among patients with medically treated severe mitral regurgitation are approximately 2.2% and 8.2%, respectively [23]. As with any valve disease,

patients with mitral regurgitation are at risk of infective endocarditis.

It is important to recognize that left ventricular systolic dysfunction precedes a detectable decrease below normal in left ventricular ejection fraction [3–6], because early systolic dysfunction is masked by the ability of the left ventricle to empty into the low-impedance left atrium. Therefore, delaying surgical intervention until the presence of symptoms or overt left ventricular systolic dysfunction clearly carries a risk of permanent left ventricular systolic dysfunction and congestive heart failure, as well as dramatically increasing surgical risks and worsening the rate of postoperative survival [24–27].

Therapy

The treatment of mitral regurgitation is critically dependent on its classification, whether primary or secondary. Recall that primary mitral regurgitation is due to a defect in the mitral valve structures itself, which results in valve incompetency. As a result, therapy for primary mitral regurgitation is targeted more at repairing or replacing the abnormal mitral valve. On the contrary, in secondary mitral regurgitation, the mitral valve itself is usually normal, and regurgitation is a result of left ventricular remodeling or annular dilatation causing incomplete valve coaptation. Thus, the focus of treating secondary mitral regurgitation involves treating the underlying left ventricular disease with some consideration for addressing the mitral regurgitation itself.

Medical Therapy

Regardless of primary or secondary etiology, medical therapy for chronic mitral regurgitation is limited. In a change from historical precedent [28], current guidelines do not recommend the use of antibiotic prophylaxis against infective endocarditis among most patients with native valve disease, including mitral regurgitation [29]. However, some clinicians argue that, in the absence of compelling data, a decision by an informed patient should guide the individual choice of whether to use antibiotic prophylaxis [30, 31]. Afterload-reducing agents can decrease the severity of functional mitral regurgitation [32–34], and as with all patients with left ventricular dysfunction, standard guideline-directed medical therapy for heart failure should be used in patients with cardiomyopathy and secondary mitral regurgitation [29]. In the absence of systemic hypertension or left ventricular systolic dysfunction, there is no indication for the use of vasodilators or other afterload-reducing medications in patients with primary mitral regurgitation [29].

For patients with acute severe mitral regurgitation, medical therapy is intended to decrease the severity of mitral regurgitation and thereby increase forward cardiac output and minimize pulmonary venous congestion. Nitroprusside is useful alone in normotensive patients with acute severe mitral regurgitation [35, 36] or in combination with an inotropic agent in patients with hypotension. Intraaortic balloon counterpulsation is a useful adjunct for patients with acute severe mitral regurgitation and hypotension or pulmonary edema.

Surgical Intervention

Surgical intervention is the definitive therapy for primary mitral regurgitation and includes the alternatives of mitral valve repair, mitral valve replacement with or without chordal preservation, and newer transcatheter technologies. Mitral valve replacement without chordal preservation results in loss of ventricular systolic shortening and decreased postoperative left ventricular systolic function, with lower functional class and impaired survival [37–41], and should almost never be performed. Mitral valve repair minimizes the use of prosthetic material, obviating the need for long-term anticoagulation and possibly reducing the risk of endocarditis. Repair can be associated with more favorable hemodynamics in comparison with valve replacement. There is no risk of prosthetic valve failure, and reoperation rate after valve repair is similar to that after valve replacement. Furthermore, mitral valve repair is associated with better preservation of left ventricular systolic function and probably improved survival in comparison with mitral valve replacement [42–46]. Despite being a more technically demanding procedure with its requirement for substantial surgical expertise, superior outcomes associated with mitral valve repair makes it the operation of choice when the valve is suitable for repair and when appropriate surgical expertise is available. Current guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) recommend selective referral to surgical centers experienced in mitral valve repair [29]. Avoiding many of the pitfalls associated with prosthetic valves allows consideration for surgical intervention with mitral valve repair earlier in the course of disease; with a sufficiently high likelihood of successful mitral valve repair, intervention is reasonable in the asymptomatic patient with severe mitral regurgitation and normal left ventricular size and systolic function. Finally, preservation of left ventricular shape and systolic function with mitral valve repair can make surgical intervention feasible among patients with severely impaired left ventricular systolic function and functional mitral regurgitation [47].

Table 19.3 Surgery for severe mitral regurgitation

Acute severe mitral regurgitation
Congestive heart failure or hemodynamic compromise
Absence of symptoms, if repair likely
Chronic primary mitral regurgitation
Any symptoms of heart failure
Any left ventricular systolic dysfunction (EF ≤ 60% or LVIDS ≥ 40 mm)
Evidence of new-onset atrial fibrillation or pulmonary hypertension, is successful repair highly likely
Undergoing cardiac surgery for other indications
Asymptomatic patients with normal left ventricle, if successful repair highly likely
Asymptomatic patients with normal left ventricle and progressive increase in LVIDS or decrease in EF
Preferential performance of mitral repair over replacement, and selective referral to surgical centers with expertise in mitral valve repair
Transcatheter mitral valve repair in patients with prohibitive surgical risk who are severely symptomatic despite optimal medical therapy for heart failure
Chronic secondary mitral regurgitation
Persistently severe symptoms of heart failure despite optimal medical therapy
Patients undergoing concomitant coronary artery bypass surgery or aortic valve surgery
Chordal-sparing mitral valve replacement preferred over repair in ischemic mitral regurgitation

EF ejection fraction, *LVIDS* left ventricular internal diameter in systole
Adapted from Nishimura et al. [29]

Mitral valve surgery is indicated for patients with severe primary mitral regurgitation and either symptoms of heart failure or evidence of left ventricular systolic dysfunction, defined as left ventricular ejection fraction ≤60% or left ventricular end-systolic diameter of greater than or equal to 40 mm [29] (Table 19.3). Although severe left ventricular systolic dysfunction before surgery is associated with increased rates of operative and later mortality, symptomatic patients nonetheless should be considered for surgical intervention. Asymptomatic patients with normal left ventricular size and systolic function and a high likelihood of successful valve repair may benefit from early surgical intervention with the goal of preventing the sequelae of chronic mitral regurgitation, including the risks of atrial fibrillation, congestive heart failure, and death associated with delayed surgical intervention [29]; however, there is not a consensus about the benefits of such 'prophylactic' mitral valve repair [48, 49]. Asymptomatic patients with severe primary mitral regurgitation and evidence of pulmonary arterial hypertension (pulmonary artery systolic pressure greater than 50 mmHg at rest or 60 mmHg with exercise) or atrial fibrillation of recent onset, and symptomatic patients with acute severe mitral regurgitation, should be evaluated for surgical intervention.

In secondary mitral regurgitation, first-line therapy consists of guideline-directed medical therapy for heart failure with reduced ejection fraction [29]. However, in some patients with chronic severe secondary mitral regurgitation who have persistent symptoms of heart failure despite optimal medical therapy, mitral valve surgery can be considered [29]. The presence of ischemic mitral regurgitation is a marker of poor prognosis [50–52]. Similarly, residual mitral regurgitation after surgical coronary revascularization is associated with a significantly decreased rate of survival over the first few postoperative years [48, 53–55]. Many investigators and clinicians prefer the use of mitral valve repair using restrictive mitral annuloplasty for ischemic mitral regurgitation caused by restrictive mitral leaflet motion [56], but recent evidence shows that mitral valve replacement is associated with a lower recurrence rate of moderate or severe mitral regurgitation compared to mitral valve repair in severe, ischemic mitral regurgitation [57]. Thus, current ACC/AHA guidelines suggest that it is reasonable to choose mitral valve replacement over annuloplasty repair in persistently symptomatic patients with severe mitral regurgitation despite medical therapy [58]. Furthermore, in light of the feasibility of mitral valve repair or replacement and the dire impact on survival of residual mitral regurgitation after coronary revascularization, aggressive intervention is warranted to address hemodynamically significant ischemic mitral regurgitation at the time of coronary bypass grafting.

In patients who are at high surgical risk for mitral valve repair or replacement, transcatheter therapies have emerged as viable alternatives for treating mitral regurgitation. Currently, the only such device approved by the U.S. Food and Drug Administration (FDA) is the MitraClip (Abbot Vascular). This is a clip-based device that is delivered percutaneously via a catheter and is deployed to grasp both the anterior and posterior mitral valve leaflets, thereby reducing mitral regurgitation by increasing coaptation similar to a surgical Alfieri stitch [59]. As a minimally-invasive option, the MitraClip is associated with fewer immediate adverse events compared to surgery and achieves similar reduction in mital regurgitation severity and overall mortality when used for primary mitral regurgitation [60, 61]. The device was first approved for use in patients with severe primary mitral regurgitation who had prohibitive surgical risk and symptoms despite medical therapy, which is reflected in current guidelines [29]. Most recently, trials studying the MitraClip in severe, secondary mitral regurgitation have also shown favorable results and have subsequently led to the expanded approval for this indication as well [62, 63]. In addition to transcatheter mitral valve repair, transcatheter mitral valve replacement with a bio-

prosthetic mitral valve is also being explored as a therapy for mitral regurgitation [64, 65].

Prognosis

Acute severe mitral regurgitation is a fulminant disease, typically accompanied by hypotension and congestive heart failure with pulmonary edema. In contrast, chronic mitral regurgitation is indolent in its course. Patients typically remain asymptomatic until late in the course of disease. However, the onset of symptoms often occurs after the onset of permanent left ventricular systolic dysfunction. Because surgical risk and long-term morbidity and mortality rates increase after the onset of left ventricular systolic dysfunction [24–27], intervention ideally should occur before the onset of either symptoms or left ventricular systolic dysfunction. As noted previously, early mitral valve repair might decrease the risks of atrial fibrillation, congestive heart failure, and death associated with delayed surgical intervention [23, 29, 48, 49]. Although ischemic mitral regurgitation is a marker of poor prognosis and probably should be treated at the time of coronary artery bypass surgery [50–55], it is not known whether intervention alters prognosis.

Follow-Up

Asymptomatic patients with mild mitral regurgitation and normal left ventricular systolic function should undergo periodic assessment, including assessment for symptoms and physical examination on approximately a yearly basis [29]. After the initial documentation of mild mitral regurgitation, echocardiographic imaging should be repeated if there are new symptoms or evidence on physical examination of worsened regurgitation. Periodic assessment with echocardiography and Doppler imaging to evaluate for change in mitral regurgitation severity is advisable, because the severity of mitral regurgitation is difficult to assess reliably on physical examination. Patients with moderate mitral regurgitation should undergo yearly assessment, including history and physical examination to assess for new symptoms or signs of heart failure, and echocardiographic imaging to monitor left ventricular size and function. Asymptomatic patients with severe mitral regurgitation should undergo assessment with history, physical examination, and echocardiography every 6–12 months, with more frequent testing if symptoms develop, if there is echocardiographic evidence of progressive left ventricular dilation, or if there is any evidence of a decrease in left ventricular systolic function. Among patients with chronic mitral regurgitation, accurate quantitative assessment of left ventricular size and systolic function are important as a baseline to which future study results can be compared.

Because preoperative left ventricular systolic function is an important predictor of postoperative survival, patients should be referred for surgical intervention before the onset of left ventricular systolic dysfunction [32]. As noted previously, the left ventricular ejection fraction remains within the normal range in patients with chronic severe mitral regurgitation after the onset of left ventricular systolic dysfunction. Therefore, ejection fraction alone is a poor measure of left ventricular systolic function in patients with mitral regurgitation, and any evidence of change in left ventricular size or systolic function should be considered in evaluating the timing of surgical intervention.

Practical Points

- Mitral regurgitation is a common condition with multiple potential causes, including diseases of the mitral valve leaflets, the subvalvular apparatus, and the left ventricle.
- The disease has an indolent course; symptoms occur late.
- Echocardiography with Doppler imaging is the test of choice for confirming diagnosis and further characterizing disease.
- Transesophageal echocardiography or cardiac MRI can be useful if transthoracic imaging is nondiagnostic.
- Distinguishing between primary versus secondary mitral regurgitation is necessary to determine therapy.
- Patients should be referred for surgical intervention before the onset of symptoms or left ventricular systolic dysfunction (left ventricular ejection fraction less than or equal to 60%).
- Surgical intervention should aim to preserve subvalvular apparatus, and mitral repair is usually the procedure of choice if feasible.
- Transcatheter options have become available in patients with prohibitive surgical risk.

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Aortic Regurgitation

20

Viren Patel and Jim X. Liu

Usual Causes

The aortic valve comprises three semilunar aortic leaflets, the sinuses of Valsalva, and the sinotubular junction. Aortic regurgitation is caused by acquired or congenital abnormalities of the aortic valve leaflets or by acquired abnormalities of the aortic root that affect the competence of what may be anatomically normal leaflets. In general, aortic regurgitation caused by aortic root disease requires dilation at the level of the sinotubular junction as isolated aortic annular dilation is relatively unlikely to occur due to the dense fibrous tissue surrounding the annulus.

Chronic Aortic Regurgitation

Chronic aortic regurgitation can be caused by congenital or acquired abnormalities (Table 20.1). A bicuspid aortic valve is the most common congenital abnormality of the aortic valve that leads to aortic regurgitation; fenestrations of the aortic valve cusps are a less frequent cause. Acquired causes of chronic aortic regurgitation resulting from disease of the valve leaflets include calcific degeneration, rheumatic disease, infective endocarditis, myxomatous degeneration, and chronic anorectic drug use. Less common etiologies of aortic regurgitation caused by abnormalities of the leaflets include discrete subaortic stenosis and aortic leaflet prolapse caused by a perimembranous ventricular septal defect.

Aortic root disease resulting in chronic aortic regurgitation can be idiopathic; associated with a bicuspid aortic valve; or caused by atherosclerosis and systemic hypertension, cystic medial necrosis with or without other features of Marfan's syndrome, or aortic dissection. Other, less commonly encountered causes of aortic root disease include connective tissue diseases such as Reiter's syndrome, ankylosing spondylitis, and rheumatoid arthritis. Luetic (syphilitic) aortitis is still described as a potential cause of aortic root disease but, in effect, is no longer encountered clinically in the United States.

Finally, dysfunction of a valve prosthesis can result in aortic regurgitation. Mild transvalvular regurgitation is an anticipated finding with most mechanical prostheses, and small amounts of paraprosthetic regurgitation are not uncommon with any prosthesis. Larger paravalvular leaks can be of clinical importance either because of their hemodynamic significance or because of associated hemolysis. Significant valvular regurgitation with a mechanical prosthesis suggests entrapment or dysfunction of the occluder; significant regurgitation in association with a bioprosthesis suggests leaflet fracture or tear.

Table 20.1 Causes of aortic regurgitation

Chronic aortic regurgitation, related to valve cusps
Congenital (bicuspid aortic valve, fenestrations)
Calcific degeneration
Rheumatic
Infective endocarditis
Myxomatous degeneration
Anorectic drugs
Prosthetic valve dysfunction
Chronic aortic regurgitation, related to ascending aorta
Idiopathic aortic root dilation
Root dilation related to bicuspid aortic valve
Root dilation secondary to hypertension
Cystic medial necrosis (including Marfan's syndrome)
Aortic dissection
Acute aortic regurgitation
Infective endocarditis
Aortic dissection
Nonpenetrating chest trauma
Prosthetic valve dysfunction

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Acute Aortic Regurgitation

Acute severe aortic regurgitation is caused by infective endocarditis, aortic dissection, nonpenetrating (or, in rare cases, penetrating) chest trauma, or prosthetic valve dysfunction.

Presenting Symptoms and Signs

Symptoms

Patients with chronic aortic regurgitation usually remain asymptomatic for years or decades. During this compensated phase, the left ventricular volume overload of aortic regurgitation is accommodated through increases in left ventricular volume and chamber compliance and through both eccentric and concentric hypertrophy. Increased stroke volume maintains normal forward cardiac output and increased left ventricular compliance maintains normal filling pressures with maintained preload reserve. The increase in chamber size results in increased wall stress, with compensatory hypertrophy in response to increased afterload. During this period, myocardial contractility and left ventricular ejection fraction remain normal. Symptoms during this phase of compensated chronic aortic regurgitation may include a sensation of pounding in the chest, palpitations, or head pounding, caused by increased stroke volume and a wide pulse pressure.

Eventually, persistent volume and pressure overload exhaust left ventricular preload reserve; in addition, hypertrophy may become inadequate for increased afterload. At this point, further increases in afterload result in decreased left ventricular ejection fraction. Exertional dyspnea is typically the first manifestation of left ventricular decompensation, with later development of orthopnea and paroxysmal nocturnal dyspnea.

Initially, left ventricular systolic dysfunction is caused by pure afterload excess and is reversible after aortic valve replacement. Later, depressed myocardial contractility causes progressive and irreversible systolic dysfunction. In addition, inadequate coronary flow reserve in the setting of left ventricular hypertrophy, along with decreased perfusion pressure associated with low diastolic pressures, can result in coronary insufficiency. Symptoms of more advanced disease eventually include angina pectoris (which may be nocturnal) and symptoms of right-sided congestive heart failure with ascites and peripheral edema.

Acute severe aortic regurgitation usually occurs in the setting of infective endocarditis, acute aortic dissection or, more rarely, after blunt chest trauma. Patients typically exhibit symptoms referable to the underlying disease, including fever with infective endocarditis, or chest or back pain with aortic dissection. In the absence of the compensatory mechanisms present in chronic aortic regurgitation, acute severe aortic regurgitation is poorly tolerated hemodynamically, and patients frequently present with pulmonary edema or cardiogenic shock.

Signs

Physical findings in patients with chronic severe aortic regurgitation reflect the combination of increased stroke volume and widened pulse pressure. Findings can be extensive with many associated eponyms (Table 20.2). In general appearance, patients can exhibit a bobbing motion of the torso or the head (de Musset's sign) synchronous with the heartbeat. Systolic pulsation of the uvula may be visible (Müller's sign). Arterial pulses are unusually prominent, with exaggerated systolic distension and exaggerated diastolic collapse on palpation (water-hammer or Corrigan's pulse). Palpation of the carotid arteries reveals a bisferiens, or double-peaking, pulse. Capillary pulsation may be visible in the nail beds when the distal nail is softly compressed (Quincke's pulse). Auscultation of large arteries may reveal a brief, loud systolic (pistol shot) sound. Auscultation of the femoral artery reveals booming systolic and diastolic sounds (Traube's sign); light pressure of the stethoscope proximally reveals a systolic murmur, with a diastolic murmur when pressure is applied distally (Duroziez's sign). The systolic blood pressure is typically elevated, and the diastolic blood pressure is often very low, revealing a wide pulse pressure.

The left ventricular apical impulse is enlarged and displaced as a result of left ventricular enlargement, and it may be visible. A systolic thrill caused by the large left ventricular stroke volume may be evident along the base of the heart or in the carotid arteries. On auscultation, the aortic component of S2 may be diminished or absent. An S3 is common and is not indicative of congestive heart failure. The murmur of aortic regurgitation is a high-pitched, blowing decrescendo

Table 20.2 Selected physical findings and eponyms associated with severe chronic aortic regurgitation

Physical finding	Eponym
Bobbing motion of the torso or the head	de Musset's sign
Systolic pulsation of the uvula	Müller's sign
Exaggerated systolic distension and diastolic collapse of arterial pulses	Water-hammer pulse, Corrigan's pulse
Capillary pulsation visible in nail bed with distal compression	Quincke's pulse
Brief, loud systolic sound on auscultation of large arteries	Pistol shot pulse
Booming systolic and diastolic sounds on auscultation of femoral artery	Traube's sign
Systolic murmur with light proximal pressure of stethoscope; diastolic murmur with distal pressure	Duroziez's sign
Diastolic murmur radiating to left ventricular apex	Austin-Flint murmur

diastolic murmur, loudest at the left or right upper sternal border. Held end-expiration with the patient upright and leaning forward and the stethoscope diaphragm held firmly against the chest aids in the auscultation of soft murmurs of aortic regurgitation. The aortic regurgitant jet may result in vibration of the anterior mitral valve leaflet, resulting in a low-pitched diastolic rumble at the cardiac apex (Austin Flint murmur) that can mimic mitral stenosis, albeit without presystolic accentuation. A systolic ejection murmur, often louder and more easily heard than the diastolic murmur, is caused by the large stroke volume and is not indicative of aortic stenosis.

Many of the typical physical findings associated with chronic aortic regurgitation are absent in patients with acute severe aortic regurgitation. Because the left ventricle is not dilated in acute aortic regurgitation, stroke volume is not increased, pulse pressure is not widened, and the associated peripheral arterial manifestations are absent. Tachycardia is typical in a compensatory attempt to maintain forward cardiac output without the benefit of increased stroke volume. Premature closure of the mitral valve may be associated with decreased intensity of S1. The diastolic murmur in acute severe aortic regurgitation is often shorter and softer than that associated with chronic aortic regurgitation, because diastolic pressure equilibration between the ascending aorta and left ventricle occurs earlier in diastole. Although chronic severe aortic regurgitation usually can be diagnosed on physical examination, the detection of acute severe regurgitation is less certain.

The AHA/ACC guidelines classify chronic aortic regurgitation into stages based on severity of aortic regurgitation, symptom status, and LV volume and LV systolic function. Stage A represents patient who are at risk of aortic regurgitation. Stage A patients have a bicuspid valve or other congenital valve anomaly, aortic valve sclerosis, disease of the aortic sinus or ascending aorta, history of rheumatic fever or rheumatic heart disease or history of infective endocarditis. Stage A patients have no or trace aortic valve regurgitation and have no hemodynamic or symptomatic issues related to the aortic valve. Stage B patients (progressive aortic regurgitation) have mild to moderate aortic valve regurgitation. These patients have normal LV systolic function and can either have normal LV volume or mild LV dilation. Stage B patient are asymptomatic. Stage C1 patients are those with asymptomatic severe aortic regurgitation, a left ventricular ejection fraction (LVEF) of >50% and mild to moderate LV dilation (Left ventricular end systolic diameter (LVESD) of ≤50 mm). Stage C2 patients also have asymptomatic severe aortic regurgitation however these patients have abnormal LV systolic function with a depressed LVEF (≤50%) or severe LV dilation (LVESD >50 mm or indexed LVESD >25 mm/m^2). Stage D patient have severe symptomatic aortic regurgitation with either normal or abnormal systolic function and moderate to severe LV dilation. Patients with stage D chronic aortic regurgitation have exertional dyspnea or angina or more severe symptoms of heart failure [1]. Management of patients with aortic regurgitation depends on accurate diagnosis of the cause and stage of aortic regurgitation.

Helpful Tests

Transthoracic echocardiography (TTE) with Doppler imaging is an ideal modality for the assessment of the presence, etiology, severity, and impact of aortic regurgitation (Table 20.3). TTE is indicated for patients with suspected aortic regurgitation to confirm the presence of aortic regurgitation, establish the severity, cause of regurgitation, and for determining clinical outcome and timing of valve intervention [1]. The dimensions, mass, and systolic function of the left ventricle should be determined, as well as the size and anatomy of the aortic root. Because absolute and subsequent change in left ventricular dimensions directly affect management, accurate quantification is important both on baseline measurement and on subsequent examinations.

Transthoracic echocardiography allows assessment of aortic valve structure and may establish the cause of aortic regurgitation with evidence of congenital abnormalities, calcific or rheumatic disease, or findings suggestive of infective endocarditis. In addition, the proximal 2–3 cm of ascending aorta can usually be visualized on transthoracic imaging, allowing assessment for gross dilation of the aortic root. In the absence of Doppler imaging, aortic regurgitation is suggested by diastolic fluttering of the anterior mitral valve leaflet, and acute severe regurgitation is associated with premature closure of the mitral valve. Doppler imaging allows reliable detection and semi-quantification of aortic regurgitation [2]. Aortic regurgitation severity is estimated by using many factors including the size of the regurgitant jet

Table 20.3 Echocardiographic imaging in aortic regurgitation (AR)

Transthoracic echocardiography
Baseline evaluation to assess presence, severity of AR
Delineation of etiology of aortic regurgitation, evaluate proximal aortic root
Assessment of left ventricular size, mass, volume and systolic function
Periodic surveillance of left ventricular size and systolic function in asymptomatic patients with severe aortic regurgitation
Establish cardiac status after change in symptoms
Evaluation after aortic valve replacement
Transesophageal echocardiography
Evaluation of AR in patients with nondiagnostic transthoracic echocardiogram
Assessment of suspected prosthetic valve dysfunction
Evaluation of thoracic aorta, aortic dissection

Adapted from Nishimura et al. [1]

in relation to the left ventricular outflow tract, vena contracta width, qualitative characteristics of the regurgitant jet, deceleration characteristics of regurgitant flow, left ventricular size, regurgitant volume and fraction, and effective regurgitant orifice area. Additionally, diastolic flow reversal in the descending thoracic aorta is a marker of severe aortic regurgitation. Transesophageal echocardiographic imaging allows optimal assessment of aortic valve structure, as well as definitive assessment of anatomy of the thoracic aorta. Transesophageal imaging is indicated if aortic dissection [3, 4] or prosthetic valve dysfunction [5, 6] is suspected.

Cardiac MRI is indicated in patients with moderate or severe aortic regurgitation and suboptimal echocardiographic images for the assessment of LV systolic function, systolic and diastolic volumes, and measurement of AR severity [1]. Cardiac MRI may also be helpful in providing anatomic evaluation of the aortic valve and aortic root. Echocardiography is the first line modality for assessment of aortic regurgitation, however cardiac MRI should be considered if there are suboptimal echocardiographic images; there is discordance between echocardiographic and Doppler findings; if there is discordance between clinical assessment and severity of aortic regurgitation by echocardiography; in patients with moderate or severe aortic regurgitation and suboptimal echocardiographic evaluation of LV volume, systolic function, and measurement of aortic regurgitation severity; in patients with a bicuspid aortic valve who have inadequate evaluation by echocardiography of the aortic sinuses, sinotubular junction, or ascending aorta [2]. Cardiac MRI measurement of regurgitant severity is less variable than with echocardiography and may be better suited for longitudinal follow up in individual patients [1, 2].

Neither electrocardiography nor chest radiography is accurate in the detection or estimation of severity of aortic regurgitation. However, the electrocardiogram may reveal evidence of left ventricular hypertrophy or interventricular conduction delay, and the chest radiograph may reveal cardiomegaly, dilation of the aortic root, or evidence of pulmonary venous congestion. Other tests that may be useful in patients with aortic regurgitation include exercise stress testing and cardiac catheterization. Exercise testing is useful for assessing functional capacity and symptoms in patients with significant aortic regurgitation and equivocal symptoms, as well as objectively assessing baseline and change in functional capacity among patients with moderate or severe aortic regurgitation. In addition, exercise testing may be helpful in patients with chronic aortic regurgitation prior to participation in athletic activities. Cardiac catheterization with coronary angiography allows assessment of coronary anatomy among patients at risk for coronary artery disease for whom surgical intervention is planned. Aortic regurgitation severity and aortic root size can be assessed with root angiography, although this data is usually available with noninvasive testing.

Differential Diagnosis

Early symptoms of exertional dyspnea associated with chronic aortic regurgitation are nonspecific and potentially referable to many cardiac and noncardiac causes. Symptoms of more advanced congestive heart failure can similarly have many cardiac causes. Symptoms of angina pectoris can obviously be suggestive of coronary artery disease.

The decrescendo diastolic murmur of aortic regurgitation can be differentiated from that of mitral stenosis if it is predominantly localized at the left or right upper sternal border. The Austin Flint murmur, with radiation to the left ventricular apex, can be differentiated from a murmur of mitral stenosis in patients in sinus rhythm by its lack of presystolic accentuation. Mitral stenosis and aortic regurgitation can be reliably differentiated by echocardiographic imaging.

Complications

Chronic severe aortic regurgitation results in left ventricular dilation and, eventually, in progressive systolic dysfunction with consequent congestive heart failure. Initially, left ventricular systolic dysfunction is caused by pure afterload excess and is reversible after surgical intervention. Later in the course of disease, myocardial contractility is impaired, and this impairment is responsible for progressive and irreversible left ventricular systolic dysfunction. As is the case with any valve disease, patients with aortic regurgitation are at risk of infective endocarditis.

Therapy

Medical Therapy

Medical therapy for chronic aortic regurgitation is limited. Current guidelines do not recommend the use of antibiotic prophylaxis against infective endocarditis among most patients with native valve disease, including aortic regurgitation [7, 8]. However, some clinicians argue that, in the absence of compelling data, a decision by an informed patient should guide the individual choice of whether to use antibiotic prophylaxis [9, 10].

Vasodilators improve hemodynamics in patients with aortic regurgitation and improve cardiac output however data from two small randomized control trials did not conclusively show that vasodilators change the natural history of severe aortic regurgitation in asymptomatic patients with normal LV systolic function [1]. Vasodilator therapy is not recommended routinely in patient with chronic aortic regurgitation and normal LV systolic function [1]. Medical ther-

apy is not a substitute for aortic valve replacement in symptomatic patients who are candidates for aortic valve replacement. However, vasodilator therapy may be helpful in treating symptoms in patients with chronic, symptomatic, severe aortic regurgitation and left ventricular systolic dysfunction if surgical aortic valve replacement is contraindicated due to noncardiac or other cardiac reasons [1]. In addition, short-term therapy with vasodilators is indicated to improve hemodynamics in patients with severe, decompensated heart failure prior to aortic valve replacement [1]. There is relatively limited evidence to support the use of chronic vasodilator therapy in asymptomatic patients with aortic regurgitation and preserved left ventricular systolic function [11, 12]; if used in this circumstance, current guidelines do recommend that vasodilator therapy should be aimed at treating systolic hypertension in patients with chronic aortic regurgitation. Dihydropyridine calcium channel blockers or angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) are the preferred medications for the treatment of hypertension in patients with chronic aortic regurgitation. A large retrospective study of patients with at least moderate aortic regurgitation demonstrated potential benefit from renin-angiotensin-aldosterone system blockade. In this study, treatment with ACEi or ARBs was associated with reduced all-cause mortality, cardiovascular events, (cardiovascular death or hospitalization) and aortic regurgitation events (heart failure hospitalization and heart failure death or aortic valve replacement) [13].

Patients with acute severe aortic regurgitation typically suffer hemodynamic compromise with fulminant pulmonary edema and cardiogenic shock. Medical therapy should be directed at aggressive afterload reduction with intravenous nitroprusside or nitroglycerin. Inotropic agents such as dopamine or dobutamine may also help improve forward flow. Diuretics are useful in the management of pulmonary edema. Regurgitant volume decreases with an increasing heart rate, owing to a shorter diastolic interval. Therefore, maintaining a rapid heart rate by temporary cardiac pacing or beta-adrenergic agonists is useful among patients with acute severe aortic regurgitation and hemodynamic compromise. Intraaortic balloon counterpulsation is contraindicated.

Aortic Valve Replacement

Surgical intervention with aortic valve replacement (AVR) is the definitive therapy for aortic regurgitation. Aortic valve repair is possible in some patients, although its use is limited to younger patients with noncalcific abnormalities of the aortic cusps or annulus, typically of congenital or myxomatous origin [14, 15]. Most adult patients requiring surgical intervention for aortic regurgitation are older and have significant associated calcification of the aortic valve annulus and cusps and of the wall of the ascending aorta; valve repair plays a much smaller role for the aortic valve than for the mitral valve.

Aortic valve replacement is indicated for patients with severe symptomatic aortic regurgitation regardless of LV systolic function (stage D). Patients with chronic severe aortic regurgitation who develop symptoms have a high risk of death if AVR is not performed [1]. In a series of 246 patients, those with severe aortic regurgitation with NYHA class III or IV symptoms had a mortality rate of 24.6% per year and NYHA class II symptoms were associated with a 6.3% annual risk of mortality [16]. In asymptomatic patients with severe aortic regurgitation, aortic valve replacement is indicated if LVEF is less than 50% with no other cause for the LV dysfunction or if the patient will be undergoing cardiac surgery for other reasons. Aortic valve replacement should also be considered in patients with asymptomatic, severe aortic regurgitation, with normal LV systolic function if there is evidence of severe LV dilation. Aortic valve replacement is also considered reasonable in patients with moderate aortic regurgitation while undergoing surgery on the ascending aorta, CABG, or mitral valve surgery [1] (Table 20.4). The risk entailed by surgery increases with progressive left ventricular systolic dysfunction or advanced symptoms, although functional status and prognosis are improved with aortic valve replacement despite preexisting severe left ventricular systolic dysfunction [17, 18].

The decision to defer aortic valve replacement for patients with severe aortic regurgitation is based on the balance between the risks and benefits of intervention; the benefits of intervention are, in essence, synonymous with avoidance of the natural history of disease and of the risks of delayed intervention. This balance favors delayed intervention among asymptomatic patients either if operative mortality rate is high or if there is substantial postoperative morbidity or mortality associated with earlier intervention. Current operative techniques allow performance of aortic valve replacement with low rates of operative morbidity and mortality among compensated patients. In addition, state-of-the-art valve

Table 20.4 Surgery for severe aortic regurgitation

Acute severe aortic regurgitation
Symptoms or hemodynamic compromise
Chronic severe aortic regurgitation
Any symptoms, with or without LV systolic dysfunction
Any LV systolic dysfunction LV (EF <50%), with or without symptoms
Patients undergoing bypass surgery, surgery on the aorta or on other heart valves with progressive or severe aortic regurgitation
Evidence of significant LV dilation (LVIDD >65 mm and low surgical risk or LVIDS >50 mm or indexed LVIDS of >25 mm/m^2)

EF ejection fraction, *LV* left ventricle, *LVIDD* left ventricular internal diameter in diastole, *LVIDS* left ventricular internal diameter in systole
Adapted from Nishimura et al. [1]

substitutes appear to provide durable prostheses with good hemodynamics and high rates of postoperative survival [19–21]. Although strict criteria have not been developed and tested, it may be prudent to consider aortic valve replacement earlier if severe aortic regurgitation and evidence of moderate or progressive left ventricular dilation are present, and if surgery can be performed by an experienced surgeon using a state-of-the-art valve substitute.

Prognosis

Prognosis is poor among symptomatic patients with severe aortic regurgitation treated with medical therapy alone. According to natural history data that predate the era of surgical aortic valve replacement, the presence of angina pectoris or symptoms of congestive heart failure were associated with mortality rates of more than 10% and more than 20% per year, respectively [22–24]. This suggests that, without surgical intervention, symptomatic aortic regurgitation appears to be associated with a prognosis as dire as that for symptomatic aortic stenosis. Asymptomatic patients with impaired left ventricular systolic function typically develop symptoms within 2–3 years of diagnosis [25–27]; the estimated rate of developing symptoms is greater than 25% per year [1].

The prognosis of asymptomatic patients with normal left ventricular systolic function has been evaluated in nine independent series (ten publications) [11, 12, 28–35] that were summarized in the ACC/AHA Guidelines on the Management of Patients with Valvular Heart Disease [1]. This data revealed a 4.3% annual rate of progression to the development of symptoms, death or left ventricular systolic dysfunction. Asymptomatic left ventricular systolic dysfunction occurred at a rate of 1.2% per year. Sudden death among patients with compensated severe aortic regurgitation is rare but has been reported, with a mortality rate of less than 0.2% per year. In general, asymptomatic patients with moderate or severe aortic regurgitation should be able to participate in normal physical activity (including mild-intensity exercise), although weightlifting and other isometric exercises should be avoided.

Age, end-systolic left ventricular diameter or volume, left ventricular end-diastolic diameter or volume, and the ejection fraction during exercise are predictors of adverse outcome. In one multivariate analysis, death or development of symptoms or left ventricular dysfunction occurred within 8 years of diagnosis among 19% of patients with left ventricular systolic diameter of more than 50 mm, among 6% of patients with left ventricular systolic diameter of 40–50 mm, and in no patient with left ventricular systolic diameter of less than 40 mm [31]. It is important to note that, of asymptomatic patients who developed adverse outcomes of death or left ventricular systolic dysfunction in the previously cited studies [29–32, 34], more than 25% had no prior development of symptoms. Furthermore, surgical risk increases after the development of either left ventricular systolic dysfunction or marked chamber dilation. Inasmuch as the disease can progress and the prognosis worsens without the development of symptoms, there is some inherent risk in delaying surgical intervention among patients who do not yet meet conventional criteria.

Prognosis after aortic valve replacement appears to improve substantially. However, women do not fare as well as men after aortic valve replacement for aortic regurgitation [36], possibly because the disease in women is more advanced at the time of surgical intervention owing to guidelines that historically have not normalized left ventricular dimensions to body stature.

Follow-Up

Asymptomatic patients with mild aortic regurgitation and normal left ventricular size and systolic function should undergo periodic assessment, including history and physical examination, on approximately a yearly basis [1]. After the initial documentation of mild aortic regurgitation, echocardiographic imaging should be repeated if there are new symptoms or evidence of worsened regurgitation on physical examination. Because the severity of regurgitation and even moderate change in left ventricular size are difficult to assess reliably on physical examination, echocardiography with Doppler imaging should be repeated periodically (approximately every 1–3 years) to evaluate for change in an otherwise stable patient.

At the time of an initial diagnosis of moderate or severe aortic regurgitation, asymptomatic patients should undergo (a) quantitation of left ventricular size and systolic function with echocardiographic imaging (b) evaluation of functional status by history or exercise testing, and (c) assessment of ascending aorta size (on echocardiography or other imaging if necessary). If surgery is not indicated, then patients should undergo serial assessment for the development of new symptoms and for changes in functional status, the severity of regurgitation, and left ventricular size and systolic function. If the chronicity and stability of aortic regurgitation is not known, then patients should undergo reevaluation, including echocardiographic imaging, after 2–3 months. After the stability of the regurgitant lesion has been established, the frequency of subsequent reevaluation and repeated noninvasive testing should be based on the severity of aortic regurgitation, the presence and severity of left ventricular dilation on echocardiography, evidence of progression or change on previous studies, and the reliability of the assessment of functional stability. It is important to recognize that a sedentary

lifestyle in many patients precludes the reliable assessment of functional status without the use of periodic exercise testing. In general, stable, asymptomatic patients with severe aortic regurgitation should be reevaluated approximately yearly or more frequently as indicated according to the criteria just described. Finally, in addition to routine testing, patients should undergo reassessment if there are new symptoms or a change in functional status.

Practical Points

- Aortic regurgitation has multiple potential causes, including diseases of aortic valve leaflets or of the ascending aorta.
- Chronic volume overload eventually leads to left ventricular dilation and systolic dysfunction.
- The disease has an indolent course; symptoms occur late.
- Symptoms include exertional dyspnea, followed by symptoms of overt congestive heart failure or angina pectoris or both.
- Echocardiography with Doppler imaging is the test of choice for confirming diagnosis and for quantifying and further characterizing regurgitation and its impact on left ventricular size and systolic function.
- Transesophageal echocardiography is useful if transthoracic imaging is nondiagnostic, with aortic root disease, and with prosthetic valves.
- The prognosis is favorable in the absence of symptoms, in patients with good functional capacity, and in patients with normal left ventricular size and systolic function.
- Patients should be referred for surgical intervention if any symptoms, left ventricular systolic dysfunction, or significant left ventricular dilation is present.

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Mitral Stenosis

21

Vincent E. Brinkman

Usual Causes

The most common cause of mitral stenosis is rheumatic heart disease [1]. Most patients will not report a history of rheumatic fever, however, and the gradual thickening and fusion of the leaflets that occurs with this process clinically manifest quite some time after the initial infection. Other causes of mitral stenosis are less common. Mitral annular calcification can over time cause restriction of the mitral leaflets, but is a very rare cause of severe mitral stenosis. Radiation exposure may also cause thickening and calcification of the valve leaflets. Other causes can include prosthetic valve degeneration, malfunction or patient—prosthetic mismatch. Finally, there are various congenital conditions that can cause stenosis (valve hypoplasia and parachute mitral valve for example) [2] but these are typically diagnosed at an early age.

Presenting Signs and Symptoms

Initially, mitral stenosis is typically asymptomatic. Dyspnea is the most common symptom. As the disease progresses, patients can present with signs of right sided heart failure. Of note, while some patients present with concomitant left ventricular failure [3], the physiology of mitral stenosis typically protects the left ventricle from significant remodeling and the ejection fraction is usually normal. The symptoms are therefore primarily related to elevations in the left atrial pressure and then decreased preload of the left ventricle.

Eventually, this increased left atrial pressure leads to pulmonary congestion and elevated right ventricular pressures. This may present as fatigue or even chest pressure during exertion. Rarely, hoarseness can occur (Ortner syndrome) and is caused by left recurrent laryngeal nerve compression due to an enlarged pulmonary artery. Hemoptysis is a possible presenting symptom as well, either due to pulmonary edema, bronchitis or pulmonary apoplexy [4]. With the increased left atrial size and pressure, atrial fibrillation is not uncommon [5] and may result in thromboembolism as the presenting complaint.

While many of these symptoms are gradual in progression, patients with severe mitral stenosis can sometimes present acutely. As this is a fixed obstruction to flow and is dependent on diastolic filling time, situations that cause an increase in heart rate (atrial fibrillation, infection, trauma, surgery) can cause an abrupt change in symptoms. Pregnancy may also bring out symptoms that were not present during normal physiologic states due to increased cardiac output and volume as well as increased heart rates.

The hallmark of the physical exam is a diastolic rumble heard best at the apex. There is typically accentuation of the murmur towards the end of diastole due to atrial contraction, but this is lost in atrial fibrillation. An opening snap can sometimes be heard as well and correlates with the severity of the mitral stenosis. The earlier that the opening snap occurs after S2, the more severe the mitral stenosis (due to increasing left atrial pressures). One should also look for signs of right sided heart failure (RV lift, elevated jugular venous pressures, loud P2 and tricuspid regurgitation).

Helpful Tests

The ECG is an easy initial test and may show left atrial enlargement. With longstanding mitral stenosis, there may also be signs of right ventricular hypertrophy. The chest x-ray with advanced mitral stenosis shows left atrial enlargement (straightening of the left heart border). The left ventricular size is typically normal with isolated mitral stenosis. Again, with advancing disease, one sees pulmonary vascular congestion and potentially right ventricular and pulmonary artery enlargement.

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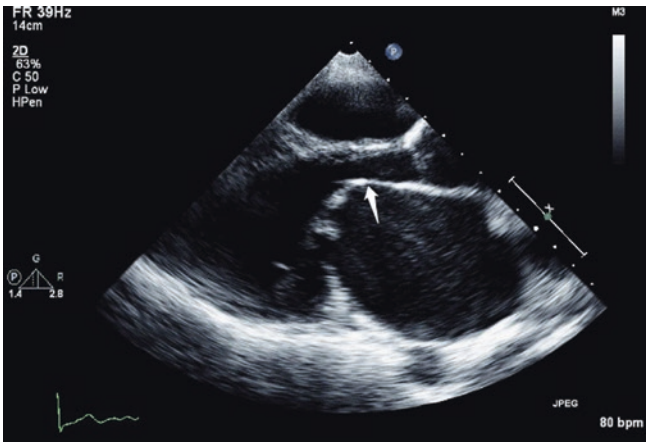

Fig. 21.1 This is an echocardiogram image from a patient with rheumatic mitral stenosis. Note the anterior mitral valve (arrow) with the characteristic "hockey stick" appearance

Echocardiography is the test of choice for the diagnosis and monitoring of mitral stenosis [6]. Two-dimensional echocardiography can evaluate the etiology of the valve disease. One can also judge the degree of thickening and calcification of the leaflets, chordae, annulus and papillary muscles. The fusion of the mitral valve commissures leads to a stereotypical "hockey-stick" appearance when the valve is opening (Fig. 21.1). In addition to the valve itself, the two dimensional examination can also evaluate the size of the left atrium and left ventricle and assess for the presence of right ventricular overload or dysfunction. If care is taken to evaluate the tips of the mitral leaflets, a direct planimetry of the mitral valve orifice can be obtained and correlates well with the anatomical area [7].

Doppler echocardiography is able to measure the pressure gradient across the mitral valve and give an indirect estimate of the valve orifice area. The mean gradient also correlates with the severity of the mitral stenosis but can be affected by the heart rate (increased heart rates can increase the mean gradient so that the heart rate at the time of the echocardiogram evaluation should always be taken into account). The pressure half time can also be measured and represents how long it takes for the pressure gradient to decrease by 50% (Fig. 21.2). This correlates with the mitral valve area by using the equation [8]:

$$\text{Mitral Valve Area} = 220 / \text{Pressure Half Time}$$

Other Doppler methods can be used at times to estimate the mitral valve area including the proximal isovelocity surface area method [9] but are not routinely employed in most laboratories. In addition, newer techniques including three dimensional measurement of the mitral valve area [10] are occasionally used and may provide more accurate measurements in the future (Fig. 21.3). In addition to the mitral valve assessment, one can measure the tricuspid regurgitant velocity in order to assess the right ventricular systolic pressures.

Echocardiography should be performed for the diagnosis of mitral stenosis or in patients with known mitral stenosis with a change in symptoms. In addition, asymptomatic patients should be followed routinely as well. The current guidelines suggest checking an echocardiogram yearly in patients with very severe mitral stenosis (valve area < 1.0 cm^2), every 1 to 2 years with severe mitral stenosis (valve area < 1.5 cm^2), and every 3 to 5 years otherwise.

Using these Doppler and two-dimensional measurements, the severity of the mitral stenosis can be estimated. A valve area ≤ 1.5 cm^2 (pressure half time ≥ 150 ms) is considered severe and a valve area of ≤1.0 cm^2 (pressure half time ≥ 220 ms) is considered very severe under the current recommended guidelines [11]. While a mean gradient of >10 mmHg is also suggestive of severe mitral stenosis, the variability of this gradient with heart rates does not make it an ideal measurement. A full assessment of the severity also looks at the end organ effects (atrial dimensions, ventricular function and signs of pulmonary hypertension) (Table 21.1).

If the transthoracic images are non-diagnostic, transesophageal echocardiography (TEE) can add valuable information but is not always necessary for the purposes of diagnosis. In the case of atrial fibrillation, however, TEE is the test of choice to rule out an atrial appendage thrombus. This is particularly important prior to balloon valvuloplasty of the mitral valve.

While echocardiography is typically the only test needed for diagnosis, a cardiac catheterization can also provide measurements of the valve gradient and indirect calculations of the valve area. By subtracting the pulmonary capillary wedge pressure from the left ventricular pressure, an estimate of the mitral valve gradient can be obtained. Rarely, a transeptal puncture can be performed for direct measurement of the left atrial pressures as well. If the cardiac output is calculated (by Fick or thermodilution methods), the mitral valve area can be determined by the Gorlin formula. As always, care should be taken to minimize the pitfalls encountered with these estimations (errors in cardiac output or pulmonary capillary wedge pressure measurements).

Cardiac MRI can also visualize the mitral valve and estimate pressure gradients [12]. At experienced centers, these studies can correlate well with echocardiographic measurements but are not routinely used due to the ease of obtaining echocardiograms.

Finally, exercise testing can be a valuable tool in assessing the degree of mitral stenosis. One can evaluate the functional capacity in patients whose symptoms are not entirely consistent. In addition, measuring the mean gradient across the mitral valve along with elevation of pulmonary pressures (>60–70 mmHg) with exercise can suggest increasing severity of the mitral stenosis [13].

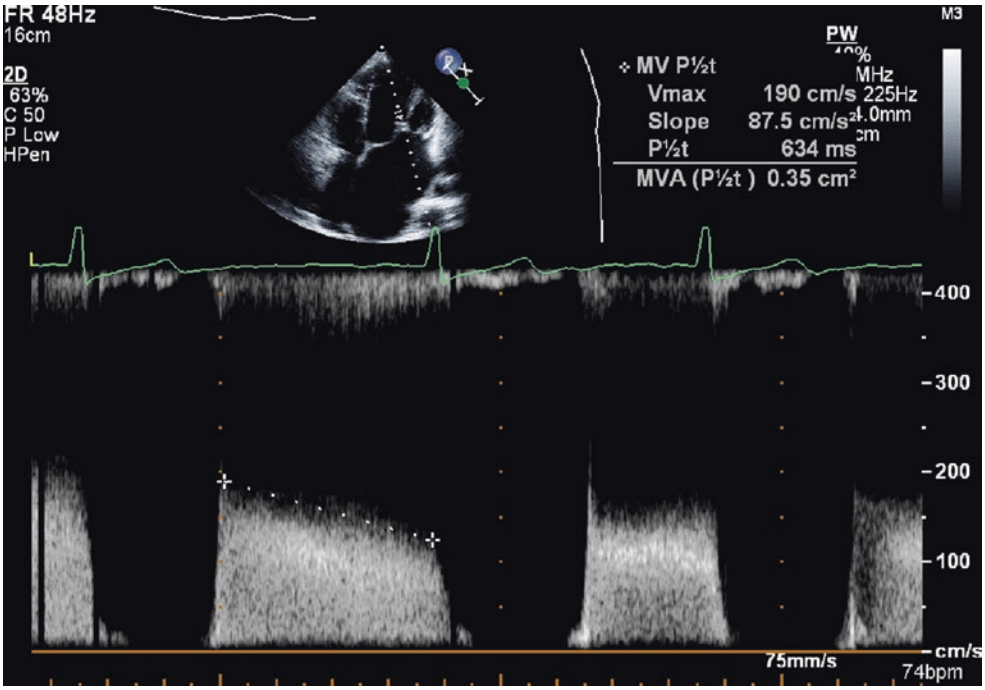

Fig. 21.2 This is a Doppler velocity tracing showing severe mitral stenosis. In this case, the pressure half time is 634 ms which calculates a valve area of 0.35 cm^2

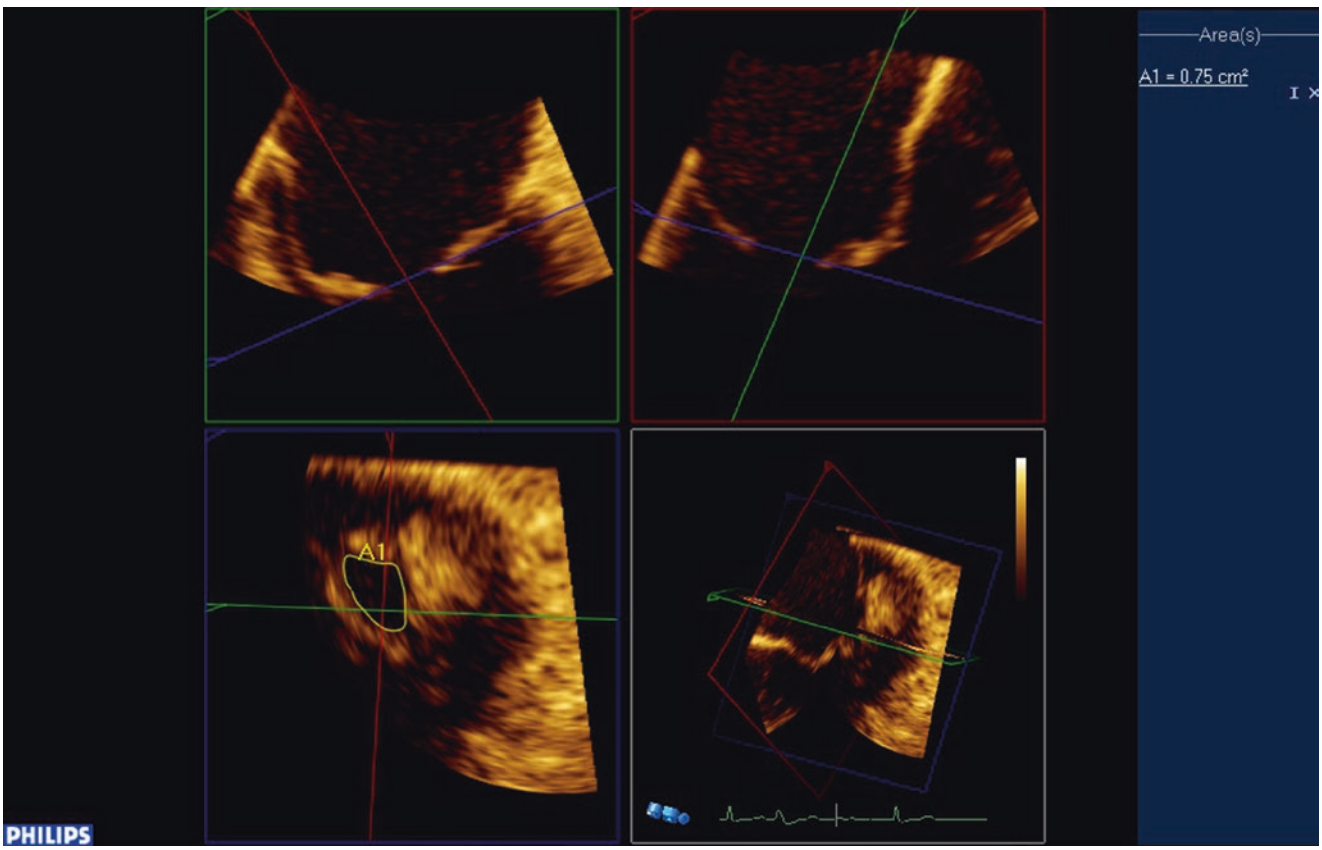

Fig. 21.3 This is a 3D capture of a stenotic mitral valve during a transesophageal echocardiogram. Using this reconstruction, one can planimeter the mitral valve area and ensure that it is truly a measurement at the leaflet tips

Differential Diagnosis

In terms of early symptoms—dyspnea, chest pressure, fatigue—the differential can be quite broad and include many cardiovascular conditions. One must have suspicion of mitral stenosis and an echocardiogram can then readily make the diagnosis. Other causes of left atrial obstruction can include cor triatriatum and atrial masses including atrial myxomas. These too, are readily distinguished with echocardiography.

Complications

The main complications from mitral stenosis initially arise due to elevated left atrial pressures caused by obstruction of blood flow into the left ventricle. This is transmitted into the pulmonary vasculature and can cause pulmonary congestion and secondary pulmonary hypertension. With end stage mitral stenosis, there is poor cardiac output due to decreased preload of the left ventricle resulting in low output heart failure. While this is rare in the United States due to early detection, it is still present in less developed countries.

Increasing left atrial size and pressure also result in an increased incidence of atrial fibrillation as well as an increased risk of atrial thrombus formation [14]. Not infrequently, a thromboembolism may be the presenting symptom in mitral stenosis. This can sometime occur in the absence of atrial fibrillation as well (Fig. 21.4a, b).

As with all valvular heart disease, mitral stenosis can also increase the risk of endocarditis. Under the current guidelines however, it is not felt that antibiotic prophylaxis is beneficial in these patients [15].

Table 21.1 Echocardiographic criteria for severity of mitral stenosis along with the recommended follow up frequency

Mitral stenosis severity	Mitral valve area	Pressure half time	Echocardiogram follow up
Mild to moderate	>1.5 cm^2	<150 ms	Every 3–5 years
Severe	<1.5 cm^2	≥150 ms	Every 1–2 years
Very severe	<1.0 cm^2	≥220 ms	Every year

Data from Nishimura et al. [11]

Therapy

Medical Therapy

Once rheumatic fever has been diagnosed, patients are at high risk for developing recurrent rheumatic fever and development of rheumatic heart disease. For this reason, it is recommended that patients who have had rheumatic fever receive antibiotic prophylaxis against reinfection. If the patient had rheumatic fever without carditis, this can be done for 5 years or until 21 years of age (whichever one is longer). If they had carditis without valve disease, this should be continued for 10 years or until age 21 (again the longer duration). If the rheumatic fever caused valvular disease, the antibiotic prophylaxis should be continued for 10 years or age 40 (again, the longer duration) [15]. Once again, it is not recommended that patients with mitral stenosis get antibiotic prophylaxis against endocarditis unless they have a history of endocarditis or prosthetic valve placement.

Patients who develop atrial fibrillation need to be anticoagulated with either warfarin or heparin due to the high risk of atrial thrombus with these two conditions. The goal international normalized ratio (INR) is 2 to 3. In addition, patients who have a known atrial thrombus or a prior embolic event and concomitant mitral stenosis should also be anticoagulated

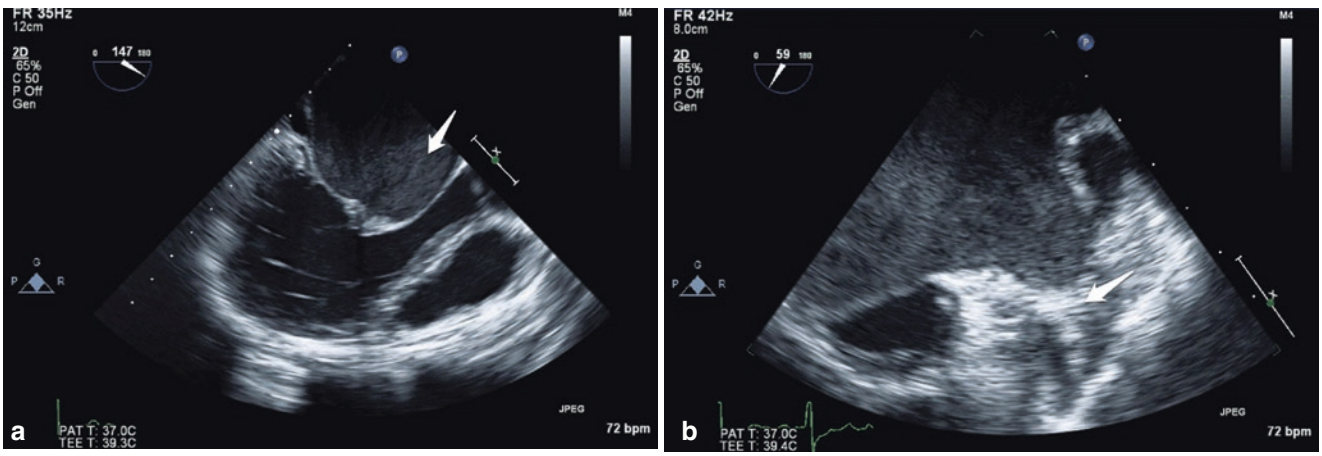

Fig. 21.4 On this image, taken during a transesophageal echocardiogram of a patient with severe mitral stenosis, there is significant spontaneous contrast noted in the left atrium (arrow, **a**). The patient also had a left atrial appendage thrombus (arrow, **b**)

even without atrial fibrillation. Although it is somewhat controversial, some organizations recommend anticoagulation in patients with severe rheumatic mitral stenosis and left atrial enlargement or spontaneous contrast [16].

In patients with atrial fibrillation, the increased heart rate significantly reduces the diastolic filling time, which can worsen the symptoms of mitral stenosis. Rate control can improve symptoms, and if adequate rate control cannot be accomplished, cardioversion could be considered. In patients with sinus rhythm, it may be beneficial to slow the heart rate as well. Some studies have not shown any major benefit with beta-blockers in patients with mitral stenosis [17], but it is still considered reasonable to try in patients who have symptoms during exercise.

Valvuloplasty

For patients who are symptomatic with mitral stenosis, percutaneous or surgical interventions should be considered and are associated with significantly better outcomes than with medical therapy alone [18].

Percutaneous mitral valve balloon valvuloplasty has been shown to be safe and effective in symptomatic patients with severe mitral stenosis. In this procedure, a transeptal approach is used to pass a balloon across the mitral valve, which is then inflated to increase the valve orifice area (Fig. 21.5). In contrast to surgical procedures, it does not require a thoracotomy or cardiac bypass resulting in a more cost effective procedure with faster recovery and less complications [19].

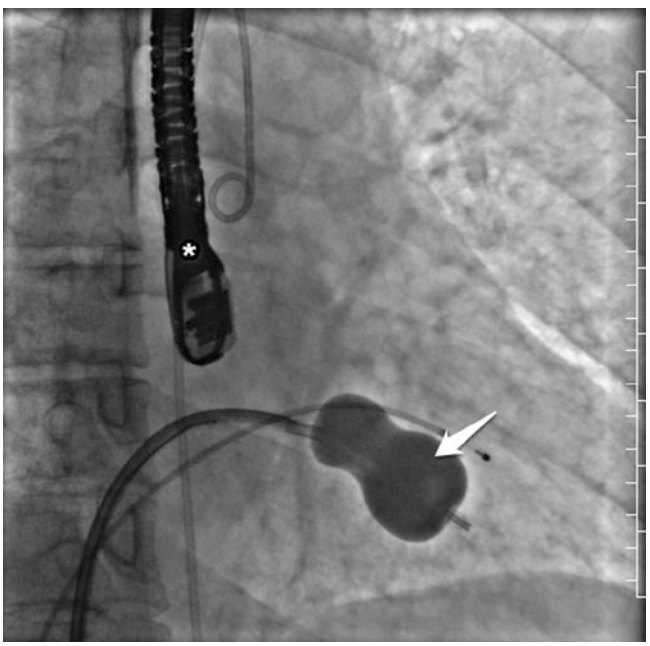

Fig. 21.5 This is a frame from fluoroscopy during valvuloplasty. The balloon is currently inflated (arrow) and the "neck" of the balloon is where the mitral valve is. This particular procedure is done under guidance of a transesophageal echocardiogram (∗) and hemodynamic monitoring

As this procedure is essentially a controlled tear of the mitral valve, heavily calcified or thickened valves tend to have worse outcomes. Scoring systems have been developed to predict which patients will have better outcomes with valvuloplasties. Traditionally, the Wilkins score [20] is used which qualitatively assesses the mitral valve mobility, subvalvular thickening, leaflet thickening and calcification. A score of 1 to 4 is given for each element and total scores of 8 or lower are considered favorable for percutaneous valvuloplasty. Patients with moderate or worse mitral regurgitation at baseline are also considered to be less favorable for a percutaneous procedure. In addition to this, patients with a left atrial thrombus are not candidates and a TEE is required to rule this out prior to attempting a valvulplasty.

One of the major complications with valvuloplasties is the development of significant mitral regurgitation which has occurred in up to 12% of patients [21]. Other complications can include death (which is rare), residual atrial septal defects, embolic events, arrhythmias and pericardial effusions [22]. Restenosis can occur after valvuloplasty in some patients and a repeat valuloplasty is still preferred in patients with favorable anatomy [23].

Surgery

Surgery is performed primarily in patients who are not candidates for valvuloplasty and may include a commissurotomy, or more typically, valve replacement. This is especially the case in patients with concomitant significant mitral regurgitation. Because surgical replacement or repairs are associated with more risk than the percutaneous procedures and also have long term implications, the threshold for symptoms is higher than for percutaneous valvuloplasty.

Management Decision Making

This section is adapted from the "2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease" [11].

Asymptomatic Patients

Very Severe Mitral Stenosis

In patients with very severe mitral stenosis (valve areas $\leq 1\ cm^2$), the valve anatomy should be evaluated to see if it is favorable for percutaneous balloon mitral valvuloplasty as

discussed earlier (PBMV). It there is no left atrial thrombus and mild or less mitral regurgitation, PBMV should be considered. If the valve is not amenable to a percutaneous procedure, the patients should be periodically monitored for the onset of symptoms. An echocardiogram should be repeated yearly or with the development of symptoms.

Severe Mitral Stenosis

In general, patients with severe mitral stenosis (valve areas between 1 and 1.5 cm^2) should be followed clinically. A procedure is not recommended until the onset of symptoms (see below). One exception to this is a patient who has new onset atrial fibrillation. As this is typically a sign of worsening hemodynamics, one should consider a PBMV if the anatomy is favorable. If the anatomy is not favorable, the heart rate should be controlled and the patient should be treated conservatively and monitored for the onset of symptoms. An echocardiogram should be repeated every 1 to 2 years.

Symptomatic Patients

Severe Mitral Stenosis

If the valve anatomy is favorable for PBMV and the patient is symptomatic, this should be performed. If the valve anatomy is not favorable, the patient will require valve surgery instead. As this comes with a higher risk than a percutaneous valvuloplasty, one should wait until the patient has significant symptoms prior to surgery (NYHA Class III symptoms). Occasionally a patient with severe mitral stenosis, NYHA Class III–IV symptoms, and unfavorable valve morphology presents who is not a candidate for surgery. In these patients, a PBMV can be considered after discussing the potential increased risk associated with this.

Moderate Mitral Stenosis

Some patients present with symptoms, but their mitral valve evaluation appears to show only moderate mitral stenosis (valve area ≥ 1.5 cm^2). In these patients, one should evaluate for hemodynamic consequences of the mitral valve disease. It is recommended to evaluate the pulmonary capillary wedge pressure with exercise and if it exceeds 25 mmHg, a PBMV should be considered if the anatomy is favorable for this procedure. If the anatomy is not favorable, the patient should be monitored periodically for worsening symptoms or worsening valve disease.

Non-rheumatic Valve Disease

Most of the guidelines and studies are focused on rheumatic mitral valve disease. Congenital disease is generally diagnosed early and the valve is surgically corrected. In the case of severe mitral annular calcification, there is little data. These valves are not amenable to percutaneous intervention and will require valve replacement surgery which can be technically challenging. Surgery is performed only when there are severe symptoms that cannot be managed medically.

Prognosis

Most patients with mitral stenosis are asymptomatic for decades. Without surgery, symptomatic patients with mitral stenosis have a 34% 10-year survival rate [24]. This is typically due to progressive right-sided heart failure, but is quite rare with modern medical care. Overall, patients who undergo surgical or percutaneous correction of mitral stenosis have a favorable prognosis [25, 26]. In general, patients who have pulmonary hypertension or right-sided failure prior to the procedure have worse outcomes [27]. This makes it important to follow patients periodically and monitor for indications of surgery prior to the onset of right sided heart failure if possible.

Practical Points

- The most common cause of mitral stenosis is rheumatic heart disease. Other less common causes include mitral annular calcification, radiation therapy or congenital conditions.
- Signs or symptoms of mitral stenosis include dyspnea, left atrial enlargement and a diastolic rumble. Atrial fibrillation can also be a presenting finding.
- The primary test for diagnosing mitral stenosis is echocardiography. If inconclusive, one may consider transesophageal echocardiography or cardiac catheterization. Severe mitral stenosis is defined as a mitral valve area of less than 1.5 cm^2. Very severe mitral stenosis is defined as a valve area less than 1.0 cm^2.
- Heart rate control can sometimes improve symptoms with mitral stenosis. Patients with atrial fibrillation and mitral stenosis should be anticoagulated with warfarin.
- Serial echocardiograms and clinical exams are recommended in patients with mitral stenosis to monitor for progression of disease.
- If the valve morphology is amenable to percutaneous balloon commissurotomy, this is preferred over mitral valve replacement.
- Patients with symptoms should be evaluated for a valve procedure. If the valve is amenable to balloon commissurotomy, this can be considered at any symptomatic level. As surgical valve replacement is somewhat higher risk, this is typically reserved for patients with at least Class III symptoms.

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Aortic Stenosis

22

Anna M. Booher, Michael J. Shea, and G. Michael Deeb

Definition

Valvular aortic stenosis is the most common valve lesion in adults in industrialized nations, and calcified aortic stenosis is the valve lesion most commonly considered for valve replacement in the United States, particularly in the elderly. The normal aortic valve has three leaflets and has an area of 2 to 3 cm^2. Aortic stenosis is often not apparent until the valve orifice area is reduced by at least 50%. In general, patients are asymptomatic until the valve area is less than 1 cm^2. The onset of symptoms is associated with a 2-year survival rate of less than 50% in untreated patients (Fig. 22.1). In contrast, adults with asymptomatic aortic stenosis up to 2 years after diagnosis have survival similar to age and gender matched controls [1].

Usual Causes

Aortic stenosis is most commonly acquired and occurs in previously normal aortic valves (Table 22.1). Seventy percent of affected patients suffer from calcific stenosis of a three leaflet valve or bicuspid valve, 15% from rheumatic stenosis, and 15% from other forms of stenosis. Acquired aortic stenosis occurs as a result of atherosclerotic-like inflammation and subsequent calcification of the aortic leaflets and usually manifests in the sixth, seventh, and eighth decades. According to the Helsinki Aging study, almost 3% of the individuals between 75 and 86 years of age have significant aortic stenosis [2].

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Approximately 1% of the population have bicuspid aortic valves (Figs. 22.2 and 22.3). Individuals with bicuspid aortic valves are more likely to develop aortic stenosis than are individuals with three leaflet valves and the condition manifests earlier, typically in the third and fourth decades. The bicuspid aortic valve is the most common pathologic finding in symptomatic patients with aortic stenosis who are younger than 65 years. Bicuspid aortic valve is four times more common among men than among women. The bicuspid valve has a single fused commissure, which results in an eccentrically oriented orifice. These anatomic characteristics, when subjected to hemodynamic stress, may result in thickening and calcification of the valve leaflets, rendering them immobile and stenotic in some patients [3]. About one fifth of the patients with bicuspid aortic valves have associated cardiac abnormalities including coarctation of the aorta, a variety of left sided obstructive lesions, VSD, patent ductus arteriosis and anomalous coronary anatomy. It is also associated with the Turner syndrome [4]. Aortic root dilation and aneurysm have been reported in up to 30% of patients with bicuspid aortic valve. Histologically, this is associated with degeneration of the aortic media. The degree of dilation is unrelated to blood pressure or aortic valve function. These findings suggest a common genetic defect and developmental abnormality [5].

In developing countries, rheumatic fever is a common cause of aortic stenosis, and usually the valve is also regurgitant. The stenosis typically occurs in a previously normal valve and is characterized by commisural fusion, followed by secondary calcification and contraction of leaflets and annulus. In these patients, the mitral valve is also commonly affected.

Symptoms

Many patients with aortic stenosis are asymptomatic. Symptoms usually manifest when the valve area is less than 50% of normal (normal valve area is >2 cm^2) or near 1.0 cm^2. Typical symptoms of aortic stenosis include angina, syncope, and shortness of breath.

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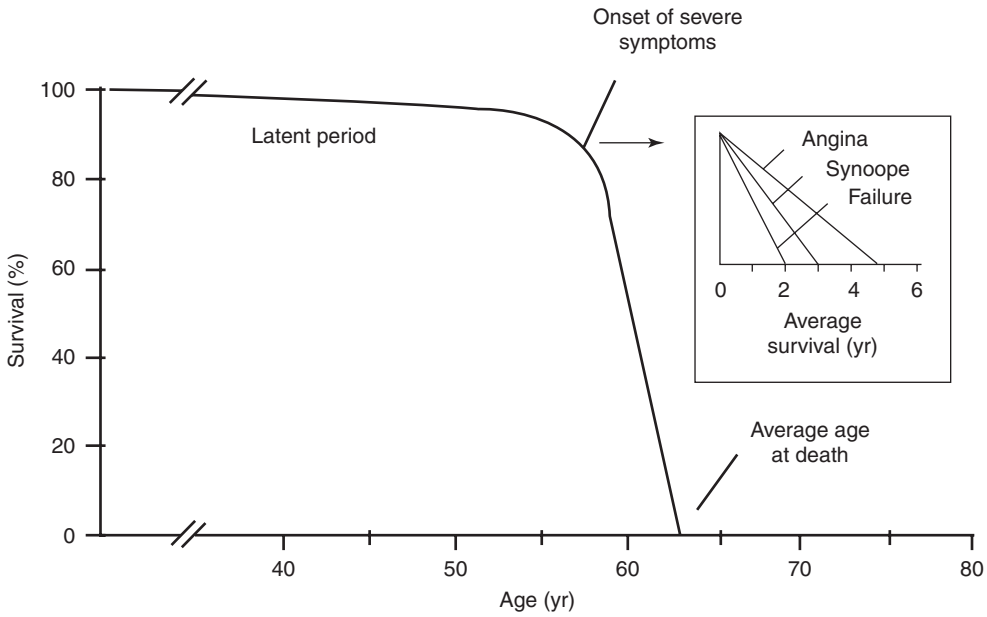

Fig. 22.1 Natural history of aortic stenosis. Of symptomatic patients in whom the aortic valve is not replaced, about half die within 5 years after angina develops, and half die within 3 years after the onset of syncope; patients with dyspnea/heart failure die within only 2 years after these develop. (Adapted from Ross and Braunwald [24])

Table 22.1 Usual causes of left ventricular outflow tract obstruction

Aortic valvular stenosis
Arteriosclerotic degeneration and calcification of valve
Congenital (most commonly bicuspid valve)
Rheumatic fever
Atherosclerosis: marked hypercholesterolemia as in homozygous type II hyperlipoproteinemia can result in massive deposition of atheroma on the valve, aortic valve, and coronary arteries
Supravalvular aortic narrowing (Williams' syndrome)
Subvalvular stenosis
Left ventricular outflow tract
Discreet diaphragm or ridge
Hypertrophic cardiomyopathy (see page X)
Discrete fibromuscular ring
Tunnel subaortic stenosis
Anomalous attachment of the anterior mitral valve leaflet

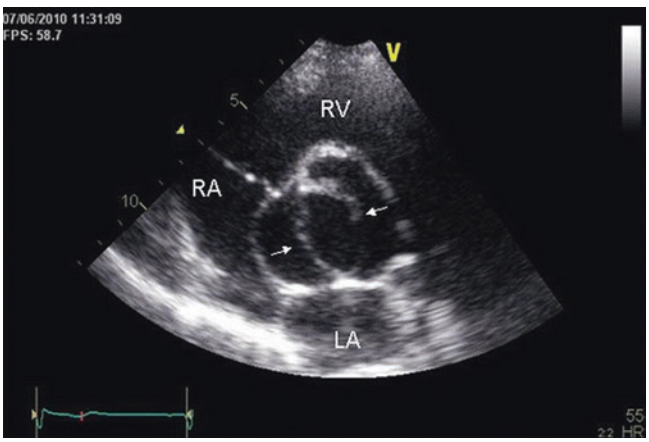

Fig. 22.2 Transthoracic echocardiography showing a bicuspid aortic valve with fusion of the right and left cusps arrows by parasternal transverse view. *RA* right atrium, *RV* right ventricle, *LA* left atrium. (From Evangelista [26]; with permission)

Angina occurs in about 70% of patients and, in the absence of coronary artery disease, results from a combination of increased myocardial oxygen demand and reduced coronary flow reserve caused by increased left ventricular mass. However, in one study, about one fourth of the patients with severe aortic stenosis also had angiographically significant coronary artery disease [6].

Syncope occurs in about 25% of patients and is often associated with exercise or exertion. (see Chap. 5). Exertional syncope has been attributed to the fact that cardiac output is restricted by the stenosed valve, when peripheral resistance falls upon exercise. Impaired vasodepressor response is a second explanation for syncope that occurs in this condition. Increased intramural pressure, stimulating baroreceptors and thereby resulting in reflex bradycardia and vasodilatation, is another mechanism by which syncope can occur. Diastolic dysfunction with inability to increase cardiac output on exercise is an additional mechanism. When the calcification associated with the stenotic aortic valve extends into the upper part of the ventricular septum, complete atrioventricular block can occur and manifests as syncope.

Shortness of breath and symptoms of congestive heart failure result from high end-diastolic pressures in the left ventricle and is often first apparent on exertion. Shortness of breath, including paroxysmal nocturnal dyspnea, is suggestive of left ventricular dysfunction and portends a poor prognosis. Orthopnea indicates severe left ventricular dysfunction. The left ventricular dysfunction in aortic stenosis can be diastolic, systolic or both. Diastolic dysfunction tends to predominate in advanced stages and is due to increased LV

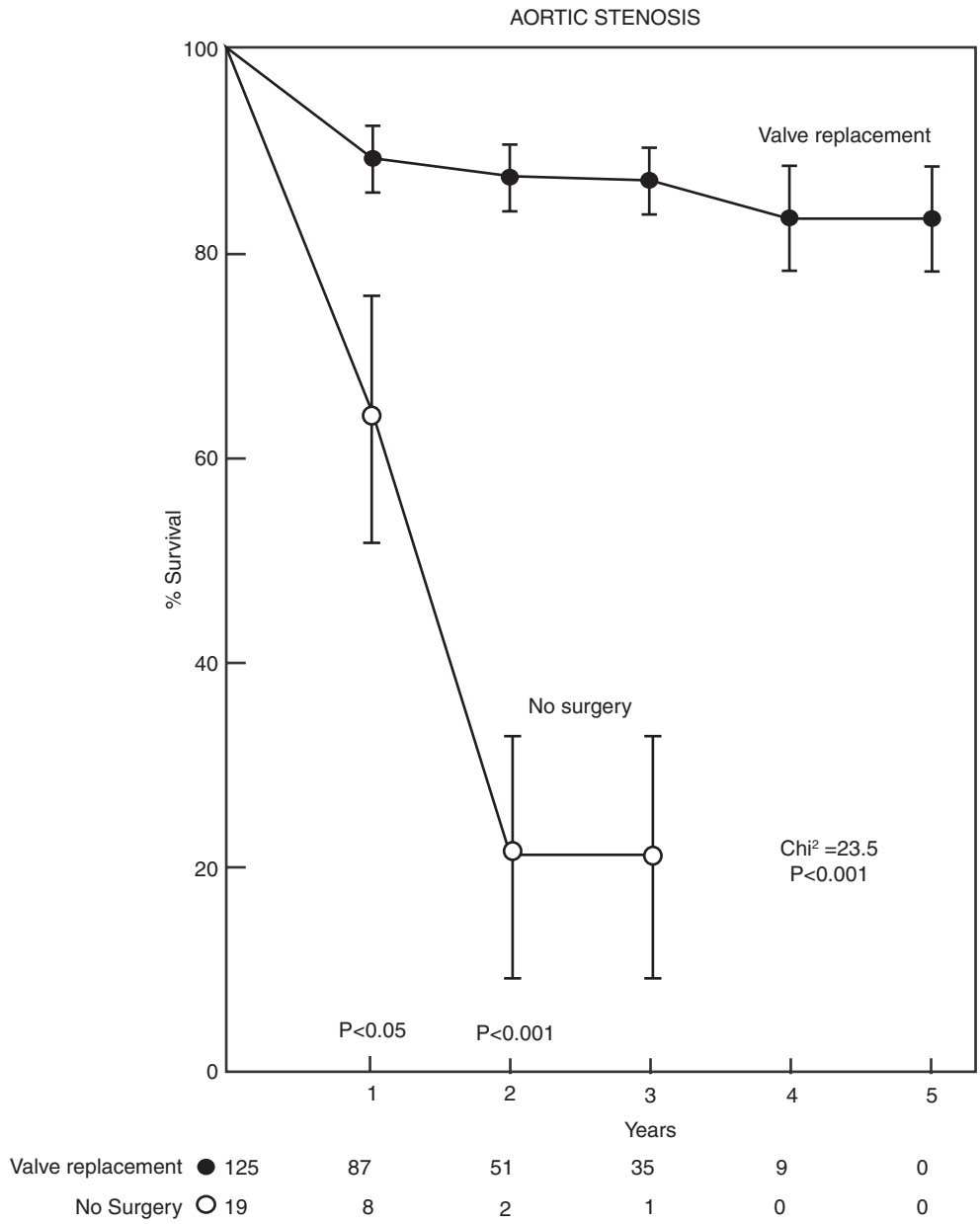

Fig. 22.3 Survival is better after aortic valve replacement than with medical therapy in patients with severe aortic stenosis. (From Schwarz et al. [15]; with permission)

myocardial thickness and myocardial fibrosis [7]. Systolic dysfunction is caused by dilatation of the left ventricle and decreased myocardial contractility. Therefore, although heart failure is a common presentation of aortic stenosis, many patients can have a normal LV systolic ejection fraction but low cardiac output. Severe aortic stenosis can manifest for the first time as congestive heart failure, and affected patients typically have a low volume pulse, an enlarged heart, and a soft murmur due to reduced cardiac output.

Other modes of presentation include infective endocarditis (see Chap. 18), sudden death, and occasionally, systemic emboli from the calcified valve (usually resulting in a stroke or amaurosis fugax). About 3–5% of patients with aortic stenosis die suddenly without prior symptoms, and the mechanism of death remains unclear, but it has been suggested that it may be a result of extreme intolerance to complete heart block, tachyarrhythmias or ischemia. Patients with severe aortic stenosis can rarely develop microangiopathic hemolytic anemia as a result of turbulent flow inducing hemolysis at the valve. Infective endocarditis should be considered in patients with aortic stenosis who present with unexplained subacute illness. Arrhythmias and conduction abnormalities have also been described in aortic stenosis. Ventricular arrhythmias are more common than supraventricular arrhythmias, and heart block may occur because of calcification encroaching on the AV node.

Signs

In mild aortic stenosis (when the peak aortic gradient is less than 50 mmHg), the pulse is normal. In severe aortic stenosis, the carotid pulse is slow in rising and has diminished volume with a notch on the upstroke—the anacrotic pulse—but it may be normal in elderly patients with noncompliant carotid arteries. With associated aortic regurgitation, a double pulse, or *pulsus bisferiens,* may be felt. The apex beat initially is thrusting and not displaced and reflects the concentric hypertrophy of the left ventricle. A displaced apex beat indicates left ventricular dilatation, which suggests that the condition is advanced or that there is associated aortic regurgitation. A systolic thrill may be felt at the base of the heart.

On auscultation there is a midsystolic, crescendo-decrescendo murmur (diamond-shaped murmur), best heard in the second right intercostal space, and the intensity of the murmur increases on expiration. The murmur usually radiates to the neck and right clavicle. Clavicular auscultation appears to be more rewarding than the traditional search for transmission of aortic murmurs to the carotid artery [8]. In mild aortic stenosis, the peak of the murmur occurs earlier in systole, and as the severity of stenosis progresses, the peak of the murmur occurs later in systole. The decrease in the loudness of the murmur is suggestive of the onset of poor left ventricular function and a low cardiac output. The murmur may display the Gallavardin phenomenon—that is, the selective transmission of the musical component toward the cardiac apex but location of the noisy component (jet noise) to the right of the upper sternum, with transmission toward the carotid arteries. The transmission of these high-frequency components of the murmur to the apex may be mistaken for mitral regurgitation.

The aortic component of the second heart sound is soft or absent when the valves are calcified. A delayed aortic component of the second sound or reverse split is suggestive of severe aortic stenosis. An ejection click may be heard at the apex in bicuspid aortic stenosis, especially in young patients. A third heart sound implies severe left ventricular dysfunction, whereas a fourth heart sound may indicate myocardial hypertrophy and non compliance as a result of severe aortic stenosis.

Helpful Tests

Electrocardiogram

The electrocardiogram usually shows left ventricular hypertrophy and, occasionally, left axis deviation. In later stages there may be negative P waves in lead V_1 caused by left atrial hypertrophy. First-degree heart block or left bundle branch block is suggestive of calcification of the conducting tissues. The presence of atrial fibrillation is suggestive of associated mitral valve disease or concomitant coronary artery disease.

Chest Radiograph

The chest radiograph may show cardiac enlargement, but, typically in the initial stages, the cardiac size may be normal in posteroanterior views. Poststenotic dilatation of the aorta may be seen but can also occur with subvalvular stenosis. Calcification of the aortic valve may be seen in lateral views, particularly in older patients. Signs of pulmonary venous congestion or pulmonary edema may be seen in left ventricular failure. Coarctation of the aorta may also show rib notching on chest radiography.

Echocardiography

Echocardiography is useful for assessment of valve anatomy, valve calcification, LV systolic and diastolic function and LV hypertrophy (Table 22.2). Women have a higher incidence of excessive left ventricular hypertrophy which can contribute to a supernormal (>70%) left ventricular ejection fraction [9]. Echocardiography is useful in the diagnosis and assessment of the severity of aortic stenosis. Complete assessment of AS requires a) measurement of transvalvular flow, b) determination of the peak and mean transvalvular pressure gradients and c) calculation of the effective valve area. The degree of aortic stenosis is graded as mild (valve area exceeding 1.5 cm^2), moderate (area exceeding 1.0 to 1.5 cm^2), or severe (area < 1.0 cm^2) (Table 22.3). Echocardiography also helps define the anatomic level of obstruction (i.e., valvular,

Table 22.2 ACC/AHA recommendations for echocardiography

Class I: There is evidence and/or general agreement that echocardiography is useful and effective
Diagnosis and assessment of severity of aortic stenosis
Assessment of left ventricular size, function, and hemodynamics
Reevaluation of patients with known aortic stenosis with changing symptoms or signs
Assessment of changes in hemodynamic severity and ventricular function in patients with known aortic stenosis during pregnancy
Reevaluation of asymptomatic patients with severe aortic stenosis every year
Reevaluation of asymptomatic patients with moderate aortic stenosis every 1 to 2 years
Reevaluation of asymptomatic patients with mild aortic stenosis every 3 to 5 years
Class IIa: The weight of evidence/opinion is in favor of usefulness/efficacy of dobutamine stress echocardiography
Reasonable to evaluate in patients with low-flow/low-graient AS an LV dysfunction

ACC/AHA American College of Cardiology/American Heart Association. Adapted from Bonow et al. [29]

supravalvular, subvalvular). A normal valve appearance excludes significant aortic stenosis in adults – leading to the possibility of sub-or supra-valvular obstruction in patients with elevated LV outflow gradients. Furthermore, echocardiography allows assessment of left ventricular size, function, and hemodynamics. It is useful in the reevaluation of patients with known aortic stenosis with changing symptoms and signs and in asymptomatic patients with severe aortic stenosis.

Table 22.3 Severity of aortic stenosis

Severity of aortic stenosis	Aortic valve area (cm^2)	Mean gradient (mmHg)	Jet velocity (m/s)
Normal aortic valve	2–3	–	–
Mild	>1.5	<25	<3
Moderate	>1.0–1.5	25–40	3.0–4.0
Severe	<1	40	>4

Doppler imaging allows assessment of the valve gradient. The valve gradient, however, depends on several factors, including left ventricular function and cardiac output, and therefore is not always a good indicator of the severity of the disease. For example, a mean valve gradient of less than 50 mmHg may be associated with severe, moderate, or even mild aortic stenosis [9, 10]. Thus, it is more prudent to use the calculated effective aortic valve area to determine the severity of aortic stenosis. This is assessed by the continuity equation.

Low-output low-gradient aortic stenosis is assessed utilizing dobutmaine challenge (Fig. 22.4).

Exercise Testing

Exercise testing in adults with symptomatic aortic stenosis has been discouraged largely because of safety issues and is

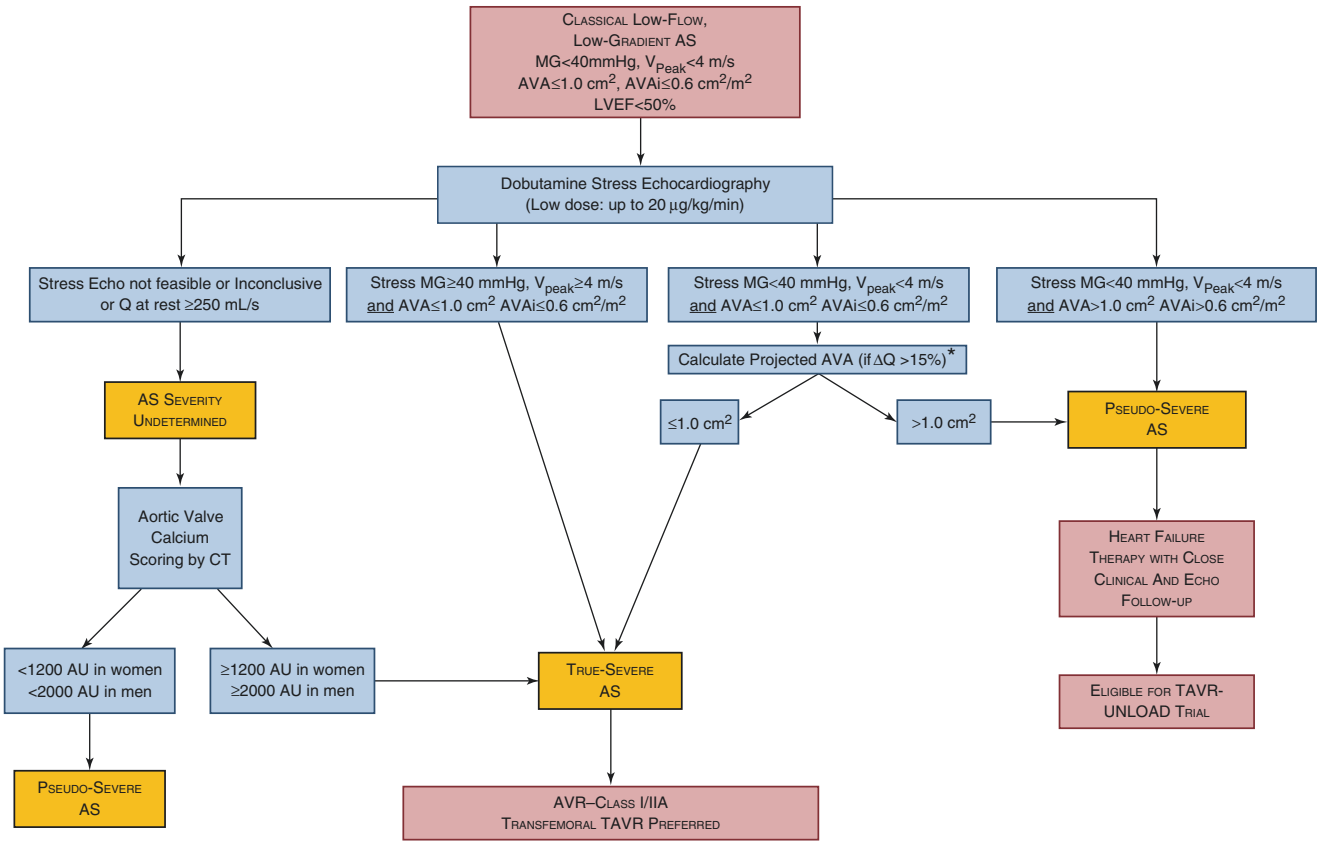

Fig. 22.4 A clinical algorithm for patients with low-output low-gradient AS utilizing dobutamine challenge. Left ventricular and ascending aortic pressure tracings at baseline and after a dobutamine challenge are shown for each patient subgroup. The three subgroups are categorized according to a change in transvalvular gradient, change in cardiac index (contractile reserve) and change in the calculated aortic valve area. *Ao* ascending aortic pressure, *AS* aortic stenosis, *AVA* aortic valve area, *AVR* aortic valve replacement, *CI* cardiac index, *CO* cardiac output, *LA* left atrial (pressure), *LV* left ventricular (pressure). (From Martinez and Nishimura [28]; with permission)

contraindicated in symptomatic patients. In asymptomatic patients with severe stenosis, an abnormal hemodynamic response (e.g., hypotension), or the demonstration of occult or under-reported symtpoms with exercise is sufficient to consider aortic valve replacement (AVR). Occasionally, in selected patients without inducible symptoms, exercise testing is also useful for providing a basis for advice about physical activity.

Cardiac Catheterization

Cardiac catheterization is useful in determining the coronary anatomy and for confirming or clarifying the diagnosis of aortic stenosis (Table 22.4). Cardiac hemodynamic measurement with left- and right-sided heart catheterization is indicated when echocardiographic assessment of valve stenosis severitiy inadequate The simultaneous recording of pressures in the left ventricle and in the systemic circulation remains the standard for documenting the presence and severity of aortic stenosis (Fig. 22.5). Key components of this procedure include (a) measurement of transvalvular flow, (b) determination of transvalvular pressure gradient, (c) calculation of the effective valve area, and (d) determination of the anatomy of the aortic root. A bicuspid aortic valve is often associated with a dominant left circumflex coronary artery and a short left main stem and occasionally anomalous position of coronary ostia.

Differential Diagnosis

Aortic Sclerosis

Aortic sclerosis can simulate aortic stenosis because, on auscultation, a systolic ejection murmur may be audible. It is more common in old age and associated with a normal carotid

Table 22.4 ACC/AHA recommendations for cardiac catheterization

Class I: There is evidence and/or general agreement that cardiac catheterization is useful and effective
Coronary angiography before AVR in patients with AS at risk for CAD
Hemodynamic measurements for assessment of severity of AS in symptomatic patients when non-invasive tests are inconclusive or when there is a discrepancy between non-invasive tests and clinical findings regarding the severity of AS
Coronary angiography before AVR in patients with AS whom a pulmonary autograft (Ross procedure) is contemplated and if the origin of the coronary arteries is not identified by non-invasive technique
Class IIa: The weight of evidence/opinion is in favor of usefulness/efficacy of cardiac catheterization
For hemodynamic measurements with infusion of dobutamine can be useful for evaluation of patients with low-flow/low-gradient AS and LV dysfunction
Class III: There is evidence and/or general agreement that cardiac catheterization is not useful and in some cases may be harmful
When non-invasive tests are adequate and concordant with clinical findings
Hemodynamic measurements for the assessment of LV function and severity of AS in asymptomatic patients

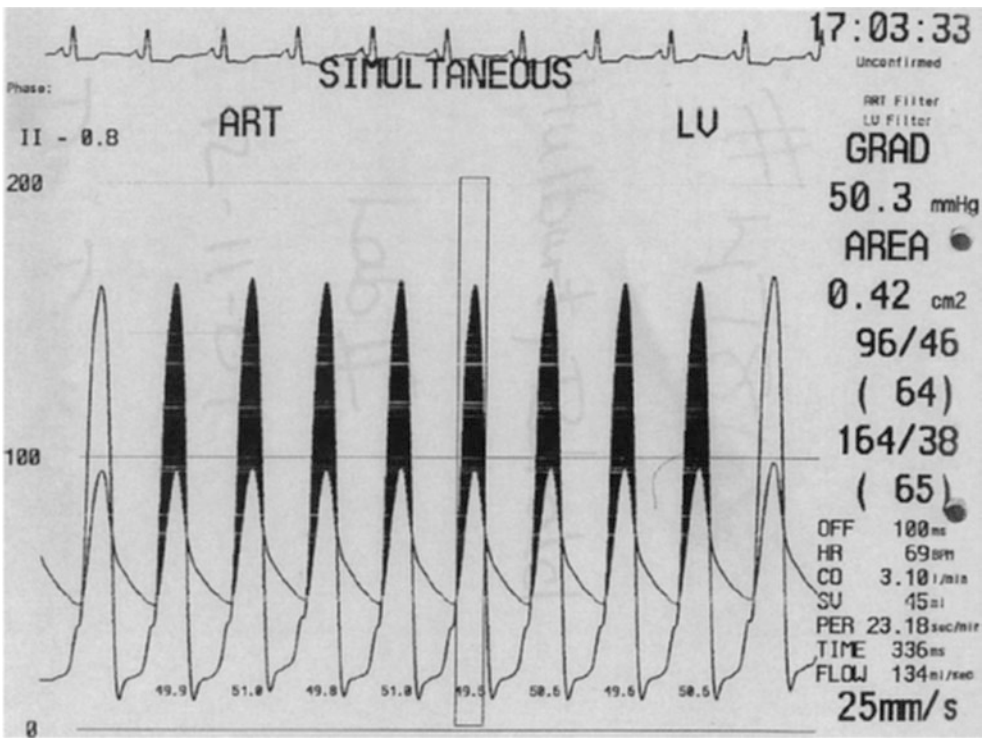

Fig. 22.5 Simultaneous recordings of pressure in the left ventricle and in a peripheral artery show the gradient (difference between the systolic pressures) across the aortic valve

pulse. Echocardiography is necessary to confirm the diagnosis, and typical findings are mild thickening of leaflets without restricted motion or elevated transvalvular gradient [11].

Flow Murmur of Pregnancy; Anemia; and Thyrotoxicosis

These conditions can mimic the murmur of aortic stenosis but are associated caused by high cardiac outuput and associated with large-volume pulse, a normal echocardiogram, and no significant aortic valve gradient.

Mitral Regurgitation

The systolic murmur of mitral regurgitation can be short and therefore be mistaken for aortic stenosis, but these murmurs usually do not radiate to the neck. Echocardiography with-Doppler examination may be the only way to confirm a mitral valve abnormality.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy may also be accompanied by a late systolic murmur. Differentiating features are a jerky pulse, murmur accentuation with a Valsalva maneuver, and echocardiographic findings of asymmetric septal hypertrophy and systolic anterior motion of the mitral valve apparatus.

Ventricular Septal Defect

Ventricular septal defect is associated with a holosystolic murmur at the left sternal edge with thrill, and Doppler echocardiographic findings of the jet across the septal defect confirm this diagnosis.

Therapy

Lifestyle

Physical activity is not restricted in asymptomatic patients with mild aortic stenosis. Asymptomatic patients with moderate to severe aortic stenosis should avoid competitive sports that involve high dynamic and static muscular demands; other forms of exercise (low to moderate intensity aerobic activity) can be performed safely, but it is advisable to evaluate such patients with an exercise test before they begin an exercise or athletic program.

Pharmacologic Treatment

Drug treatment has no place in the treatment of severe aortic stenosis in patients who are candidates for surgical valve replacement. In patients who are not surgical candidates, medical therapy is used to palliate symptoms.

Patients with pulmonary edema may benefit from diuretics, angiotensin-converting enzyme inhibitors and careful use of b-blockers. In patients with angina, cautious use of nitrates and beta blockers may provide symptomatic relief. Patients with atrial fibrillation should undergo cardioversion as this rhythm is poorly tolerated in severe AS; when the latter is unsuccessful, treatment with amiodarone or digitalis may be beneficial.

As the pathology of aortic valve stenosis is likely related to the process of vascular atherosclerosis, treatments to prevent the progression of aortic stenosis, including lipid lowering therapy, have been evaluated. Several retrospective studies showed some improvement in the progression of aortic stenosis in patients on statin drugs. Others have shown that there is benefit in slowing disease progression, particularly in those with higher LDL cholesterol levels [12]. However, a more recent randomized trials showed no benefit on rate of progression while being treated with high dose atorvastatin or simvastatin with ezetimibide [13, 14]. In general, many patients with aortic stenosis will have a traditional indication for statin therapy and should be treated appropriately.

Aortic Valve Replacement

AVR is the standard of care for symptomatic patients because the mortality of this disease reaches 25% per year in medically managed patients compared with relatively normal survival after successful AVR [15] (Fig. 22.3). AVR results in regression of left ventricular hypertrophy and improves survival, symptomatic state, and can lead to improvement in left ventricular function. Age alone is not a contraindication. The calculated valve area and the presence of symptoms, not the absolute transvalvular pressure gradient, is usually the primary determinant of the need for AVR. The choice of the prosthetic valve depends on several factors, including the known risks and benefits of each device, the patient's preferences, and individual circumstances of the patient (see Table 22.5).

The prognosis after surgery depends on age of the patient and comorbid conditions, including left ventricular function, LV mass, the presence of contractile reserve and the presence of coronary artery disease. A subset of patients with aortic stenosis who had a low mean atrioventricular gradient and severe left ventricular dysfunction (left ventricular ejection fraction less than 0.35) have increased operative and perioperative risk but overall experienced good results when treated with AVR [16–18].

Table 22.5 ACC/AHA recommendations for aortic valve replacement

Class I: There is evidence and/or general agreement that AVR is useful and effective
Symptomatic patients with severe aortic stenosis (AS)
Patients with severe aortic stenosis undergoing CABG
Patients with severe aortic stenosis undergoing surgery on the aorta or other heart valves
Severe AS and LV systolic dysfunction (ejection fraction <0.50)
Class IIa: The weight of evidence/opinion is in favor of usefulness/efficacy of AVR
Patients with moderate AS undergoing CABG or surgery of the aortia or heart valves
Class IIb: Usefulness/efficacy is less well established by evidence/opinion
Asymptomatic patients with severe AS and an abnormal response to exercise (e.g., hypotension)
Asymptomatic patients with severe AS if there is likelihood of rapid progression (age, calcification, and CAD) or is surgery might be delayed at the time of symptom onset
Mild AS when there is evidence that progression may be rapid (such as moderate to severe valve calcification)
Asymptomatic patients with severe AS and valve area < 0.6 cm^2
Class III: There is evidence and/or general agreement that aortic valve replacement is not useful and in some cases may be harmful
Prevention of sudden death in asymptomatic patients who have none of the findings listed class IIa/IIb recommedations

ACC/AHA American College of Cardiology/American Heart Association, *AVR* aortic valve replacement, *AS* atrial stenosis, *CABG* coronary artery bypass graft, *LV* left ventricular. Adapted from Bonow et al. [29]

Predictors of operative mortality include size of the prosthetic valve:—smaller stented prostheses (21 mm) are associated with a 47% mortality rate, whereas larger ones (23 mm) are associated with a 15% mortality rate [19]. Patients with a small valve annulus that does not permit the use of a 23-mm prosthesis then should be considered for the use of homografts, stentless valves, or enlargement of the aortic root/annulus.

Although asymptomatic patients with severe aortic stenosis have a normal life span, AVR may be when any one or more of the following features are present: left ventricular systolic dysfunction, abnormal response to exercise (e.g., hypotension or arrythmia), ventricular tachycardia, and valve area less than 0.6 cm^2. Patients with severe aortic stenosis, with or without symptoms, who are undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves should undergo AVR at the time of surgery. In asymptomatic patients with moderate aortic stenosis, it is generally acceptable to perform AVR in patients who are undergoing mitral valve or aortic root surgery or coronary artery bypass surgery. It is important to educate the patient with aortic stenosis about the expected course of the disease and encourage the patient to seek medical attention as soon as symptoms develop so that appropriate intervention can be performed promptly.

Balloon Valvuloplasty

This procedure is useful in infants (in whom the results of open surgery are poor) and in children and young adults (in whom the valve apparatus is not calcified).

Balloon valvuloplasty of calcific aortic stenosis in adults is associated with considerable rates of morbidity and mortality, and it is therefore recommended as a "bridge" to surgery in hemodynamically unstable patients who are at high risk for the need for AVR, as palliation in patients with serious comorbid conditions, or in patients who require urgent noncardiac surgery [20].

Percutaneous Aortic Valve Replacement

In patients with severe aortic stenosis who are not traditional open surgical candidates, the mortality rate is high. In recent years there has been increased interest in a less invansive way to replace the aortic valve in these high risk patients without exposing them to the additional risks associated with open heart surgery and cardiopulmonary bypass. Transcatheter percutaneous aortic valve replacement (TAVR) was first explored in animal models in the 1990's. In 2002, Cribier et al. demonstrated feasibility of this therapy in inoperable patients with severe aortic stenosis [21]. Early experience used a femoral venous approach with a transeptal puncture to access the left heart. Later technology has used percutaneous femoral artery access. The results of the first large scale clinical trial of this technology was published in 2010. The PARTNER B trial compared TAVR to medical therapy (which included balloon aortic valvuloplasty in 83% of cases). TAVR reduced the rate of death, repeat hospitalization and severity of symptoms, despite a higher risk of stroke and vascular (access site) events [22]. Subsequently, the PARTNER A trial evaluated high-risk patients who were surgical candidates and found that TAVR was associated with similar rates of 1 year survival compared with surgical AVR. However, the risk of stroke and vascular complications were higher in the TAVR group [23]. Both PARTNER A and B used the Edwards SAPIEN valve system (Edwards Lifesciences). In November 2011, the Edwards SAPIEN device was awarded FDA approval for use in high risk patients. Several other devices are currently under study (Fig. 22.6).

Early limitations of this technology include large size delivery systems that lead to high rates of femoral access site complications. However, this limitation is less important as the technology evolves to allow for smaller delivery systems. Additionally, other modes of entry for patients without adequate femoral access have developed including subclavian/axillary access and trans-apical puncture methods. In 2019 the indications for TAVR have been expanded to include lower risk patients and has been shown to be safe

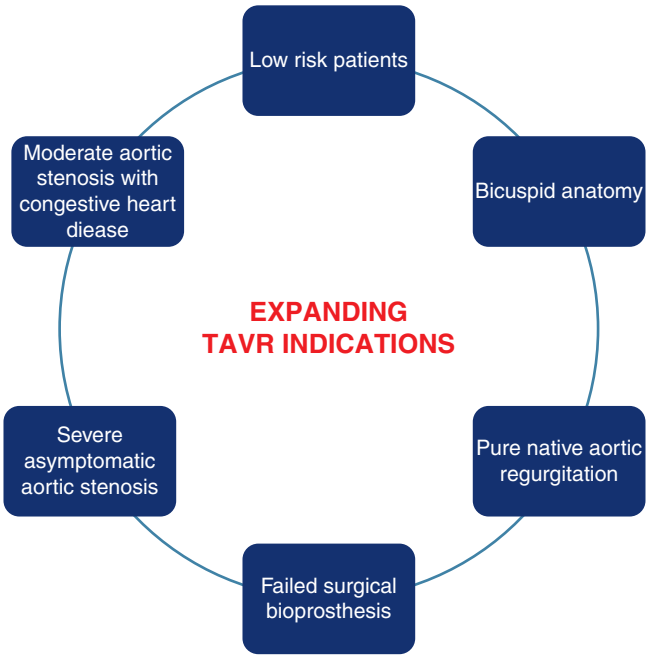

Fig. 22.6 Expanding indications for transcather aortic valve replacement (TAVR). (From Franzone et al. [27]; with permission)

in some patients with Bicuspid aortic valves. This technology continues to advance at a rapid pace.

Prognosis and Follow-Up

Asymptomatic patients with aortic stenosis have a normal life span (Fig. 22.1). However, once symptoms develop, the risk of mortality is substantially increased. Of patients in whom the aortic valve is not replaced, about half die within 5 years after angina develops, and half die within 3 years after the onset of syncope; patients with dyspnea or heart failure die only 2 years after these develop [24]. Up to 20% of patients with severe congenital aortic stenosis die during childhood, mainly because of progressive heart failure. Patients with mild to moderate aortic stenosis should be monitored for progression of valve stenosis or onset of symptoms and educated as to what symptoms to look for.

Patients who have undergone valve replacement should be monitored for failure of the valve prosthesis (particularly biologic valves) and treated with prophylaxis for endocarditis [25].

Practical Points

- Aortic stenosis is common and increases in incidence with increased age
- The onset of symptoms is associated with a 2-year survival rate of less than 50%. In contrast, adults with asymptomatic aortic stenosis have an excellent clinical prognosis.
- Clinical signs of severe aortic stenosis include narrow pulse pressure, soft second heart sound, delayed or reverse split of second heart sound, heaving apex beat, fourth heart sound, and signs of cardiac failure.
- The valve gradient depends on several factors, including left ventricular function, and is therefore not a good indicator of the severity of the disease alone. It is more prudent to use the aortic valve area and appearance to determine the severity of aortic stenosis.
- Exercise testing in adults with symptomatic severe aortic stenosis has been discouraged largely because of safety concerns and is contraindicated in symptomatic patients. In asymptomatic patients, an abnormal hemodynamic response (e.g., hypotension) or eliciting occult or underreported symptoms is sufficient for considering AVR.
- Adults with mild AS can participate in competitive sports. Patients with asymptomatic moderate AS can participate in lower intensity sporting activities if exercise testing (at expected levels of exertion) demonstrates high risk features. Patients with severe AS or symptomatic moderate AS should not engage in competitive activities.
- Medical therapy is not proven to be effective in delaying the progression of AV stenosis and should not take the place of surgical evaluation in patients with severe symptomatic stenosis.
- Balloon valvuloplasty of aortic stenosis is associated with considerable rates of morbidity and mortality, and it is therefore recommended as a "bridge" to surgery in hemodynamically unstable patients who are at high risk for the need for AVR, as apalliation in patients with serious comorbid conditions, and in patients who require urgent noncardiac surgery.
- Surgical aortic valve replacement remains the standard of care in the treatment of severe symptomatic aortic stenosis. However, new technologies, including transcatheter aortic valve replacement, have promise in treating high risk patients who may otherwise not be tranditional surgical candidates.

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Tricuspid/Pulmonary Valve Disease

23

Vincent E. Brinkman

Usual Causes

Tricuspid Valve

Tricuspid regurgitation is the most common right sided valve lesion encountered. Minimal regurgitation of the tricuspid valve is incredibly common and found incidentally in most patients. In fact, some studies have demonstrated small degrees of tricuspid regurgitation in up to 70% of individuals by echocardiography [1]. In the absence of any other signs or symptoms, this is a benign finding. In the case of "pathologic" tricuspid regurgitation, it can be due to functional regurgitation. or valve leaflet pathology. Functional regurgitation is related to anything that increases the right ventricular pressure or volume which in turn causes dilation of the tricuspid annulus. Most commonly, this is related to left sided heart disease. Some examples would include left sided heart failure or mitral stenosis and regurgitation. In addition to left sided heart disease, conditions like a right ventricular myocardial infarction or a pulmonary embolism can lead to right ventricular dilation and tricuspid regurgitation. Intrinsic tricuspid valve disease can also occur. This is typically due to rheumatic heart disease (which almost always occurs in conjunction with mitral and aortic valve involvement). It could also be due to congenital defects like Epstein's anomaly. Tricuspid stenosis is relatively rare, but can also be due to rheumatic heart disease, congenital disease or some systemic illnesses such as carcinoid syndrome [2].

Pulmonic Valve

Pulmonic stenosis is most often caused by a congenital defect causing fusion of the valve leaflets but may also be caused by carcinoid syndrome or rheumatic heart disease. Pulmonic regurgitation is oftentimes the result of surgery to correct pulmonic stenosis—as in patients with a history of tetralogy of Fallot [3]. In addition to this, conditions that cause dilation of the main pulmonary artery can result in pulmonic regurgitation. Examples may include pulmonary hypertension or some connective tissue diseases.

Presenting Symptoms and Signs

Many times, the right sided valve lesions are due to left sided heart disease and it can be hard to sort out the primary cause of the symptoms. The left-sided heart disease will often be the predominant driver of the symptoms with the right sided signs or symptoms being seen as secondary. As the right-sided valve disease progresses, people can have symptoms of right sided heart failure which include fatigue, peripheral edema, abdominal fullness, ascites, dyspnea and shortness of breath. With isolated right sided valve lesions, one should not expect to see pulmonary congestion, although again, right-sided valve lesions often present due to left sided heart disease.

Tricuspid Valve

Mild or moderate tricuspid valve regurgitation typically does not cause significant symptoms. Severe tricuspid regurgitation can over time result in progressive right heart failure with symptoms of fatigue and shortness of breath along with lower extremity edema and abdominal fullness. With this, patients often have a sense of early satiety as well. On exam, there is a holo-systolic murmur best heard at the left sternal border. The murmur typically increases with inspiration correlating with increased flow across the tricuspid valve. The jugular veins are distended with prominent V waves. With progressive right sided dilation and failure, one may also hear a right sided S3 gallop and feel a precordial lift.

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Oftentimes, the patients will have concomitant pulmonary hypertension resulting in a loud pulmonic component of the second heart sound. Peripheral edema can be present along with hepatomegaly and a pulsatile liver.

Tricuspid stenosis typically occurs with left sided valve lesions and the findings can be hard to appreciate at times. On auscultation, a low pitched diastolic murmur can sometimes be heard at the left sternal border preceded by an opening snap. These sounds also increase with inspiration. Examination of the neck veins can show a prominent "a" wave as the atria contract against the stenotic tricuspid valve. As with tricuspid regurgitation, advanced disease typically results in signs of right sided heart failure.

Pulmonic Valve

Most primary pulmonic valve lesions are congenital in nature and present at an early age. With acquired valve disease, the most common cause of pulmonic regurgitation is pulmonary hypertension resulting in dilation of the pulmonary valve annulus. Therefore, the primary driving symptoms are from pulmonary hypertension rather than isolated regurgitation. In the case of isolated pulmonic regurgitation, most patients will be asymptomatic for quite some time. In patients that develop symptoms, it is primarily due to progressive right ventricular enlargement and results in right sided heart failure symptoms. The murmur of pulmonic insufficiency is diastolic and is typically best heard along the left sternal border. With progressive right ventricular remodeling, right sided gallops, a right ventricular lift or elevated right atrial pressures may be detected.

Pulmonic stenosis is typically characterized by a midsystolic crescendo / decrescendo murmur best heard at the left sternal border. An ejection click can sometimes be heard as well. This click is one of the few exceptions with right sided valve lesions that gets softer with inspiration. Again, patients with pulmonic stenosis are typically asymptomatic for quite some time. Symptoms, when the do develop, are due to progressive right sided failure as described above.

Helpful Tests

Electrocardiograms can sometimes show changes related to right sided valve lesions but are often non-specific. With isolated tricuspid stenosis, one will see right atrial enlargement but normal right ventricular sizes. With advanced, isolated tricuspid regurgitation, one can see right atrial and right ventricular enlargement. With pulmonic regurgitation, you can see right ventricular enlargement as well. With pulmonic stenosis, one can see right ventricular hypertrophy which can also be seen in patients with pulmonary hypertension.

A chest X-ray may show chamber enlargement with right sided valve lesions. Tricuspid and pulmonic regurgitation place a volume load on the right ventricle resulting in right ventricular enlargement. Right atrial enlargement can be seen in patients with tricuspid regurgitation and stenosis. In patients with isolated pulmonic stenosis, initially, the right ventricular hypertrophy is concentric. You may be able to see post stenotic dilation of the main pulmonary artery. As above, many of these valve lesions present secondary to left sided heart disease, but with isolated right sided valve lesions, one should not see signs of pulmonary congestion.

Echocardiography is the primary means of diagnosing and monitoring cardiac valve conditions. While transesophageal echocardiography can be used, transthoracic echocardiograms are often times of better quality as the right sided structures lie in the anterior portion of the chest. In addition to assessing for the presence and severity of the various valve conditions, one can also assess their etiology. The presence of left sided heart disease or valve conditions is easily evaluated as well as the two dimensional appearance of the right sided valves. It is especially important to assess the right ventricular size and function in order to evaluate the hemodynamic affects that the valve has on the heart. One can make qualitative judgments on the function and size of the right ventricle, but owing to the irregularity of its shape, this can be hard to do sometimes. Other parameters including tissue Doppler and annular displacement can be used as surrogate markers of right ventricular function [4]. In addition, signs of right ventricular pressure overload including flattening of the ventricular septum may suggest elevated right ventricular pressures. Cardiac MRI lends itself nicely to the evaluation of the right ventricular size and function and is likely the gold standard for this where it is available [5].

With tricuspid regurgitation, the appearance of the valve is noted along with the shape and size of the color Doppler regurgitant jet, presence or absence of hepatic vein flow reversal and the shape of the Doppler velocity tracing (Fig. 23.1). Taking these all into account, the regurgitation is reported as mild, moderate or severe [6]. Using the peak Doppler velocity of the tricuspid regurgitation (Fig. 23.2), an estimation of the right ventricular systolic pressure (RVSP) is obtained using a modified Bernoulli equation:

$$\mathrm{RVSP} = 4\left(\text{Peak tricuspid regurgitation velocity}\right)^2 + \text{right atrial pressure}$$

The right atrial pressure is estimated from the appearance of the inferior vena cava. If there is no pulmonic stenosis, the RVSP can then be used as a surrogate for the pulmonary artery pressure.

Tricuspid stenosis can be seen as thickening and calcification of the valve leaflets and the severity can be estimated by the Doppler gradient across the valve. Valve areas ≤1 cm^2 are considered significant. As this is typically a very low gradient valve, mean pressure gradients ≥5 mmHg are considered severe [7].

Pulmonic regurgitation is present to a small degree in most patients and is of little consequence in the absence of other signs or symptoms. As with tricuspid regurgitation, the appearance of the valve, color Doppler jet and quantitative Doppler parameters are taken into account in order to judge the severity of the regurgitation. With pulmonic stenosis, the primary method of judging the severity is with the Doppler derived valve gradient (Fig. 23.3). Peak gradients >36 mmHg are considered elevated and gradients >64 mmHg are considered severely elevated [7]. This is again calculated using the modified Bernoulli equation.

Cardiac catheterization can also be used to assess right sided pressures and valve gradients. With a good quality echocardiogram and adequate tricuspid regurgitation, it is likely not necessary to perform a cardiac catheterization to simply measure the right ventricular pressures. However, heart catheterization remains the gold standard for confirmation of the pulmonary pressures and in patients with inadequate tricuspid regurgitation to calculate the pressures non-invasively.

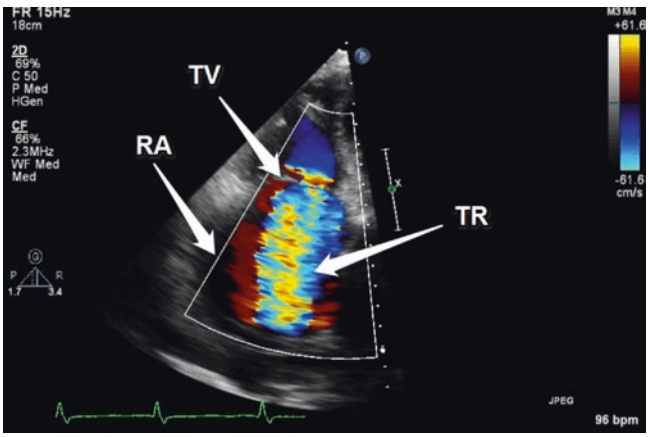

Fig. 23.1 This image shows the color Doppler jet from severe tricuspid regurgitation (TR) going across the tricuspid valve (TV) into the right atrium (RA)

Differential Diagnosis

Tricuspid Stenosis

The majority of tricuspid stenosis cases are secondary to rheumatic heart disease [8]. It almost always occurs in conjunction with mitral and aortic valve disease. Other causes may include congenital disease, eosinophilic endocarditis (Loeffler endocarditis), prosthetic valve dysfunction and carcinoid disease. In addition to valve morphology, large vegetations or right-sided cardiac tumors including renal cell cancer extending into the right atrium can mimic the symptoms of tricuspid stenosis (Table 23.1).

Carcinoid is a rare tumor involving primarily the GI tract that affects primarily right sided valves. Patients initially present with diarrhea and episodes of flushing and are diagnosed by elevated urinary levels of 5-hydroxyindoleacetic

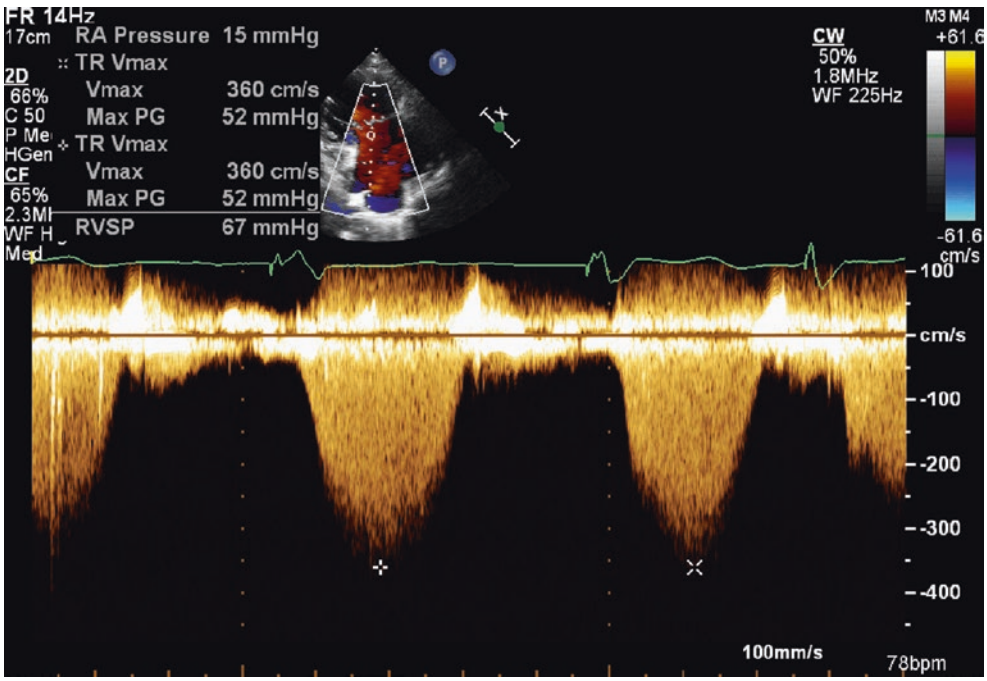

Fig. 23.2 This image shows the Doppler velocity tracing across the tricuspid valve. The peak velocity across the valve is 360 cm/s. Using the modified Bernoulli equation, the makes a maximum pressure gradient of 52 mmHg. Adding an estimated right atrial pressure of 15 mmHg makes an estimated right ventricular systolic pressure of 67 mmHg

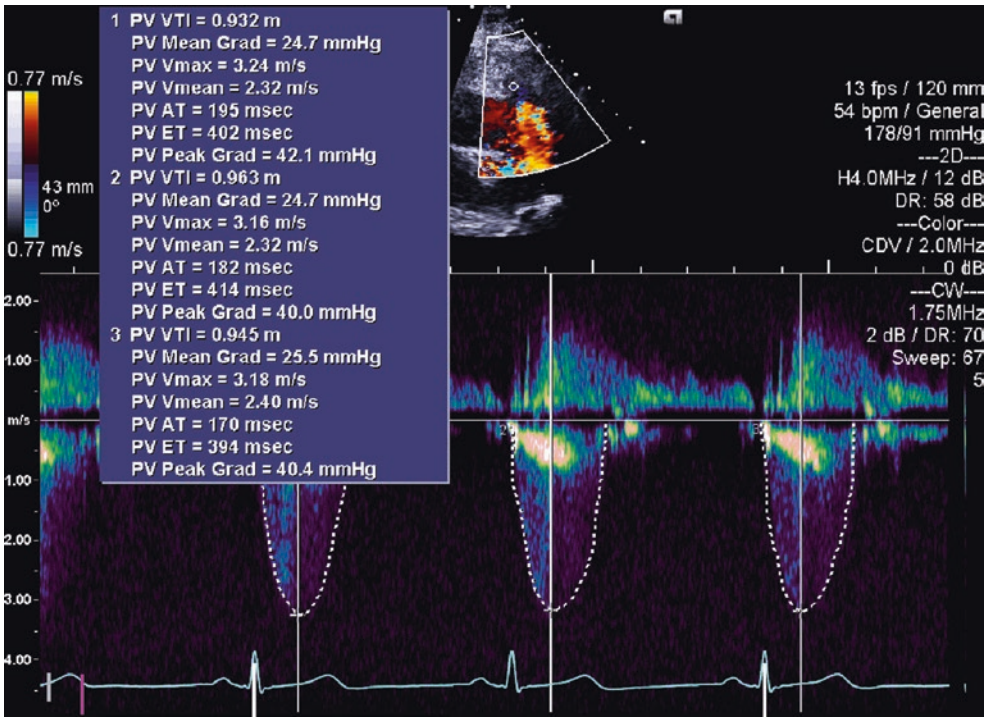

Fig. 23.3 This image shows a Doppler velocity tracing across the pulmonic valve. In this case, the peak velocity is 3.2 m/s which translates to a peak gradient of 40 mmHg

Table 23.1 Causes of tricuspid stenosis

Congenital disease
Rheumatic heart disease
Carcinoid syndrome
Loffler endocarditis
Prosthetic dysfunction
Atrial tumors or renal cell carcinoma
Endocarditis

acid. Vasoactive substances secreted by the tumor cause progressive scaring of the right sided heart valves (Fig. 23.4). The lung metabolizes these substances so that the left sided valves are spared unless there is pulmonary carcinoid or a right to left shunt (atrial septal defect) [9].

Tricuspid Regurgitation

Tricuspid regurgitation can be grouped into primary (disease directly affecting the valve leaflets) and secondary (structurally normal valves) (Table 23.2). Primary tricuspid valve disease is the rarer of the two [10]. As described above, carcinoid valve disease, Loeffler endocarditis and rheumatic heart disease may also cause tricuspid regurgitation. There are several congenital defects that can also cause significant regurgitation including Epstein's anomaly. In Epstein's disease, the tricuspid valve leaflets are displaced apically. Patients can present in childhood and adulthood and have varying degrees of tricuspid regurgitation [11]. In addition to this, the tricuspid valve can be injured by trauma, endocarditis or radiation therapy or result from tricuspid valve prolapse or prosthetic dysfunction. There can also be direct damage or tethering of the leaflets from pacemaker wires, endomyocardial biopsies or central line placement.

Secondary tricuspid regurgitation is caused by anything that dilates the right ventricle and tricuspid annulus. This results in failure of leaflet coaptation and then regurgitation. Most often, this is from left ventricular disease and may be caused by left ventricular failure, diastolic heart failure or left sided valve disease (mitral stenosis or regurgitation primarily). In addition to left sided heart disease, pulmonary hypertension, right ventricular infarctions or right ventricular volume overload from an ASD can cause right ventricular enlargement leading to tricuspid regurgitation. Determining whether the regurgitation is secondary or primary can often be hard. The main diagnostic clues can typically be distinguished by echocardiography. In addition to visualizing the valve morphology, one can measure the right ventricular pressures. If these are significantly elevated, it points to a secondary cause.

Pulmonic Stenosis

Typically, pulmonic stenosis is from congenital disease including tetralogy of Fallot or a bicuspid pulmonic valve [12, 13]. Many of these are diagnosed in childhood, however, they can first present as adults as well. Other causes may include carcinoid valve disease, rheumatic disease or prosthetic dysfunction (Table 23.3).

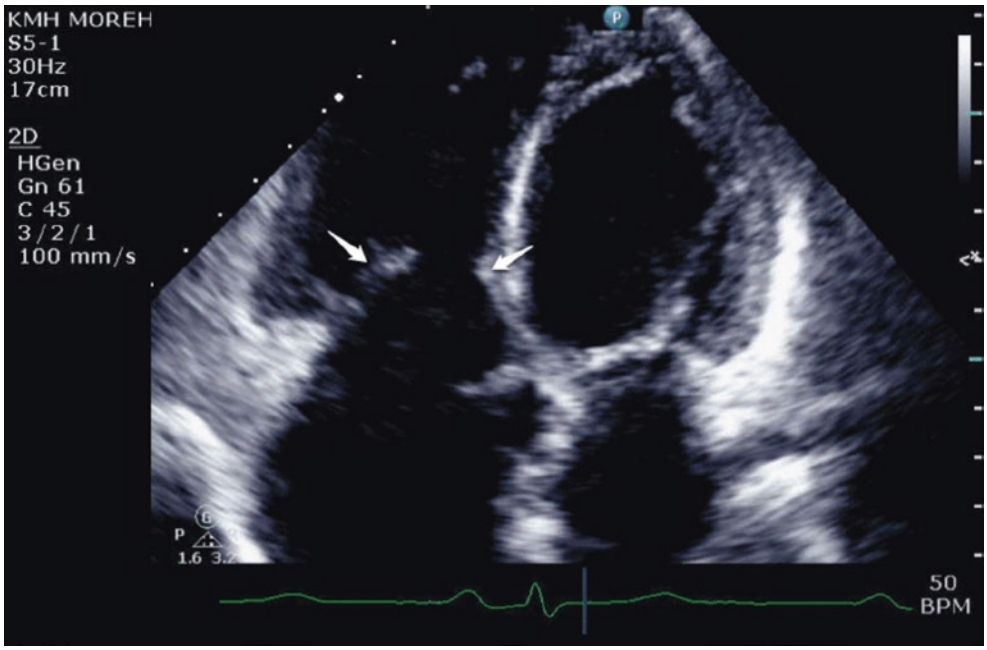

Fig. 23.4 This is a view of a tricuspid valve with carcinoid syndrome. Notice the thickened and retracted tricuspid leaflets (arrows). This image is obtained in systole and the leaflets are not able to coapt resulting in severe tricuspid regurgitation

Table 23.2 Causes of tricuspid regurgitation

Primary
Rheumatic heart disease
Congenital disease (Epstein anomaly)
Tricuspid valve prolapse
Papillary muscle rupture after myocardial infarction
Endocarditis
Carcinoid syndrome
Loffler's endocarditis
Trauma
Pacemaker wires
Central line placement
Prosthetic dysfunction
Secondary
Pulmonary hypertension
Left ventricular failure
Right ventricular failure
Left sided valve disease
Pulmonic regurgitation or stenosis
Atrial septal defect with volume overload
Right ventricular infarction

Table 23.3 Causes of pulmonic stenosis

Congenital valve disease
Rheumatic disease
Subvalvular or supravalvular stenosis
Carcinoid
Endocarditis
Prosthetic dysfunction

Pulmonic Regurgitation

Similar to tricuspid regurgitation, the differential includes diseases that affect the valve itself or diseases that cause secondary pulmonic regurgitation (diseases that cause dilation of the annulus) [12]. The valve leaflets can be affected by carcinoid syndrome, endocarditis, rheumatic disease or congenital disease. In addition, regurgitation can be secondary to valve procedures (prior congenital surgery or valvuloplasty) or catheter placement (primarily Swan-Ganz catheters if they are withdrawn incorrectly with the balloon inflated). Diseases that cause secondary regurgitation include pulmonary hypertension or a pulmonary artery aneurysm which may sometimes occur with Marfan's disease (Table 23.4).

Table 23.4 Causes of pulmonic regurgitation

Primary
Prior surgery (valuloplasty)
Congenital
Endocarditis
Trauma
Carcinoid syndrome
Secondary
Pulmonary artery aneurysm (Marfan's or idiopathic)
Pulmonary hypertension

Complications

Ultimately, significant right sided valve disease leads to progressive right sided volume and pressure overload. Symptoms include fatigue and dyspnea and eventually result in right sided heart failure with edema, hepatomegaly, liver dysfunction and ascites. Some patients develop severe symptoms leading to intractable right sided heart failure and death. Other patients may remain relatively asymptomatic for years even with severe primary regurgitation [14].

Endocarditis is another potential complication and right sided endocarditis is often due to intravenous drug use. Typically, tricuspid valve endocarditis is much more frequent, but pulmonic valve endocarditis does occur. In one review, 12% of endocarditis cases involved the tricuspid valve compared to 1% involving the pulmonic valve [15]. Structural issues with the right sided valves increase the risk, but many patients with right sided endocarditis had normal valves prior to infection. Chronic indwelling catheters and devices such as pacemakers also increase the risk of endocarditis. Staph Aureus is the most common pathogen with viridans streptococci, enterococci, and coagulase-negative staph also being common [15]. In addition to the sepsis which often accompanies endocarditis, the patients may suffer from embolic events or abscess formation.

Therapy

Tricuspid Stenosis

The medical therapy of tricuspid stenosis is primarily volume management with loop diuretics in order to relieve the symptoms of edema and hepatic congestion. There is little data in terms of intervention on the tricuspid valve for isolated tricuspid stenosis as this is not a common issue. In general, surgery is performed on the valve (repair or replacement) if there is severe stenosis and the patient is also undergoing surgery for left sided valve disease. Percutaneous balloon valvuloplasties have been evaluated, but are not typically done as most patients with tricuspid stenosis also have concomitant regurgitation [16]. If the patient remains symptomatic despite optimal diuretic therapy, surgery may be considered [17].

Tricuspid Regurgitation

As most tricuspid regurgitation is secondary to left sided heart disease or pulmonary hypertension, the treatment focuses on optimizing those conditions. For isolated tricuspid regurgitation, the medical therapy is again primarily volume management. Loop diuretics can reduce symptoms of edema and congestion. In patients with severe tricuspid regurgitation undergoing left sided valve surgery, it is recommended that patients have tricuspid valve surgery [17]. This is true for both primary and secondary causes of the regurgitation. Preferably, this is done with valve repair, but sometimes the leaflet anatomy dictates valve replacement. In patients with only moderate secondary tricuspid regurgitation or a history of right-sided heart failure undergoing surgery for left sided valve disease, tricuspid valve repair is also recommended when feasible.

For patients with isolated, severe, primary tricuspid regurgitation, medical therapy is recommended initially. If patients remain symptomatic despite medical therapy and do not have pulmonary hypertension, surgery can be beneficial. There is not much data, but some studies suggest that the mortality rate is quite high in patients with primary severe tricuspid regurgitation who develop right sided heart failure. Because of this, it is reasonable to consider operating on patients without symptoms or with minimal symptoms if there are signs of right ventricular enlargement or hypokinesis [18].

Pulmonic Stenosis

Many causes of pulmonic stenosis are diagnosed and treated in childhood, but some patients are discovered in adulthood. In patients who need intervention on their pulmonic valve, a balloon valvotomy is the preferred method and is generally successful. If the valve anatomy is amenable and there is less than moderate pulmonic regurgitation, a balloon valvotomy is recommended when the peak gradient exceeds 60 mmHg or if the patient is having symptoms and the peak gradient exceeds 50 mmHg [19]. If the valve is not amenable to a balloon valvotomy (for example if the patient has severe regurgitation or a hypoplastic annulus), surgical replacement is recommended.

Pulmonic Regurgitation

If the pulmonic regurgitation is due to pulmonary hypertension, treatment should focus on the pulmonary hypertension and surgical intervention is not recommended. For primary, severe pulmonic regurgitation, valve replacement is recommended when symptoms develop. In addition to this, if an asymptomatic patient has severe regurgitation and evidence of moderate to severe RV enlargement or dysfunction, or develops new arrhythmias (atrial or ventricular), valve replacement should be considered [19]. Percutaneous valve replacements have also been studied and may play a larger role in the future [20].

Prognosis and Follow-Up

For all right sided valve disease, periodic monitoring is recommended to assess for symptoms and signs of right sided heart failure. In addition, patients with moderate or worse valve disease should have periodic echocardiograms to assess the severity of the valve lesion, cardiac function and right ventricular pressures.

Tricuspid Valve

Tricuspid valve stenosis rarely occurs in isolation and the prognosis is typically dictated by the co-existing valve issues

(mitral and aortic stenosis for example) or underlying disease (carcinoid). There is little data on outcomes specifically related to tricuspid stenosis after surgery, but in general, it is felt to be favorable [21]. In the case of carcinoid syndrome, the outcome after surgery is a bit worse. One study showed an operative mortality of 35% without major symptom improvement [22]. More recent studies have shown improved mortality, but the optimum timing of surgery is still not clear [23].

Minimal tricuspid regurgitation is a benign finding and is seen on the majority of echocardiogram studies without any adverse outcomes. Severe tricuspid regurgitation on the other hand, has been associated with worse outcomes. In one study, severe tricuspid regurgitation was associated with a 64% survival rate compared to 90% of patients with mild regurgitation [24]. Much of this can be attributed to the underlying conditions that predispose to severe tricuspid regurgitation including pulmonary hypertension and heart failure. However, the general trend of worsening survival with worsening regurgitation seems to be true for isolated primary tricuspid regurgitation as well [25]. In one series, patients with severe tricuspid regurgitation due to flail leaflets had significant mortality (39% at 10 years) with 75% of the patients having major events (arrhythmias, heart failure, surgery or death). Patients in this study that underwent valve surgery generally did well with symptomatic improvement [18].

Pulmonic Valve

In general, patients with mild or moderate stenosis have an excellent prognosis and progression to severe stenosis is quite slow. Patients treated surgically (either with balloon valvotomy or surgical repair) also seem to have an excellent prognosis in general. Only 5% of patients in one series required re-intervention [26].

Pulmonic regurgitation has primarily been studied in regards to patients who have undergone repair for Tetralogy of Fallot. Several studies have shown that severe pulmonary regurgitation can lead to right ventricular failure and potentially death if uncorrected [27]. If the valve is repaired prior to the development of severe right ventricular failure, the outcomes are excellent (92% five year survival) and right ventricular dimensions and function have been shown to improve [28].

Practical Points

- Tricuspid regurgitation is very common. Minimal tricuspid regurgitation is often found incidentally and is usually benign.
- "Pathologic tricuspid regurgitation" is most commonly caused by increased right ventricular pressures or volumes. This is typically caused by left sided heart disease. Other causes could include congenital disease, pulmonary hypertension or tricuspid leaflet issues. Tricuspid stenosis is typically caused by rheumatic heart disease, congenital defects or sometimes carcinoid syndrome.
- Pulmonic valve disease is typically related to a congenital defect although this can rarely be seen with other conditions as well.
- Most of the time, symptoms with tricuspid or pulmonic valve disease will be dictated by the left sided conditions (heart failure, mitral regurgitation, pulmonary hypertension, etc.). However, symptoms related to tricuspid or pulmonic valve disease can present as right sided heart failure including abdominal fullness, edema or ascites.
- Echocardiography is the test of choice to diagnose these conditions. Transesophageal echocardiography and cardiac MRI can also be helpful.
- Diuretics can be helpful for symptoms of right sided heart failure. As many of these conditions are secondary to left sided heart disease, therapy is initially aimed at improving these conditions first.
- Tricuspid stenosis can be treated with percutaneous valvuloplasty or valve replacement if symptoms persist despite medical therapy of the underlying conditions.
- Tricuspid regurgitation is often repaired at the time of surgery for left sided valve lesions. For isolated tricuspid regurgitation, valve surgery (repair or replacement) can be consider if symptoms persist despite medical therapy or if there is evidence of worsening right ventricular function.

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Acute Pericarditis/Pericardial Effusion

24

Elina Yamada, Mani A. Vannan, and Mauro Moscucci

Acute Pericarditis

Definition

The pericardium is a double-layered wrapping around the heart, with the outer and inner layers called parietal and visceral pericardium, respectively. The cavity between these two layers usually contains a small amount (15–50 mL) of an ultrafiltrate of plasma, which serves to lubricate the surfaces. Clinically relevant disorders of pericardium are: acute inflammation (acute pericarditis), pericardial effusion with or without hemodynamic compromise (tamponade), constrictive pericarditis, congenital absence of the pericardium, and pericardial cysts.

Acute pericarditis is a condition that presents with the following clinical signs and symptoms: chest pain, pericardial friction rub and typical electrocardiographic (ECG) changes. At least two of these features must be present to support the diagnosis.

Usual Causes

A wide variety of conditions can affect the pericardium, as listed in Table 24.1. The yield of the standard diagnostic evaluation is very low, about 16%. Idiopathic post viral, neoplastic, connective tissue disorders and uremia account for most acute pericarditis diagnosed in the clinical setting. When upper respiratory symptoms precede acute cardiac involvement, the most common etiology is *post viral pericarditis.* Coxsackie A or B virus or echovirus are the common agents [1]. The term *acute idiopathic pericarditis* applies when there is no clear etiology identified and it is presumed to be viral or autoimmune. Viral serologic testing has a very low diagnostic yield and does not change management. Therefore it is not routinely recommended. Among the entities listed in Table 24.1, the human immunodeficiency virus (HIV) is an increasingly common etiology for acute pericarditis [2, 3] that is the most frequent cardiovascular manifestation of AIDS. The condition may be caused by HIV itself or may result from opportunistic infections or neoplasms (such as lymphoma). The presence of pericardial effusion in HIV syndrome is associated with poor prognosis.

Acute pericarditis should be considered in the differential diagnosis in the presence of hemodynamic deterioration after cardiac procedures or with new radiographic cardiomegaly.

Symptoms

A cardinal symptom of acute pericarditis is *chest pain.* The typical pain of pericardial inflammation is a retrosternal sharp pain radiating to the back near the trapezius edge. It is usually worse when the patient is in a supine position, and it is either relieved or ameliorated by sitting up. Chest pain may, however, be variable in location, nature, intensity, and radiation. It can be located retrosternally and radiate to the left arm, mimicking ischemic cardiac chest pain. It may radiate to the epigastrium, mimicking abdominal disease, or worsen on deep inspiration, mimicking pleural pain. Constitutional symptoms are nonspecific and may include dyspnea, general malaise, weakness, hiccups, and cough. A low-grade fever may be present, but occasionally the body temperature may be as high as 40 °C.

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Table 24.1 Causes of acute pericarditis

Idiopathic
Infectious
Bacterial
Viral
Mycobacterial
Fungal
Protozoal
AIDS associated
Neoplastic
Primary
Secondary (breast, lung, melanoma, lymphoma, leukemia)
Immune inflammatory
Connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, acute rheumatic fever, mixed connective tissue disease, Wegener's granulomatosis)
Arteritis (temporal arteritis, polyarteritis nodosa, Takayasu's arteritis)
Acute myocardial infarction (MI) and post-MI (Dressler's syndrome)
Postcardiotomy
Posttraumatic
Metabolic
Nephrogenic
Aortic dissection
Myxedema
Amyloidosis
Iatrogenic
Radiation injury
Procedures (cardiac cath, implantable defibrillator, pacemakers catheters, ablation)
Drugs (hydralazine, procainamide, daunorubicin, isoniazid, anticoagulants, cyclosporine, methysergide, phenytoin, dantrolene, mesalazine)
Cardiac resuscitation
Traumatic
Blunt trauma
Penetrating trauma
Surgical trauma
Congenital
Pericardial cysts
Congential absence of pericardium
Mulibrey nanism syndrome

AIDS acquired immunodeficiency syndrome

Signs

Tachycardia and tachypnea are usually nonspecific signs reflecting the general syndrome. However, they may indicate myocardial inflammation and/or hemodynamic compromise. The presence of a pericardial rub is the most specific sign of acute pericarditis. It is a squeaky or scratchy sound best heard at the left lower parasternal border with the diaphragm of the stethoscope [4]. It may be present in one (15%), two (33%) or three phases (56%) of the cardiac cycle, and the intensity of the sound may change with position and respiration. Furthermore, it may be present or absent within a given day. Suspension of respiration may allow distinction from a coexistent pleural friction rub.

Helpful Tests

Electrocardiogram

The ECG usually shows normal sinus rhythm except in the case of complicating arrhythmias. Atrial arrhythmias, when present, are usually associated with concomitant myocarditis or unrelated cardiac disease. There may be diffused ST segment elevation and PR segment depression (Fig. 24.1), which then undergoes a typical evolutionary change as listed in Table 24.2. These evolutionary changes in the ECG are pathognomonic of acute pericarditis even in the absence of an audible pericardial friction rub [5, 6]. ECG changes always reflect a degree of myocardial involvement, inasmuch as the parietal pericardium is electrically inert. Bundle branch block, intraventricular conduction delay or Q waves may suggest myocardial involvement.

Early repolarization variant is in the differential of the acute ST elevation pattern seen in pericarditis. Studies have shown that ST elevations usually occur in both limb and precordial leads in most cases of acute pericarditis whereas about half of cases with early repolarization variant present with no ST changes in limb leads.

Chest Radiograph

The chest radiograph may be entirely normal or may show evidence of cardiomegaly when it is associated with pericardial effusion or myocarditis complicated by cardiac enlargement. In the setting of acute left ventricular failure, pulmonary congestion or signs of pulmonary edema may be seen.

Echocardiography

Although in acute idiopathic or post viral pericarditis, significant pericardial effusion occurs in only a minority of cases, some degree of effusion may be present in up to 60% of all cases of acute pericarditis. The 2015 European Society of Cardiology Guidelines gave a class I recommendation for echocardiography in cases where pericardial disease is suspected. Echocardiography provides estimation of size and site of the effusion, and comprehensive assessment of hemodynamic compromise caused by the pericardial effusion (Table 24.3 and Figs. 24.2, 24.3, 24.4). Left ventricular systolic function may be affected when there is associated myocarditis, and echocardiography is helpful in estimating the degree of myocardial dysfunction. A surface or transesophageal echocardiography may detect a ruptured aortic dissection causing pericardial effusion, or a pericardial tumor. Furthermore, echocardiography is useful for detection of complications of pericarditis such as constrictive pericarditis. Although echocardiography can diagnose constrictive physiology, it is not a reli-

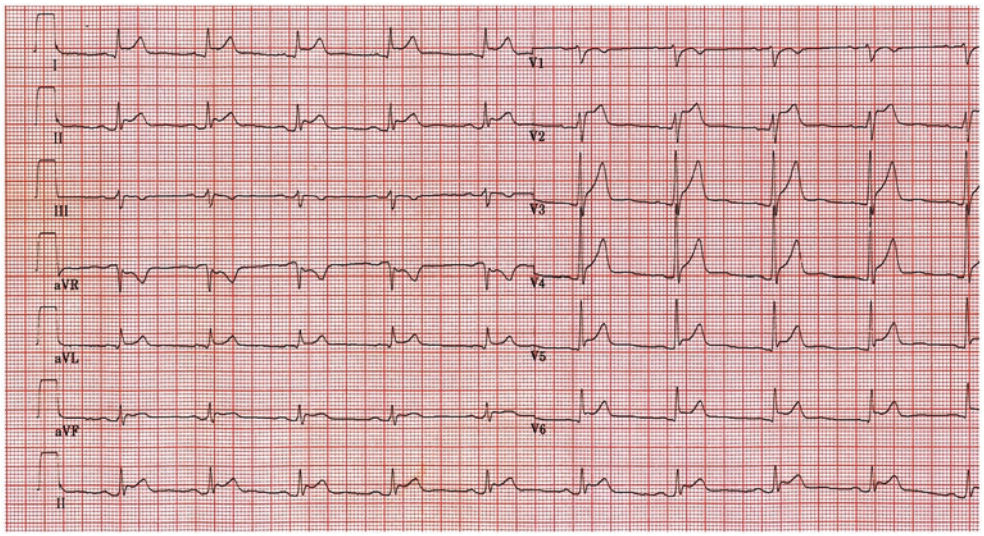

Fig. 24.1 Electrocardiogram in a patient with acute pericarditis, showing diffuse ST segment elevation and PR segment depression

Table 24.2 Electrocardiographic changes in acute pericarditis

Stage	Time course	ECG changes
1	ST segment elevation occurs within hours of onset of chest pain and may persist for days	Upward concave ST segment elevations, usually not exceeding 5 mm; PR segment depression (except in aV_R)
2	Hours to days following stage 1	ST segments return to baseline: T waves are normal or show loss of amplitude
3	T wave inversions may persist indefinitely (especially when associated with TB, uremia or neoplasm)	T wave inversions
4	Usually completed within 2 weeks, but variability common	ECG normalizes

ECG electrocardiographic, *TB* tuberculosis

Table 24.3 Echocardiography in pericardial effusion

Echolucent space between visceral and parietal layers of the pericardium
Typically does not extend beyond the left atrium and is anterior to the descending aorta in the parasternal long-axis view
Size and circumferential extent can be determined
Loculated effusions may be present after cardiac surgery, radiation, and infection
Partial organization and fibrin strands may be identified
RV early diastolic collapse and RA late diastolic collapse indicate elevated pericardial pressure (elevated RV pressures as in pulmonary hypertension may mask this sign)
Right-sided chambers collapse is not necessarily tamponade (PPV of 58%, NPV of 92%)
>40% and >25% peak velocity respiratory variation in TV and MV Doppler flows may indicate hemodynamic compromise (obesity, COPD, LV dysfunction, and large pleural effusion can also cause respiratory variation)
Ascending aorta dissection flap may be detected as possible etiology of pericardial effusion
Echocardiography is helpful in guiding pericardiocentesis

COPD chronic obstructive pulmonary disease, *LV* left ventricular, *TV* tricuspid valve, *MV* mitral valve, *NPV* negative predictive value, *PPV* positive predictive value, *RA* right atrial, *RV* right ventricular

able technique to assess pericardial thickening. Magnetic resonance imaging and computed tomography are superior techniques in detecting pericardial thickening [7]. Repeat follow-up echocardiography is not routinely recommended in asymptomatic patients with known small pericardial effusion.

Biomarkers and Other Blood Tests

Troponin I was elevated in 8–22% of cases, according to two studies that included 187 patients with acute idiopathic pericarditis [8, 9]. The enzyme rise is usually transient but if it persists beyond 1 week, myocarditis may be present. However, it does not appear to be associated with complications such as recurrent or constrictive pericarditis.

Erythrocyte sedimentation rate and serum C-reactive protein are usually elevated and white blood cell count may be high as well. In addition, initial blood work-up of acute pericarditis includes: antinuclear antibody titer, rheumatoid factor, HIV serology if appropriate, blood cultures if infectious etiology is suspected, and tuberculin skin test in high risk patients. Viral studies are not routinely recommended due to the low diagnostic yield and no impact on management.

Differential Diagnosis

Acute Coronary Syndrome

It may be difficult to differentiate acute pericarditis from acute coronary syndrome, especially if the chest pain is located retrosternally, radiates down the left arm, or it is associated with elevation of cardiac enzymes such as troponin I, and there are no other typical findings of acute pericarditic pain.

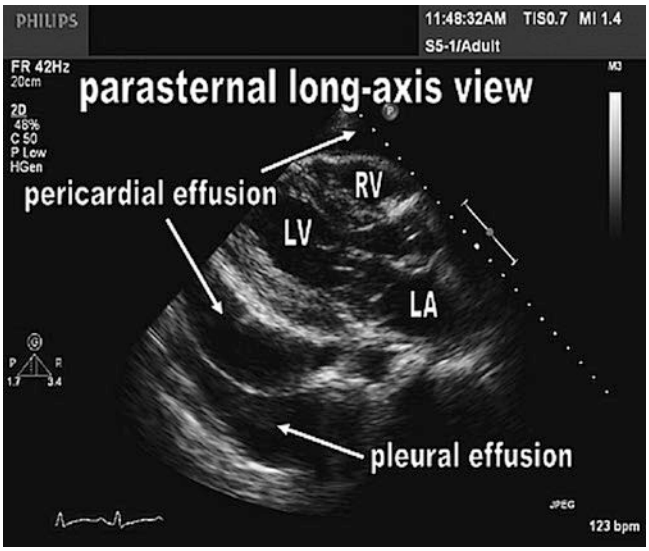

Fig. 24.2 Two-dimensional echocardiogram in the parasternal long-axis view shows a large circumferential pericardial effusion and a pleural effusion. *LV* left ventricle, *LA* left atrium, *RV* right ventricle

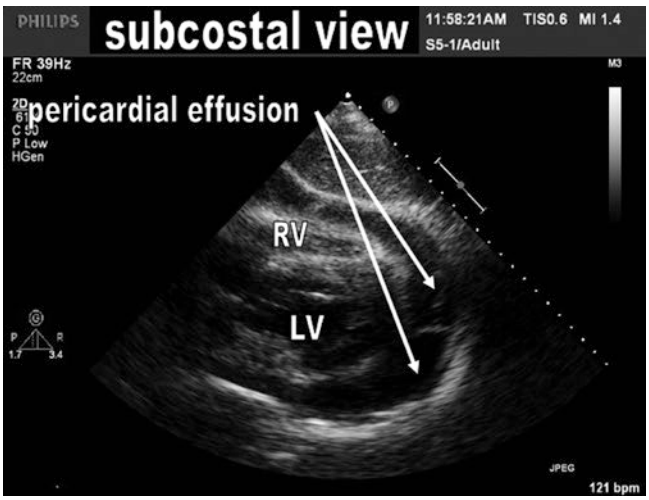

Fig. 24.3 Large circumferential pericardial effusion with fibrin strands shown in the subcostal view. *LV* left ventricle, *RV* right ventricle

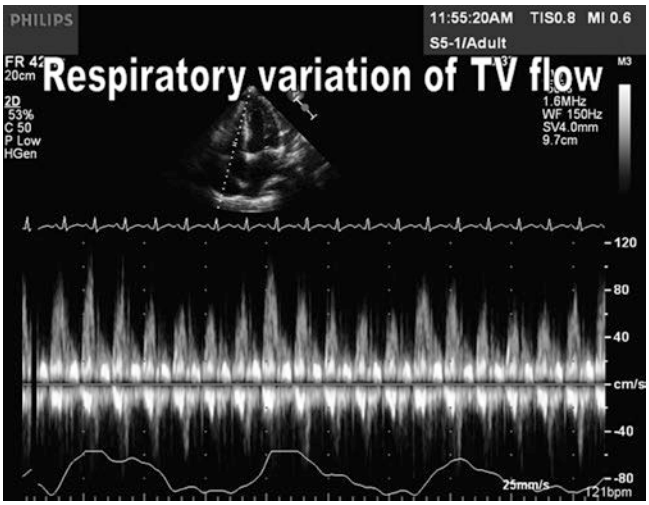

Fig. 24.4 Respiratory variation of tricuspid valve flow detected by Doppler flow imaging in a patient with cardiac tamponade. *TV* tricuspid valve

Elevation of troponin I level is a marker of myocardial injury, and significant elevation may be seen in younger patients with the post viral syndrome with myopericarditis [10]. Regional ECG ST segment changes may mimic acute myocardial infarction [8]. Echocardiography may be helpful to differentiate the two conditions if there are segmental wall motion abnormalities suggesting myocardial ischemia. In addition, findings of PR segment depression, concave ST segment elevation and lack of simultaneous T wave and ST segment changes, lack of Q wave evolution, and absence of reciprocal ST segment changes, all support the diagnosis of acute pericarditis. However, myocarditis may manifest with regional wall motion abnormality, which make the differential diagnosis more challenging. Ultimately, the clinical presentation helps confirm the diagnosis of acute pericarditis rather than myocardial ischemia.

Acute Pleurisy

Pulmonary infarction or pneumonia may be associated with inflammation of the adjacent pleura, which may mimic chest pain of acute pericarditis. However, the clinical presentation, ECG changes and chest radiography are helpful in distinguishing these conditions.

Therapy

Hospital Admission

Most cases of acute pericarditis can be treated in an outpatient setting. However, if there is persistent severe chest pain, other cardiac symptoms or signs suggesting tamponade, acute coronary syndrome, acute aortic dissection, or heart failure, hospital admission is warranted. Inpatient evaluation and treatment is also indicated when there is evidence of high fever, leukocytosis, immunosuppressed state, history of oral anticoagulant therapy, or acute trauma. The presence of moderate to large pericardial effusion on echocardiography usually warrants hospital admission for close observation and evaluation for pericardiocentesis.

Pharmacologic Treatment

Nonsteroidal anti-inflammatory drugs (NSAID) remain the mainstream for treatment of acute pericarditis. The 2015 European Society of Cardiology (ESC) guidelines recommended NSAIDs as first line therapy for acute pericarditis not associated with auto-immune disease [11]. Aspirin dose

ranges from 500 to 1000 mg every 8 h and is the preferred agent when pericardial effusion complicates acute myocardial infarction. Ibuprofen dose ranges 600–800 mg every 8 h and indomethacin 25–50 mg every 8 h as the preferred NSAIDs, with dose adjusted to symptoms and CRP levels. The dose and length of treatment is dictated by symptoms, but usually the chest pain improves within 1 week and the NSAIDS can be tapered down in 3–4 weeks, based on symptoms and CRP levels. With NSAIDS or steroids, gastrointestinal protection should be provided.

Colchicine (0.5 mg twice daily or once daily if <70 kg) for 3 months has been shown to prevent recurrent pericarditis in the COPE and CORE trials and therefore should be the agent of choice to combine with NSAID [11–14] in cases with elevated CRP or in recurrences. Recurrent pericarditis occurs in about 15–30% of patients with idiopathic acute pericarditis who are not treated with colchicine.

Although use of concomitant anticoagulation drugs is concerning for increased risk for hemorrhagic pericarditis and tamponade, studies have not shown to be the case, except in iatrogenic pericardial effusion.

Pericardiocentesis

Approximately 15% of patients who develop a large pericardial effusion in association with acute pericarditis develop signs of cardiac tamponade. Therapeutic pericardiocentesis is warranted when there are signs of hemodynamic compromise by a pericardial effusion.

The 2015 ESC guidelines gave a class IC recommendation for the use of pericardiocentesis as a diagnostic purpose when purulent, tuberculous or neoplastic pericarditis is suspected. In these circumstances, it is also advisable to drain as much of the pericardial fluid as possible. A catheter may be left in place for a couple of days for further pericardial drainage until fluid return is less than 25 mL in 24 h, because the effusion frequently recurs under these conditions.

Pericardiectomy

Pericardiectomy is rarely required in acute pericarditis. Failure of medical treatment and recurrent symptoms of idiopathic or post viral pericarditis are usual indications for pericardiectomy. Pericardiectomy may be required after surgical drainage in bacterial or fungal pericarditis to prevent constrictive pericarditis.

Clinical Course

Most acute pericarditic syndromes resolve within 4 weeks with no long-term sequelae and with complete resolution of symptoms with NSAIDs, steroids, and colchicine. Approximately 25% of patients with acute pericarditis develop refractory or recurrent symptoms, and about 10% shows constrictive physiology findings on echocardiographic Doppler examination, 4 weeks after the onset of initial symptoms.

Pericardial Effusion

Definition

Pericardial effusion is the accumulation of more than the physiologic amount of fluid (>50 mL) in the pericardial sac.

Usual Causes

Acute pericarditis caused by different etiologies listed in Table 24.1 can be complicated by pericardial effusion. At least 50 mL of pericardial fluid must be present for it to be appreciated by imaging techniques such as echocardiography. The most common causes of large, chronic pericardial effusions are malignancy, idiopathic pericarditis, uremia, infection (including HIV), connective tissue disorder, and radiation therapy [15]. However, large collections of pericardial fluid can occur with cardiac trauma, complicate cardiac diagnostic or interventional procedures, electrophysiology procedures, cardiac surgery, myocardial infarction, and acute pericarditis of any etiology.

Symptoms

Clinical manifestation of pericardial effusion may vary from absence of any symptoms to life-threatening conditions such as cardiac tamponade. When present, symptoms are nonspecific such as dull retrosternal ache and dyspnea.

Large, chronic effusions can be entirely asymptomatic, reflecting the ability of the pericardial sac to stretch and adapt to increasing volume. On the other hand, a rapid accumulation of as little as 200 mL of fluid can produce hemodynamic compromise such as in pericardial effusion complicating an acute ruptured dissecting aorta.

Signs

Signs directly caused by effusion are usually insensitive and non-specific. Cardiac dullness beyond the apex and dullness at the infrascapular region (Ewart's sign) can be confounded by left lower lobe pulmonary disease or left pleural effusion [16]. Tachycardia, narrow pulse pressure, and pulsus paradoxus (inspiratory decline in systolic blood pressure exceeding 12 mmHg) reflect hemodynamically significant pericardial effusion. Pulsus paradoxus may be absent in the

presence of significant left ventricular systolic dysfunction. Fever may be present if there is an underlying infectious or inflammatory process.

Helpful Tests

Electrocardiogram

QRS complexes with low voltages as a result of short-circuiting of cardiac potentials by fluid are the characteristic manifestation of pericardial effusion. Low voltage in EKG is defined as the total amplitude of each QRS complex in all the six limb leads of less than 5 mm, and of less than 10 mm in the precordial leads. However, this sign is non-specific and may be absent in large pericardial effusions. Sinus tachycardia may reflect hemodynamic compromise, and electric alternans, cyclic beat to beat shift in the QRS axis, may indicate a swinging heart within a large pericardial effusion.

Chest Radiograph

The chest radiograph may be entirely normal in small to modest-sized effusions. In large effusions, cardiomegaly with loss of usual cardiac contours raises the suspicion of pericardial fluid collection.

Echocardiography

Echocardiography is the definitive test for the diagnosis of pericardial effusion and for the assessment of the hemodynamic impact of the effusion (Figs. 24.2, 24.3, and 24.4). The range of the echocardiographic findings is shown in Table 24.3.

Cardiac Tamponade

Definition

Tamponade is a spectrum of hemodynamic derangements that can be divided into three phases [17]. Phase I is characterized by equalization of right atrial and intrapericardial pressures, but not right ventricular or pulmonary capillary wedge pressure (PCWP). In phase II, there is equilibration of right atrial and right ventricular pressures but not PCWP, so that cardiac output is not significantly impacted. Phase III is the clinically evident syndrome of hypotension, tachycardia, tachypnea, and pulsus paradoxus (typically exceeding 20 mmHg). At phase III, intrapericardial pressures have equalized with right atrial, right ventricular pressures and PCWP, and there is significant decrease in cardiac output. Thus, phase III represents the most severe hemodynamic abnormality in the spectrum of pericardial compression and is characterized by pressure and flow abnormalities. Phase II is characterized predominantly by pressure abnormality and a modest degree of flow abnormality (pulsus paradoxus, if present, is usually less than 20 mmHg), whereas phase I consists of only pressure abnormality and is at the mildest end of the spectrum (it may not be clinically evident).

Echocardiography helps to identify these phases. For example, when there is right-sided heart collapse (phase II), the patient may be mildly symptomatic (tachypnea and tachycardia may be present, but not pulsus paradoxus). There may not be a need to perform urgent pericardiocentesis in all such cases. However, when hypotension, pulsus paradoxus, and electrical alternans are present, there is an urgent need to tap the pericardial fluid. Thus, the decision to perform pericardiocentesis should incorporate clinical and echocardiographic findings.

Low-pressure tamponade occurs when the right atrial pressure is less than 10 mm HG, usually because of hypovolemia. In such cases, low intracardiac pressures equilibrate with intrapericardial pressures, compromising cardiac output. Cautious fluid replenishment is usually sufficient, although a subgroup of patients with low-pressure tamponade benefit from pericardiocentesis.

Therapy

Needle Pericardiocentesis

The usual approach for pericardiocentesis is subxiphoid under fluoroscopic or echocardiographic guidance. Monitoring of cardiac rhythm and blood pressure is the minimal requirement for performing a safe procedure. ECG monitoring with electrodes at the needle tip is not essential. Hemodynamic monitoring of intracardiac and pericardial pressures is useful when there is suspicion of coexistent restriction or constriction. Removal of all the pericardial fluid is preferred, because it normalizes intracardiac pressures and improves cardiac output. Failure of normalization of filling pressures after pericardiocentesis is an indication of *effusive constrictive pericarditis,* in the absence of myocardial dysfunction. In cases where there is high likelihood of recurrence of pericardial effusion, a multihole flexible catheter is left in the pericardial space for a couple of days. Pericardial fluid should be sent for analysis of red and white cell count, protein and glucose level, smears, cultures and cytologic studies. The diagnostic yield of pericardiocentesis and pericardial biopsy are overall low when performed for diagnostic purpose: 6% and 5%, respectively in a study of 231 patients with acute pericarditis [1]. In the same study, the yield was higher (29% and 54%, respectively) when the procedure was done for therapeutic purpose in large effusions. In another study, analysis of pericardial fluid in large effusions led to diagnosis in 26% of cases, and pericardial biopsy was useful in 23% [15]. Needle pericardiocentesis is usually a safe procedure when there is a large circumferen-

Table 24.4 Complications of needle pericardiocentesis

Acute RV and LV dysfunction and shock
Pulmonary edema
Myocardial (usually RV), vascular (coronary vein or artery) laceration
Pulmonary and liver laceration
Reflex hypotension
Cardiac arrhythmias

LV left ventricular, *RV* right ventricular

tial effusion, but complications are possible [18–21], as shown in Table 24.4. In malignant effusion, extended catheter placement has been shown to decrease recurrence of effusion.

Surgical Pericardiocentesis

Surgical drainage may be performed through a subxiphoid incision or a thoracotomy. This approach is often necessary when the effusion is loculated, posteriorly to the left ventricle, when there are fibrinous adhesions, or when there is need to obtain adequate pericardial tissue for etiologic diagnosis.

Recurrent Pericardial Effusions

Balloon pericardiotomy or a surgical pleuro-pericardial or peritoneal-pericardial window (the latter window preferred because of larger surface area for fluid absorption) may be necessary to treat recurrent collections as in uremic and malignant pericardial effusions (up to 40%) [22]. Surgical pericardiectomy may be required in such cases.

Practical Points

- Diagnosis of acute pericarditis is usually possible on the basis of clinical history, symptoms, and ECG findings.
- ECG findings reflect underlying myocarditis, because the pericardium is electrically inert.
- Absence of audible pericardial rub does not exclude the diagnosis of acute pericarditis.
- Some degree of pericardial effusion is seen on echocardiography in about two thirds of cases.
- Most cases of acute pericarditis resolve completely without long-term sequelae.
- Rapid accumulation of even modest amounts of pericardial fluid can cause hemodynamic compromise.
- Cardiac tamponade is a spectrum of hemodynamic abnormalities and not an all-or-none phenomenon.
- Diagnosis of pericardial tamponade requires incorporation of echocardiographic and clinical data.

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Pericardial Constriction

25

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Usual Causes

In pericardial constriction (constrictive pericarditis), a variably thickened layer of visceral or parietal pericardium, or both, surrounds some or all of the cardiac chambers and progressively restricts filling of the ventricles. Because of anatomic pericardial encasement of the heart with resultant marked elevations in atrial pressure, 75% of ventricular filling occurs very rapidly and at high velocity during the first third of diastole, thus causing the characteristic "dip and plateau" or "square root sign" on the left and right ventricular pressure tracings. In most cases, diastolic filling is restricted in both ventricles, which become increasingly interdependent; that is, filling of both ventricles depends on the relative motion of the interventricular septum during diastole, the phenomenon known as ventricular coupling.

Classic "chronic constriction" is conventionally thought of as a process that proceeds over many months to years. However, the clinical spectrum of constrictive pericarditis has changed since the early 1970s in the western hemisphere, primarily because tuberculosis has become relatively infrequent, whereas cardiac surgery has become relatively commonplace. In contrast to the "chronic" variant of constriction, in which symptoms evolve over the course of many months and years and which represents progressive fibrosis of the pericardium, most cases are now "subacute," with constriction evident in the 3- to 12-month period after the pericardial insult (e.g., viral infection of the pericardium or cardiac surgery). The patient with constriction after radiation to the mediastinum for treatment of cancer is the primary exception to this rule, when constriction develops months to years after treatment. Two other variants also exist. In the patient with active pericarditis, the inflamed pericardium can thicken rapidly over a few weeks and produce "acute" symptoms of constriction. Finally, usually after cardiac surgery and at times with acute pericarditis, "transient" constriction develops with elevated jugular venous pressure and clinical signs of constriction. This constrictive pattern resolves after institution of antiinflammatory therapy with nonsteroidal antiinflammatory agents or steroids. Whether these patients go on to develop chronic constriction at a later date is not known.

Knowledge of three other clinical syndromes of constriction that may be acute, subacute, or chronic but are not "classic" is important. In "regional" or local constriction, pericardial thickening is present only over certain chambers of the heart and occurs most frequently shortly after cardiac surgery, when pericardial inflammation and thickening occur over the right side of the heart, or with neoplasm. Affected patients have evidence of pulmonary or systemic venous congestion but usually not both. Effusive-constrictive disease is the variable combination of findings of cardiac tamponade and constriction in some patients. Abnormal pulsus paradoxus is more common in these patients than in patients with constriction. A jugular venous waveform in which the *x* descent is steeper than the *y* descent is also suggestive of effusive-constrictive disease, and the presence of Kussmaul's sign in a patient with pericardial effusion is suggestive of effusive-constrictive disease rather than isolated cardiac tamponade. More often than not, the diagnosis is suspected when elevation in jugular venous pressure persists after pericardiocentesis. Finally, latent or "low-volume" constriction should be suspected in the patient with persistent dyspnea, fatigue, and mild lower extremity edema after aggressive diuresis normalizes the central venous pressure. Volume replacement unmasks constrictive hemodynamics.

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Before the modern medical and surgical era, pericardial constriction was most commonly caused by tuberculosis or thought to be idiopathic. Of 231 cases of constriction verified by surgery or autopsy at the Mayo Clinic from 1936 to 1982, the causes were idiopathic factors in 73%, pericarditis in 10%, pyogenic infection in 6%, radiation in 5%, and, least frequently, arthritis, post–cardiac surgery, or "other causes" in 2% each [1]. In the period from 1985 to 1995, causes in order of incidence were idiopathic in 45 of 135 cases (33%); post–cardiac surgery events (18%); after pericarditis (16%); after radiation (13%); "other causes," including neoplasm, trauma, and drugs (10%); inflammatory arthritides (7%); and, in rare cases, pyogenic infection (3%). These findings have been confirmed by other investigators [2, 3]. Other pathologic conditions reported less frequently to cause pericardial constriction include mesothelioma; uremia (chronic, in which affected patients are on dialysis); hemopericardium after trauma or thrombolytic therapy or related to coagulopathies; Dressler's syndrome after myocardial infarction; vasculitis; drugs, including those used for lupus (hydralazine and procainamide) and migraine prophylaxis (methysergide); hypereosinophilia syndromes; amyloidosis; Whipple's disease; and sarcoidosis (Table 25.1).

Table 25.1 Potential causes of pericardial constriction

Idiopathic
Cardiac surgery
Acute pericarditis (viral)
Mediastinal irradiation
Hodgkin's lymphoma
Breast cancer
Lung cancer
Inflammatory arthritis or vasculitis
Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Rheumatic fever
Infection
Tuberculosis
Fungal
Bacterial
Trauma
Blunt trauma
Penetrating trauma
Hemopericardium
Traumatic
Postthrombolytic
Postsurgical
Coagulopathy
Neoplasm
Mesothelioma
Metastatic cancer
Drugs
Procainamide
Hydralazine
Methysergide
Others
Whipple's disease
Amyloidosis
Sarcoidosis
Asbestosis

Presenting Symptoms and Signs

The patient with pericardial constriction most often presents with symptoms of venous congestion resembling right-sided heart failure with normal left and right ventricular systolic function. Most common complaints by patients include lower extremity swelling, dyspnea and effort intolerance related to pulmonary venous congestion and abdominal discomfort from hepatic distension. In the patient with the acute variant of pericarditis with constrictive physiology, chest pain may be the predominant complaint. In advanced cases of constriction, ascites occurs and may be more remarkable than the lower extremity edema, although some patients present with anasarca. Most patients cannot recall any history of antecedent pericarditis. Many of these patients have undergone extensive prior evaluation for hepatic disease with cirrhosis or congestive heart failure before the diagnosis of constriction is suspected. Unsuspected findings on two-dimensional and Doppler echocardiography performed for the diagnosis of congestive heart failure prompted an evaluation for constrictive pericarditis in 40% of patients who underwent pericardiectomy at the Mayo Clinic in the 10 years before 1997 [4].

Most patients with constriction have at least mild tachycardia, especially with even minor exertion. In these patients, stroke volume cannot increase with exercise, and the major compensatory mechanism is an increase in heart rate. Patients with chronic constriction may exhibit atrial fibrillation. Blood pressure is usually normal, but it may be low or even hypertensive. The patient who has undergone aggressive diuresis may have orthostatic hypotension. Abnormal pulsus paradoxus is rare, occurring only if effusive-constrictive disease or chronic obstructive pulmonary disease is present. The patient with severe limitations of cardiac output may manifest peripheral cyanosis with cool extremities. The patient with hepatic failure or cirrhosis from increased hepatic venous pressure may be jaundiced. Funduscopic examination may reveal that retinal veins are engorged. The hallmark of pericardial constriction is elevated jugular venous pressure with rapid and sharp *x* and *y* descents, which produce the characteristic W wave on the jugular venous tracing. Often, the jugular venous pressure is so elevated that the veins must be examined with the patient in the sitting position, or even standing, in order to see the top of the venous column. In some patients who have undergone overdiuresis, the jugular venous pressure may not be elevated, but the classic physical findings are unmasked with volume infusion. Kussmaul's sign (the paradoxical increase in jugular venous pressure during inspiration) is present in most patients. A cardiac impulse may not be palpable, leav-

ing the patient with a "quiet precordium," although an early diastolic impulse corresponding to the pericardial "knock" is occasionally detected. The first and second heart sounds are normal. The loud early diastolic S3 or "knock" may be confused with splitting of S1. Hepatomegaly, ascites, and even splenomegaly may be detected on abdominal examination, and lower extremity edema is common. If constriction is regional and restricted to the right side of the heart, systemic venous congestive symptoms may be present, whereas pulmonary congestion may not.

Helpful Tests

The electrocardiogram almost universally displays nonspecific T wave abnormalities. Voltage is usually normal but may be decreased or increased. The chest radiograph shows normal cardiac size but may reveal an enlarged superior vena cava or azygous vein, or both, and often shows bilateral pleural effusions. In the modern era, pericardial calcification is only very rarely identified on chest radiographs.

Transthoracic echocardiography with spectral Doppler imaging may be the first clue to the diagnosis of pericardial constriction. Transthoracic echocardiography is unreliable for the detection of pericardial thickening. Pericardial thickness as measured by transesophageal echocardiography correlates well with measurements by computed tomography ($r > 0.95$, $p < 0.0001$), but this technique has not been widely accepted [5]. Two-dimensional echocardiography reveals the restricted motion of the myocardium and the ventricular interdependence with a flat left ventricular posterior wall, absence of diastolic ventricular expansion, and bowing of the interventricular septum toward the left ventricle during inspiration with an abnormal septal "bounce" in early systole. The inferior vena cava is usually dilated, but this can represent elevated central venous pressure from any cause. Doppler echocardiography reveals marked and reciprocal variation in peak mitral and tricuspid inflow velocities with respiration defined as more than a 25% increase in peak mitral E wave velocity in the first beat after the onset of inspiration [6, 7]. The E wave deceleration time is short and varies excessively with respiration. These Doppler findings detected constriction in 88% of affected patients with in one study [8]. Of the remaining patients with constriction documented at surgery, 75% exhibited characteristic respiratory variation after the Doppler examination was repeated in the head-up tilt or sitting position to reduce preload. A pulmonary venous systolic/diastolic flow ratio of more than 0.65 during inspiration and a percentage change in peak pulmonary venous diastolic flow from expiration to inspiration of more than 40% correctly differentiated pericardial constriction from restrictive cardiomyopathy in 86% of patients [9]. Measurement of hepatic vein flow with spectral Doppler imaging reveals loss of the normal multiphasic flow pattern. Hepatic venous flow is monophasic and occurs mainly in systole. Doppler tissue imaging is helpful in the differentiation of pericardial constriction from restrictive cardiomyopathy: Longitudinal axis expansion velocities are markedly reduced in restrictive cardiomyopathy and normal in constriction [10]. Reversal of the mitral valve annular e′ velocities, with the septal higher than the lateral annular velocity is noted.

Gated cine–computed tomography and magnetic resonance imaging are especially useful for the measurement of pericardial thickness [11, 12]. Pericardial thickness exceeding 3.5 mm suggests the diagnosis of constriction with increase in specificity when pericardial thickness is more than 6 mm (Fig. 25.1). In addition, markedly dilated atria with very small, tube-shaped ventricles may be seen. Also, the distribution of pericardial thickening may assist the surgeon in planning pericardiectomy (Fig. 25.2). Tagged cine–magnetic resonance imaging may be useful for diagnosing local or regional constriction [13].

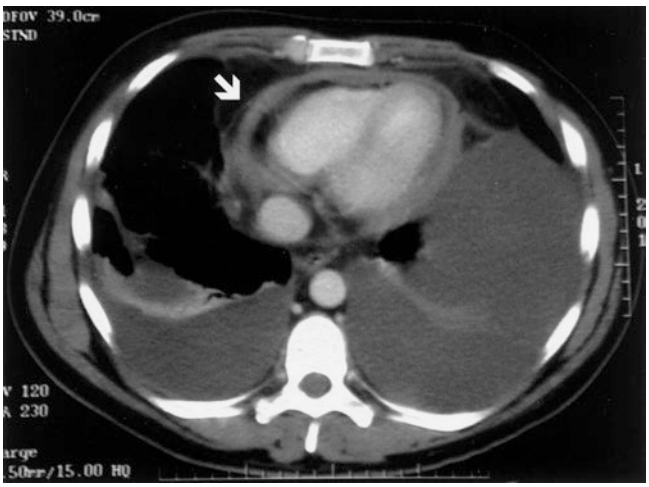

Fig. 25.1 Computed tomographic scan of the heart with pericardium measuring >10 mm thick (*arrow*)

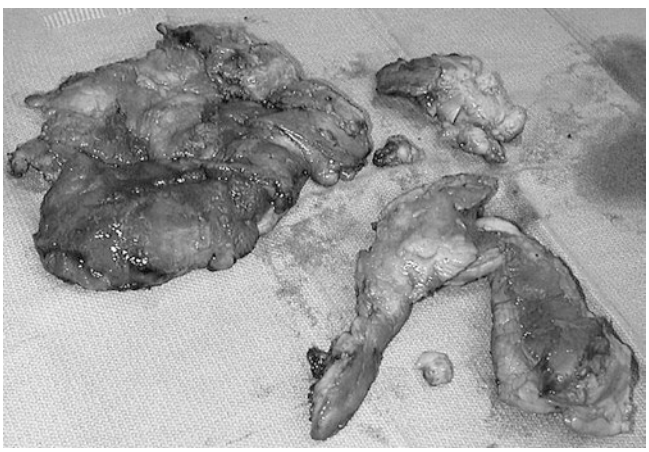

Fig. 25.2 Surgical specimen of extremely thick pericardium from the patient whose computed tomographic scan is shown in Fig. 25.1

The combination of Doppler echocardiography in the supine and sitting position and either computed tomography or magnetic resonance imaging confirms the diagnosis of constriction in 90–95% of patients. Cardiac catheterization with hemodynamic measurement is required in the remainder. Coronary angiography should be performed in all patients undergoing catheterization, because the thickened pericardium can cause extrinsic compression with narrowing of coronary arteries that can cause myocardial ischemia under conditions of stress. Typically, the coronary arteries are visualized within the cardiac silhouette, appear to be subepicardial rather than in the usual epicardial location, and have decreased mobility in systole.

Classically, the diastolic pressures in all cardiac chambers are elevated with near equalization (less than 5 mmHg), unless the patient is volume depleted. The left and right ventricular pressure tracings show the typical "square root sign" with diastolic "dip and plateau," which is also seen in patients with restrictive cardiomyopathy. In constriction, right ventricular and pulmonary artery systolic pressures are only moderately elevated (less than 55 mmHg), and the right ventricular end-diastolic pressure is approximately one third of systolic pressure. In the patient who does not display these classic findings because of volume depletion, enough volume should be administered intravenously in the catheterization laboratory to raise the central venous pressure, and the measurements should be repeated. In one study in which high-fidelity manometric catheters were used to measure left and right ventricular pressures, discordance between the right and left ventricular pressures during respiration (from ventricular interdependence) accurately separated patients with constriction from those with other causes of heart failure [14]. Nevertheless, an occasional patient requires exploratory thoracotomy with inspection and removal of the pericardium or myocardial biopsy to make the diagnosis.

Differential Diagnosis

The diagnosis of pericardial constriction can be difficult and is often delayed for many months after the onset of symptoms. One study showed little difference in the time from symptom onset to diagnosis in the modern era, despite technical advances in imaging and catheterization. In a cohort of patients with constriction diagnosed from 1936 to 1983, time to diagnosis was 14 months (range, 1–348 months), in comparison with 11.7 months (range, 0.1–349 months) in patients diagnosed between 1985 and 1995 [1]. The differential diagnosis of constrictive pericarditis includes venous obstruction, such as occurs in superior vena cava syndrome from neoplasm; low-protein states, including nephrotic syndrome and cirrhosis; other causes of ascites, including intraabdominal cancers; and diastolic heart failure. Physical examination, imaging techniques, and simple laboratory evaluation can clarify the diagnosis in most patients. Pericardial constriction can be differentiated from restrictive cardiomyopathy in most patients by the combination of Doppler echocardiography and either cine–computed tomography or magnetic resonance imaging. Peak initial diastolic mitral annular velocity (e′) obtained with Doppler tissue imaging has been shown to differentiate constrictive pericarditis from restrictive cardiomyopathy with high sensitivity and specificity [15]. Plasma brain natriuretic peptide (BNP) was found to be markedly elevated in restrictive cardiomyopathy but just above normal in contrictive pericarditis in a small study [16]. Cardiac catheterization with detailed hemodynamic measurement elucidates the diagnosis in the majority of the remainder. In rare cases, exploratory thoracotomy or myocardial biopsy is necessary (Table 25.2).

Table 25.2 Differentiation of pericardial constriction from restrictive cardiomyopathy

Evaluation method	Constriction	Restrictive cardiomyopathy
Physical examination	Kussmaul's sign usually present	Kussmaul's sign may be present
	Pericardial knock	
	Valve regurgitation rare	Mitral and tricuspid regurgitation common
Doppler echocardiography	>25% increase in mitral and tricuspid inflow velocity with inspiration	Inspiratory changes absent
CT/MRI	Pericardial thickness >3.5 mm	Pericardium normal
Cardiac catheterization with hemodynamic measurements	RAP = RVEDP = LEVDP (≤5 mmHg)	LVEDP >5 mmHg higher than RVEDP, although may be equal
	RVSP <55 mm	RVSP may be >55 mmHg
	RVEDP >1/3 RVSP	RVEDP <1/3 RVSP
	Reciprocal changes in RVEDP and LVEDP with inspiration	No reciprocal changes in RVEDP and LVEDP with inspiration

CT computed tomography, *MRI* magnetic resonance imaging, *RAP* right atrial pressure, *RVEDP* right ventricular end diastolic pressure, *LVEDP* left ventricular end diastolic pressure, *RVSP* right ventricular systolic pressure

Complications

Unless constrictive pericarditis is transient and responds to antiinflammatory medications, elevations of central venous pressure are progressive, and cardiac output continues to diminish. Ascites and anasarca may develop with brawny lower extremity edema, hepatic cirrhosis, pulmonary congestion, refractory pleural effusions, renal failure, and death.

Therapy

Small doses of diuretics may be useful for the management of edema in these patients, but they should be utilized judiciously because hypotension and renal failure may ensue. However, only radical pericardiectomy provides cure for these patients [17]. With the earliest reports of pericardial resection for constriction in 1913 by Rehn and Sauerbruch, followed by Churchill's report in 1929 [18, 19], the operative approach to "constrictive" limitation of cardiac function began. These early approaches entailed the use of a left anterior lateral thoracotomy, and over the years, various incisions have been used, including left anterior lateral thoracotomy, median sternotomy, and bilateral anterior lateral thoracotomies.

Each of these approaches offers benefits; median sternotomy is favored at our institution. Patients are monitored with arterial lines and pulmonary artery lines and are in the supine position. Upon exploration through the sternotomy, the phrenic nerves are identified, and meticulous dissection is carried out in an area that allows facile identification of a plane between visceral and parietal pericardium or, at a minimum, an adequate plane to begin dissection. Avoiding injury to coronary arteries, the phrenic nerves, and the myocardium is critical, and judicious resection is imperative when calcific deposits invade the myocardium. Once a plane has been achieved, attention is directed to the freeing of the left ventricle first, to prevent right ventricular dilation and failure, which can occur if the right ventricle is freed before the left side [20].

The resection is carried out with wide excision of the pericardium from the left phrenic nerve to the right phrenic nerve and extends from the great arteries on to the inferior diaphragm. The right atrium and superior and inferior vena cava are totally freed, if it is safe to do so. Visceral pericardium or epicardium is removed if involved; if removal is treacherous, the tissue is incised to allow free cardiac expansion. Although the pericardium is not routinely excised posterior to the phrenic nerves, the heart is freed from the pericardium posteriorly using the anterior established plane. Cardiopulmonary bypass is considered only if it is imperative to resect more pericardium or hemodynamic compromise does not allow safe anterior resection.

As pointed out in a review from the Mayo Clinic, etiology of constriction has evolved to include more patients with iatrogenic causes, including previous cardiac surgery as well as postradiation for neoplasia [1]. With this trend, three variables were found to be independent predictors of survival after resection: age, preoperative New York Heart Association class, and a postirradiation cause. In the Mayo series, pericardiectomy offered significant relief of symptoms, but it was noted that approximately one third of the patients were found at some point in follow-up to have recurrence of Class III or IV symptoms. Although the mechanism for this may be uncertain and may reflect the primary cause of the constriction and the type of the original procedure, it is imperative that these patients be followed lifelong.

Early studies of pericardiectomy for pericardial constriction demonstrated significant morbidity, including early right ventricular failure, mortality from bleeding, and low cardiac output states. In that era, constriction was generally more chronic, with a considerable incidence of pericardial calcification and fibrosis, which may have increased operative mortality. In a more recent study, operative mortality decreased from 14% in the period 1936 to 1982 to 6% in the modern era [1]. Operative mortality rates are lower for patients who underwent surgery earlier in the course of their symptoms; therefore, pericardiectomy should be performed early in the course and should not be delayed until the patient no longer responds to diuretics.

Prognosis and Follow-Up

As noted previously, patients respond well acutely to pericardiectomy, usually with prompt postoperative diuresis, although a low output state still remains a problem for some patients and resulted in perioperative death in 4% of patients in one series [1]. Occasionally, patients have a less dramatic response to surgery, with diuresis over weeks or months. Pericardiectomy is incomplete in some patients because pericardium adherent to the myocardium cannot be removed without risk of myocardial perforation. At 10 years of follow-up, functional class improved markedly from New York Heart Association Class 2.7 ± 0.7 at baseline to 1.5 ± 0.8 at follow-up, and 83% of patients were free of symptoms [1]. Late results, however, have not been as promising as might be expected. Diastolic function remains abnormal in 42% of patients late after pericardiectomy and correlates with persistent symptoms [19]. Ten-year survival rates are significantly lower for patients who have undergone pericardiectomy than for age and sex-matched controls (57% ± 8% vs. 81%; $p < 0.001$). Late death was predicted by age, functional class, and a postradiation cause of constriction [1]. In rare cases, a patient may require repeat surgery if constriction recurs. Because of the risk of late morbidity and mortality, patients who have undergone pericardiectomy require serial long-term follow-up assessments.

Practical Points

- Pericardial constriction should be suspected in patients with symptoms of elevated central venous pressure and normal left ventricular function.
- In the modern era, the most common causes of constrictive pericarditis are postsurgical, postradiation, and the "idiopathic" group, which is probably postviral.
- The combination of physical examination, Doppler echocardiography, and either computed tomography or magnetic resonance imaging establishes the diagnosis of constriction in more than 90% of patients.
- If the typical Doppler finding of an inspiratory increase in peak mitral inflow E wave velocity of more than 25% is not present, repeating the Doppler examination in the head-up tilt or sitting position increases the detection of constriction.
- If latent or "low-volume" constriction is suspected, administration of intravenous fluids may assist in the diagnosis.
- Patients who have undergone pericardiectomy for constriction require continued surveillance.

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Abdominal Aortic Aneurysms

26

Venkataramu Krishnamurthy, David M. Williams, James C. Stanley, Gilbert R. Upchurch Jr, and John E. Rectenwald

An abdominal aortic aneurysm (AAA) is a relatively common and often fatal condition that primarily affects elderly individuals. The incidence and prevalence of AAA is certain to rise with an aging population. AAAs and aortic dissections are responsible for at least 15,000 deaths yearly and in 2000 were the 10th leading cause of death in white men 65–74 years of age in the United States [1]. Most AAAs are asymptomatic, and unfortunately physical examination lacks sensitivity for their detection [2].

The infrarenal aorta is the site of 80% of all aortic aneurysms [3]. The normal infrarenal aortic diameters in patients older than 50 years are 1.5 cm in women and 1.7 cm in men. AAA is defined as ≥50% increase in aortic diameter compared with the normal proximal aorta [4]. However, by convention, an infrarenal aorta 3 cm in diameter or larger is considered aneurysmal [5].

Table 26.1 Various causes of abdominal aortic aneurysms

Degenerative
Abnormal matrix (collagen-elastin) degradation
Atherosclerosis
Connective tissue disorder
Cystic medial necrosis
Marfan's syndrome
Ehlers-Danlos syndrome
Pseudoxanthoma elasticum
Trauma
Dissection
Vasculitis
Takayasu's arteritis
Infection
Bacterial (salmonella, tuberculosis)
Syphilis
Fungal

Etiology and Pathogenesis

Various causes for AAA have been suggested (Table 26.1). Proteolytic degradation of the extracellular matrix proteins (elastin and collagen) in the aortic wall appears to be the major underlying mechanism in the development of AAA [6, 7]. The matrix metalloproteinases enzymes play a crucial role in this [8–17]. Other contributing factors include oxidative and biomechanical wall stress, as well as an autoimmune process with extensive lymphocytic and monocytic infiltration with deposition of immunoglobulin G in the aortic wall [7]. Arteriosclerosis, a common finding in AAAs, is believed to be a secondary, not a primary, etiologic factor in AAA development. Cigarette smoking elicits an increased inflammatory response within the aortic wall [18], contributing to the development of the AAA as well.

Genetic predisposition appears important to AAA development; 12–19% of first-degree relatives of a patient, predominantly men, with an AAA will develop an aneurysm [19, 20]. To date, no single gene mutation or protein deficiency has been associated with the common infrarenal AAA. However, a decrease in aortic wall type III collagen has been noted in individuals who have a first-degree relative with an AAA, in comparison with those without a family history of AAAs [21]. Increases in the frequency of the Hp 2-1 haptoglobin phenotype, as well as the Kell-positive and MN blood groups, have also been noted in patients with AAAs. In contrast, there is a decrease in the incidence of AAAs in

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patients with type A Rh-negative blood group [12]. In addition, one study suggests that a polymorphic alteration in the human lymphocyte antigen–DR B1 is important in the development of inflammatory AAAs [22]. A DNA linkage analysis of 233 families with at least two individuals diagnosed with AAA identified two chromosomal regions (chromosomes 19g13 and 4q31) that may be correlated with AAA inheritance [23].

Clinical Evaluation: The medical, social, and family histories are important in identifying risk factors for development, expansion, and rupture of AAA [24–29]. The Aneurysm Detection and Management Veterans Affairs Cooperative Study Group (ADAM) trial found an increased risk for AAA related to advanced age, greater height, coronary artery disease (CAD), atherosclerosis, high cholesterol levels, hypertension, and, in particular, smoking [30]. AAA typically affects elderly males having a mean age above 70 years, with a male to female ratio of 4–6 to 1 [19, 20, 31–36]. Among those undergoing AAA repairs, 12–19% have a first-degree relative with an AAA [20, 37]. An AAA is over seven times more likely to develop in a smoker than a nonsmoker, with the duration of smoking, rather than total number of cigarettes smoked, being the key variable [29]. In general, the risk for developing an AAA is lower in African Americans, and diabetic patients.

Unless treated, most AAAs continue to expand until rupture occurs; this is the most serious complication of AAA. Size of the aneurysm itself is an important risk factor for rupture. In accordance with the law of Laplace, a geometric increase in aortic wall pressure occurs with linear increases in AAA size. Thus, an increase in aortic diameter from 2 to 4 cm induces, not a two-fold, but a four-fold increase in the pressure/cm^2 on the aortic wall. Rupture is directly proportional to aortic wall pressure. Aneurysm expansion greater than 4–8 mm over a 12-month period suggests that the AAA is unstable and is an indication for early intervention.

Most AAAs are asymptomatic; factors independently associated with an increased risk of expansion and rupture include female gender, large initial aneurysm diameter, low forced expiratory volume in one-second (FEV1), current smoking history, and elevated mean blood pressure (Fig. 26.1) [24, 38, 39]. Women are two to four times more likely to experience rupture than men [40]. Aneurysms in transplant patients also appear to have high expansion and rupture rates [27].

The risk of death after AAA rupture depends on how quickly an emergency operation can be performed. Unfortunately, nearly 60% of patients with ruptured AAAs die before reaching a hospital, and only 50% of the remainder survive an emergency operation. Thus, AAA rupture carries an 80% rate of mortality [41–44]. This high mortality may be reduced with the increasing trend in the utilization of Endovascular Aortic Aneurysm Repair (EVAR) for ruptured AAA [45, 46].

Palpation of the lateral borders of the aorta between the examiner's fingertips in the epigastric region on abdominal examination may reveal the existence of an AAA. An occasional AAA patient will be aware of prominent abdominal pulsations when recumbent. However, anterior aortic pulsations alone are more likely to be caused by an ectatic, nonaneurysmal vessel, not an AAA. AAAs in the 3- to 3.9-cm range are palpable 29% of the time, whereas those greater than 5 cm are palpable 76% of the time [47]. Physical examination alone as a diagnostic maneuver is clearly not sensitive enough to exclude the diagnosis of an AAA.

Patients with AAAs may also have aneurysms of the femoral or popliteal arteries that may be recognized on physical examination. A study of 251 patients with AAAs from the University of Michigan documented a 14% incidence of aneurysms of the femoral and popliteal arteries, all occurring in male patients [48]. The presence of these extremity aneurysms may serve as a clue to the existence of an AAA as well. It is important to recognize that patients with femoral and popliteal artery aneurysms have an 85% and a 62% chance of having a co-existing AAA, respectively [49, 50].

Abdominal Ultrasound (US), when performed by experienced personnel, has extremely high sensitivity (100%) and specificity (96%) for the detection of an infrarenal AAA. Ultrasound is the screening imaging modality of choice. The United States Preventive Services Task Force [51] recommends that screening for AAA by US benefits patients who have a relatively high risk for dying from an aneurysm. This includes those age 65 years or older, male sex, and smoking at least 100 cigarettes in a lifetime. The guidelines recommend one-time screening with ultrasound for AAA in men 65–75 years of age who have ever smoked. In contrast, Society of Vascular Surgery (SVS) guidelines recommend US screening for all men at or older than 65 years age, irrespective of history of smoking [52]. These guidelines also recommend US screening to start at 55 years age for men with family history of AAA and for women older than age 65 who have smoked or have a family history of AAA.

Clinical Decision Making: Outcomes for repair of symptomatic AAAs are significantly worse than for asymptomatic aneurysms. Mortality rates being, 25% with symptomatic, 35% with ruptured AAAs, and 5% with asymptomatic AAA [53]. Operative morbidity is also higher in symptomatic and ruptured AAA. Emergent repair is recommended for patients with ruptured AAA and urgent repair for those believed to be symptomatic. Elective repair is recommended for patients presenting with a fusiform, asymptomatic AAA >5.5 cm in diameter, in the absence of significant co-morbidities.

In general, small fusiform aneurysms, less than 4.0 cm maximum diameter, are at low risk of rupture and continued

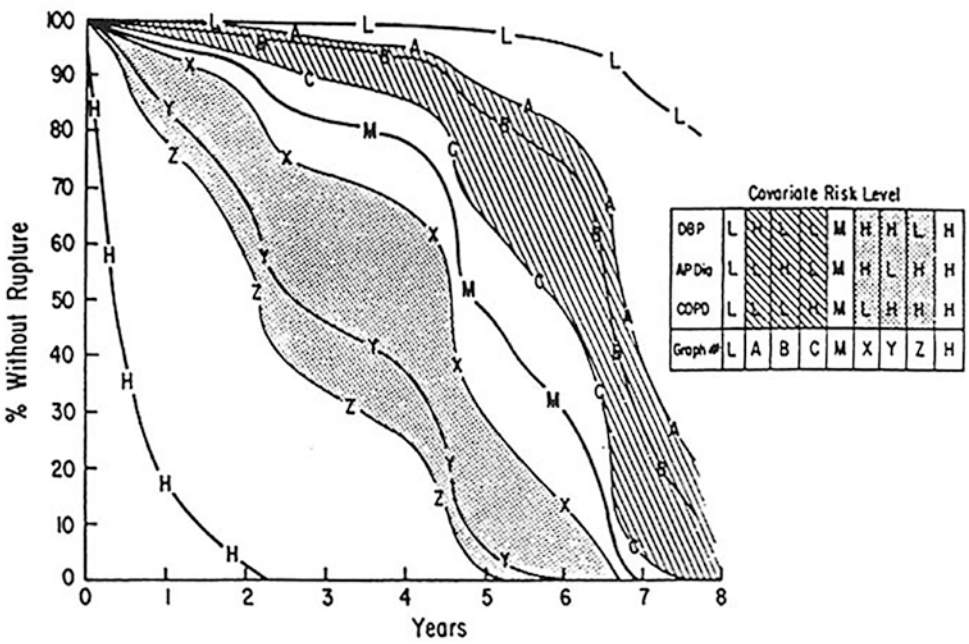

Fig. 26.1 The interaction of initial anteroposterior diameter, the presence of chronic obstructive pulmonary disease, and diastolic blood pressure in contributing to abdominal aortic aneurysm rupture risk. (Adapted from Cronenwett et al. [39])

surveillance is recommended. However, there is no consensus regarding the most appropriate role for either immediate treatment or surveillance for patients with AAAs between 4.0 and 5.4 cm [54, 55]. Treatment in this group must be individualized in each patient.

Aneurysm size is the major factor in triaging *asymptomatic* patients with AAA who are clinically stable. The risk of rupture increases as the AAA size of increases; 1-year incidence of rupture is 9% for AAAs 5.5–6.0 cm in diameter, 10% for 6.0–6.9 cm, and 33% for AAAs of 7.0 cm or more [51]. Elective surgical repair is recommended for AAAs equal to or larger than 5.5 cm. Surgical repair of AAAs smaller than 5.5 cm has not shown any distinct survival advantage. Surveillance, using serial US, is in this group is a safe practice in compliant patients [54–56].

Published SVS guidelines [52] recommend follow-up surveillance imaging at 12-month intervals for patients with an AAA of 3.5–4.4 cm in diameter. Surveillance imaging at 6 month intervals is recommended for those patients with an AAA diameter between 4.5 and 5.4 cm. For otherwise healthy patients, follow-up imaging is recommended at 3 years for those between 3.0 and 3.4 cm in diameter and at 5 years for aneurysms between 2.6 and 2.9 cm. Candidacy for surgical repair and relevant assessment should be performed when AAA exceeds 4.5 cm diameter or when AAA grows by more than 0.6–0.8 cm per year on serial US [57, 58]. Educating patients about signs and symptoms of AAA rupture is also important. They should be advised to seek emergent medical help if they experience any new or unusual pain in the back, groin, testicles, legs, or buttocks.

Symptomatic patients with AAA usually experience pain in the abdomen, back or groin areas. The classic triad of hypotension, abdominal/back pain and a pulsatile abdominal mass has been described, but such is actually uncommon in a given patient with ruptured AAA. A high index of suspicion is necessary for making a timely diagnosis of this life-threatening condition. Symptomatic AAAs represent true surgical emergencies and warrant immediate operative intervention, without extensive time-consuming diagnostic studies. However, in clinically stable patients, an urgent CT scan may be obtained to evaluate the presence and size of AAA and to rule out rupture.

AAAs may present with presumed exacerbation of chronic back pain or with new onset of abdominal, flank, or back pain, radiating to the groin, secondary to acute AAA expansion or rupture. Without imaging studies or a high index of suspicion, this pain may be confused with that of diverticulitis, renal colic, irritable bowel syndrome, inflammatory bowel disease, ovarian torsion, or even acute appendicitis.

Treatment

Careful attention to operative strategy, as influenced by anatomic features of the AAA, along with careful treatment of medical co-morbidities is critical to achieving an optimal outcome in these patients. In addition, appropriate postoperative patient surveillance and timely interventions for late complications is also necessary to minimize subsequent aneurysm-related death or morbidity. With evolving newer endovascular techniques, cost-effectiveness has become a critical element of offering treatment for AAA.

It is important to recognize the common comorbidities affecting patients with AAA, particularly cardiac, pulmonary, and renal dysfunction. The American College of Cardiology/American Heart Association Task Force on Practice Guidelines has provided an algorithm for appropriate preoperative testing [59]. Coronary artery disease (CAD) is of particular relevance in that it is the leading cause of early and late mortality after AAA repair [60]. Although several studies documented lower incidence of perioperative cardiac events with EVAR compared to open surgical repair [61–63], the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial did not demonstrate any such benefit [64]. In general, while elective open AAA repair can generally be considered to carry a higher risk for a perioperative cardiovascular event, EVAR should be considered a procedure that is associated with intermediate to high cardiac risk in the range of 3–7%. Thus, reducing the risk of cardiac morbidity during the course of open repair or EVAR is important.

Active cardiac conditions warranting evaluation include: unstable or severe angina, recent MI (<1 month), decompensated heart failure (new onset, worsening, or New York Heart Association [NYHA] Class IV), significant arrhythmia (atrioventricular [AV] block, poorly controlled atrial fibrillation, new onset ventricular tachycardia), or severe valvular heart disease (symptomatic, aortic valve area <1 cm^2 or pressure gradient >40 mmHg). These patients will benefit by medical optimization prior to treatment of their AAA. In the absence of any active cardiac condition, further non-invasive testing is only indicated if it will change management. However, a 12-lead ECG within a month of the planned repair should be obtained in all patients. In patients with stable cardiac symptoms routine coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) prior to elective vascular surgery does not appear to significantly alter the risk of postoperative MI, death or long-term outcome [65].

Preoperative renal insufficiency has been documented to increase the morbidity and mortality of AAA repair [66]. In a review of 8125 intact abdominal aneurysm operations in the state of Michigan, the presence of renal failure was associated with 41% mortality as compared with 6% for those patients without significant renal disease [67]. Contrast induced nephropathy (CIN) is another consideration when considering contrast enhanced CT scans preoperatively or following EVAR [68]. Carbon dioxide has been effectively used as a non-nephrotoxic contrast agent during EVAR in AAA patients who have baseline renal insufficiency and/or at risk for CIN. Pre- and post procedure hydration with normal saline or 5% dextrose/sodium bicarbonate is recommended for all AAA patients at increased risk of CIN [69].

Several studies have reported that COPD is an independent predictor of operative mortality after AAA repair [66, 70]. However, Upchurch et al. demonstrated that abnormal preoperative pulmonary function tests and arterial blood gas values were not predictive of such poor outcomes to defer aneurysm repair [71]. Nevertheless if COPD is severe, formal pulmonary consultation is recommended to best optimize its medical therapy.

Presence of diabetes by itself has not been shown to increase mortality following AAA repair, but it is associated with an increase in length of hospital stay [72]. Therefore, conventional glucose control during the perioperative period, with a target of 180 mg or less per deciliter (<10.0 mmol/L), is recommended.

Preoperative Imaging: Plain abdominal or lumbosacral radiographs are insensitive in diagnosing AAA; yet these studies may be useful to exclude conditions such as bowel perforation that mimic symptomatic/ruptured AAA in the emergency setting.

Ultrasound is the most useful means of establishing the diagnosis of an AAA. It is a noninvasive and inexpensive test that can provide reliable measurements of the aortic diameter (Fig. 26.2). US findings correlate closely with operative measurements of AAA, and interobserver variability of less than 5 mm in AP diameter has been demonstrated in 84% of measurements [73]. Errors and limitations with US are most often attributed to inexperienced technicians, lack of interpretive skills, or excessive bowel gas. Planned endovascular treatment of AAA, however, may require more detailed anatomic details, and often necessitates either CT or MRI studies.

CT scan is highly predictive of AAA size. Interobserver variability of less than 5 mm exists in 91% of AP measurements. Of importance is that CT may reveal other intraab-

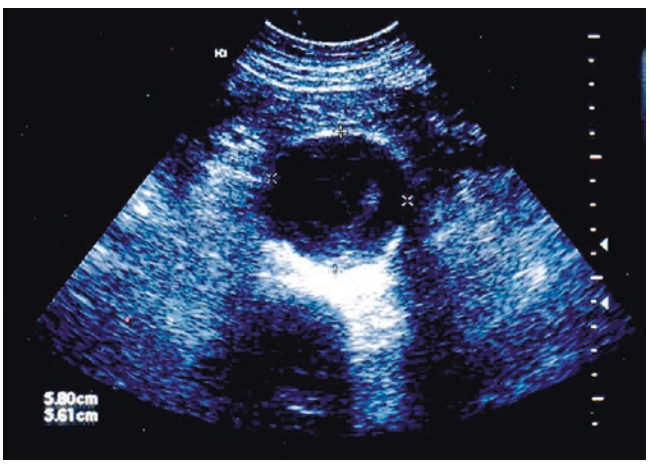

Fig. 26.2 Duplex ultrasonography documenting an abdominal aortic aneurysm

dominal pathologic processes [73]. It is superior to US in assessing AAA wall integrity, the location and amount of calcification within vessel walls, venous anomalies, retroperitoneal blood, aortic dissection, infection or inflammation, proximal and distal extent of the aneurysm, presence of accessory or anomalous renal arteries and coexistent arterial occlusive disease (Fig. 26.3). Limitations of CT studies include the need for nephrotoxic iodinated contrast administration, radiation exposure, and higher cost. Current generation Spiral or helical CT scans provide excellent resolution and multi-planar reconstruction capability. It has become the study of choice for assessing AAAs before EVAR, as well as for identifying postoperative endoleaks in patients receiving endografts (Figs. 26.4 and 26.5).

Magnetic resonance angiography (MRA) with gadolinium and the use of a breath-holding technique is comparable with CT scanning for AAA measurements (Fig. 26.6). An earlier reported University of Michigan experience with 43 AAAs revealed that MRA correctly identified maximum AAA diameter and had 94% and 98% sensitivity and specificity, respectively, for identifying significant stenoses of the splanchnic, renal, or iliac arteries [74]. MRA limitations include the inability to scan claustrophobic patients or those who have pacemakers, defibrillators, or metallic implants, including certain vascular stents. Another disadvantage of MRA is its inability to image calcified plaque, a finding important in endovascular interventions. Lastly, the use of gadolinium in patients with renal insufficiency carries a risk of severe dermatofibrosis.

Digital subtraction catheter angiography is usually obtained when the AAA is suspected to involve the renal or splanchnic

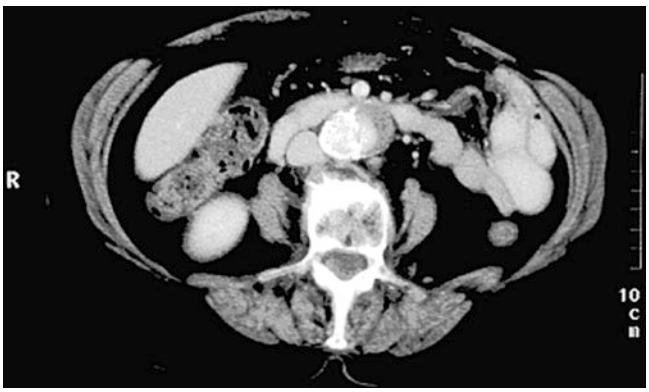

Fig. 26.3 Computed tomographic scan of the abdomen, demonstrating a mycotic abdominal aortic aneurysm

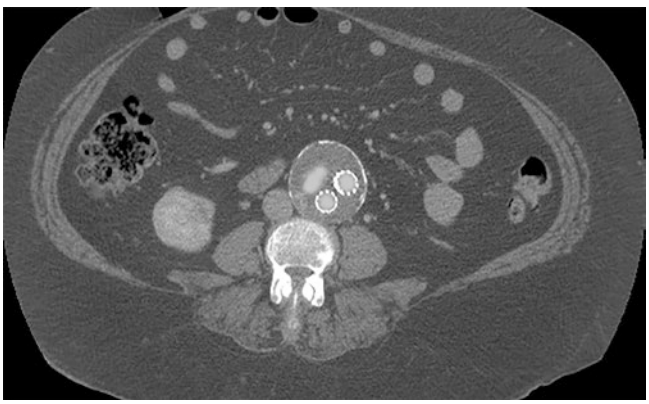

Fig. 26.4 Computed tomographic scan demonstrating the presence of an endoleak after endovascular repair that resolved after a secondary intervention

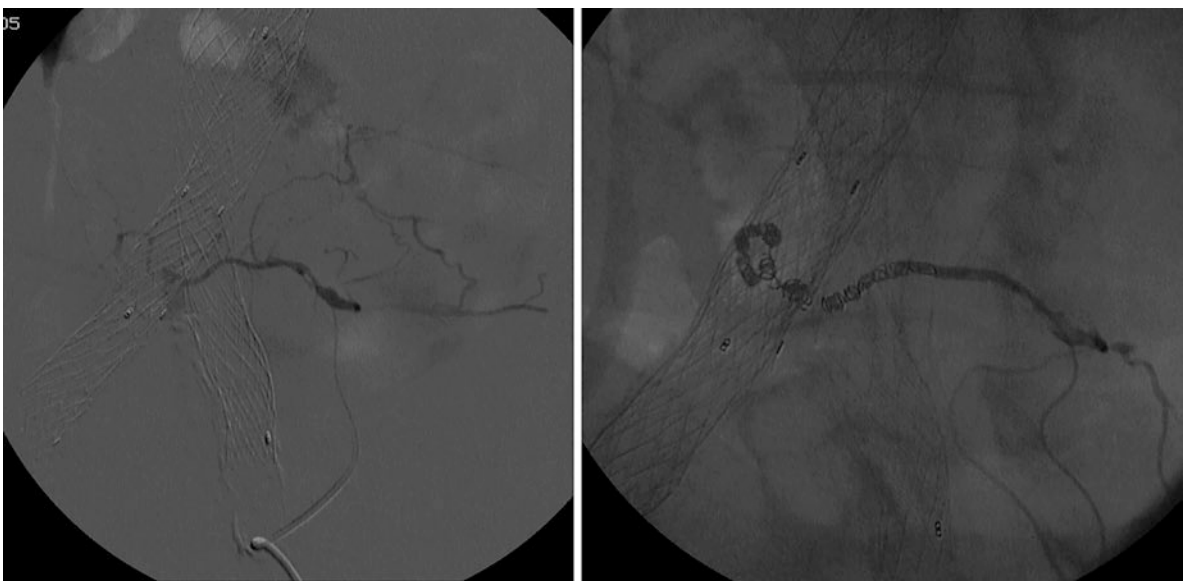

Fig. 26.5 Highly selective angiogram via the left ascending lumbar artery demonstrating filling of the aneurysm sac via a left lumbar artery after endograft repair of a AAA. Note outflow through the corresponding left lumbar artery. Successful coil embolization of both right and left lumbar arteries were the treatment for this Type II endoleak

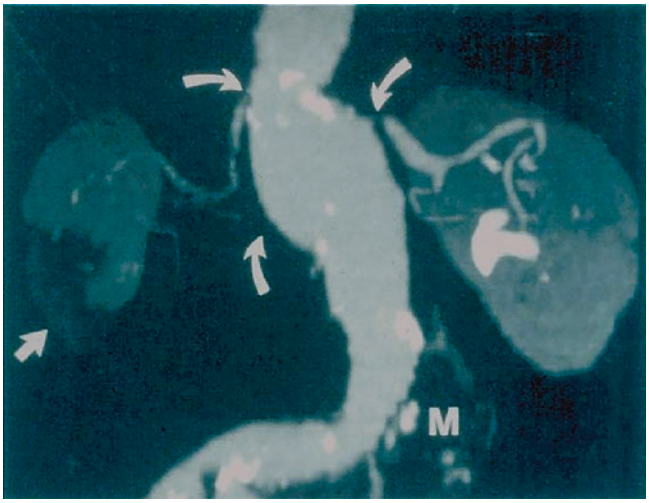

Fig. 26.6 Magnetic resonance angiography documenting renal artery involvement with an abdominal aortic aneurysm

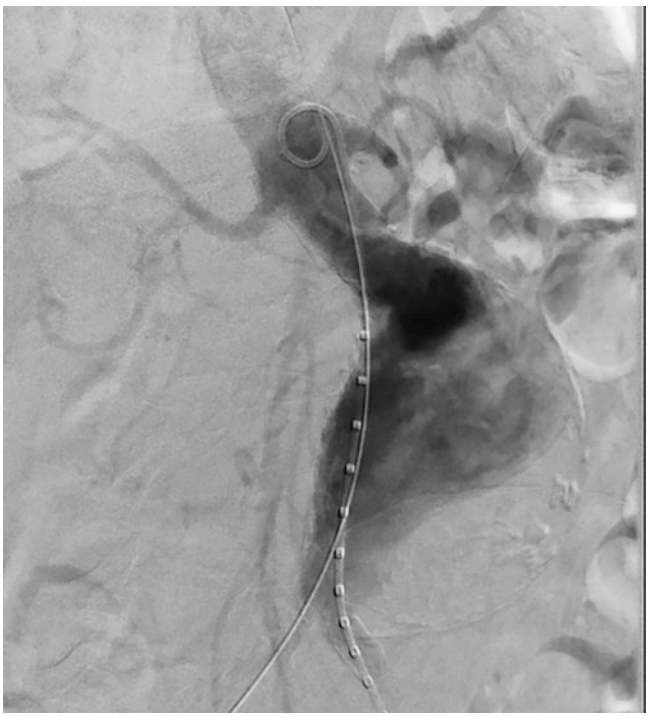

Fig. 26.7 Arteriography performed preoperatively before repair of a complex juxtarenal abdominal aortic aneurysm associated with bilateral high-grade renal artery stenosis

vessels or in patients suspected of having associated moderate or severe lower extremity ischemia (Fig. 26.7). These studies identify the cephalad extent of the AAA, the number and location of renal arteries, the state of the splanchnic arteries, and the status of the iliac arteries, as well as the presence of occlusive disease in the lower extremity arteries. Complications of angiography include puncture site bleeding or thrombosis, atheroembolism, and impairment of renal function as a result of iodine contrast nephrotoxicity.

Surgical Treatment

Elective operative intervention by open surgical repair or endovascular graft placement lessens the likelihood of death from AAA rupture. Conventional open operative procedures in elective circumstances using the National Inpatient Sample database carried a 4.3% mortality rate in 2000 [43]. Women fared worse than men after aneurysmectomy for both intact and ruptured aneurysms. In fact, the average elective mortality spanning over an 11-year period in women was 10.7%, in comparison with 6.8% in men in this experience. The explanation for this is not evident, but suggests both a biologic element and a practice bias, that places women at a disadvantage for the conventional operative treatment of AAA.

Conventional Surgical Treatment of Intact AAA

An expeditious operation is important for an open repair of an AAA [75]. An aortic operation longer than 5 h is independently associated with an increase in risk for mortality and significant cardiopulmonary complications (odds ratio, 5.11; 95% confidence interval, 1.69–15.52; $p < 0.004$). Other factors associated with poor surgical outcome include operative hypothermia, excessive blood loss, and the need for supraceliac aortic cross clamp. Specific comments about operative technique warrant mention.

Surgical approaches are individualized for each patient, with transperitoneal or retroperitoneal aortic exposure based both on the surgeon's preference and on the character of the aortic disease. The transperitoneal approach is preferred when there is a need to revascularize the right kidney or when the aneurysmal disease extends into the right iliac artery. The retroperitoneal approach may be preferable in the presence of obesity or a history of multiple prior laparotomies, which creates hostile adhesions in the abdomen [76]. Although the retroperitoneal approach does not significantly decrease mortality or major cardiopulmonary morbidity, it does expedite the return of postoperative bowel function [77, 78].

In the past, thrombotic complications of clamping the aorta and renal failure have been important issues. In contemporary practice, patients receive systemic anticoagulants with intravenous heparin prior to aortic clamping, and a diuresis is established, usually with mannitol administration or loop diuresis in azotemic patients. The aneurysm is then incised, and any intraluminal thrombus is removed before the aortic graft is sewn in place. The prosthetic grafts currently used are either woven or knitted Dacron or extruded Teflon. After the graft is in place and aortic blood flow is restored, the graft is covered with the aneurysm sac or other retroperitoneal tissue, so as to prevent contact with the intes-

tines. Such contact may lead to later graft-enteric erosion, which is considered a life-threatening complication necessitating graft removal. All patients with aortic grafts should be administered antibiotics for invasive procedures, including dental restorations and cleaning performed at a later date, similar to prophylaxis for bacterial endocarditis in patients with prosthetic cardiac valves.

Conventional Surgical Treatment of Ruptured AAA

The surgical approach to the patient with a ruptured AAA must be focused on saving life. Nearly half these patients subjected to emergency surgery die from complications within the first 30 days after operation [44, 79–81]. Attention to controlling hemorrhage, restoring aortic blood flow, and avoidance of attempts to reconstruct less diseased vessels, such as asymptomatic stenoses of renal arteries or marginally aneurysmal iliac arteries, becomes very important.

Supraceliac aortic cross clamping is often used initially to control continued bleeding, especially in patients with large retroperitoneal hematomas. The proximal aortic cross clamp may then be moved to below the renal arteries once the infrarenal aortic neck has been isolated. Adequate blood replacement and maintenance of normothermia are critical elements in these emergency procedures.

After the aortic reconstruction, the adequacy of the blood flow to the colon and lower extremities should be assessed before the patient leaves the operating room. A delayed abdominal closure should be considered after treatment of a ruptured AAA [82]. In many instances massive fluid resuscitation and a large retroperitoneal hematoma in these patients may cause the abdominal closure to result in a compartment syndrome with decreased perfusion of the splanchnic and renal circulations. Delayed abdominal closure, with the use of a wound vac or a silo similar to that used in pediatric patients confers improved survival benefits in these patients.

Given the potential improved survival of patients with ruptured AAA repaired endovascularly, there has been a growing trend toward an "endovascular first" approach in these patients. In this approach, stable patients with ruptured AAA are preferentially repaired with an aortic endografts whenever possible and open surgery is reserved for patients with anatomy unsuitable for endografts placement.

Complications after Open Repair of AAA

Most mortality after aortic surgery is secondary to myocardial ischemia. Common risk factors leading to major postoperative cardiac event include advanced age, male gender, history of diabetes necessitating medication, previous myocardial infarction, and a history of congestive heart failure [83, 84]. Improved preoperative preparation and postoperative care have decreased the rate of mortality after elective AAA repair since the 1960s [43, 70].

Table 26.2 Results of open surgical repair of nonruptured abdominal aortic aneurysms

Study	Year	Study period	Patients	Deaths	Mortality (%)
Crawford	1981	1955–1980	860	41	4.8
McCabe	1981	1972–1977	364	9	2.5
Diehl	1983	1974–1978	350	18	5.1
Hertzer	1984	1978–1981	840	55	6.5
Donaldson	1985	1972–1983	476	24	5.0
Reigel	1987	1980–1985	499	14	2.8
Green	1989	1983–1987	379	8	2.1
Johnston	1989	1986	666	32	4.8
Leather	1989	Not stated	299	11	3.7
Sicard	1989	1983–1988	213	3	1.4
Golden	1990	1973–1989	500	8	1.6
AbuRahma	1991	1983–1987	332	12	3.6
Ernst	1992	1980–1989	710	25	3.5
Total			6488	260	4.0

Adapted from Ernst [85]

Patients undergoing elective surgery for intact AAAs have fewer postoperative complications and a lower mortality rate than do patients treated on an emergency basis for ruptured AAAs. Increasing complexity of the operation with involvement of the renal and visceral vessels also increases the operative morbidity and mortality. The numbers of AAA repairs done by the hospital and by the surgeon also influences outcome [26].

Operative mortality rates for treating intact AAAs range from 1.4 to 6.5%, with a mean of 4% (Table 26.2). In contrast, the rate of mortality after ruptured AAA repair nears 50% and has changed very little since the 1960s, despite improved preoperative and postoperative care (Table 26.3). Early complications after elective AAA repair include cardiac events (15%), pulmonary insufficiency (8%), renal insufficiency (6%), bleeding (4%), embolization (3%), and wound infection (2%). Late postoperative complications include graft infection and aortoenteric fistula (both 1%). The late complications usually become evident within 3–5 years after the aortic reconstruction [85].

Endovascular Repair of AAA (EVAR): Intact AAA

EVAR has rapidly became a preferred method for infrarenal AAA repair, accounting for more than half of all such procedures (Table 26.4) [86].

Endograft Designs: Several endovascular grafts have been approved by the Food and Drug Administration in the United States for treatment of infrarenal AAAs (Fig. 26.8).

These grafts differ significantly in design and utility. Three of these devices are modular covered stent grafts deployed as a main aortic prosthesis with an ipsilateral iliac artery limb, followed by docking of a contralateral iliac artery graft limb. The AAAdvantage aortic endograft, Medtronic's successor to its AneuRx endograft, relies solely on the radial force of its proximal aortic stents at the infrarenal aortic neck to fixate and hold the endograft into position [87, 88]. The Cook Zenith, Medtronic Talent and Endurant endografts employs an uncovered Z-stent with small barbs for additional suprarenal graft fixation in addition to radial force at the infrarenal aortic neck [87]. The W.L. Gore Excluder endograft uses both radial fixation as well as hooks at its most proximal infrarenal stent to secure the endograft into position [89]. In contrast, the Endologix Powerlink endograft utilize a unibody graft design, with rigid interlinked wire stents to maintain columnar strength and aortic fixation [90, 91]. The Powerlink endograft is fixated not only by radial force in the infrarenal aortic neck, but is also placed on the aortic bifurcation preventing stent graft migration. Additional graft designs are being evaluated in a number of clinical trials.

Table 26.3 Results of open surgical repair of ruptured abdominal aortic aneurysms

Study	Year	Study period	Patients	Deaths	Mortality (%)
Crawford	1981	1955–1980	60	14	23
McCabe	1981	1972–1977	73	38	52
Wakefield	1982	1964–1980	116	60	52
Hoffman	1982	1975–1979	152	58	38
Donaldson	1985	1972–1983	81	35	43
Meyer	1986	Not stated	97	45	46
Shackleton	1987	1975–1985	106	43	41
Chang	1990	1983–1989	63	16	25
Ouriel	1990	1979–1988	243	133	55
Sullivan	1990	1978–1989	69	24	35
AbuRahma	1991	1983–1987	73	45	62
Harris	1991	1980–1989	113	72	64
Johansen	1991	1980–1989	180	124	69
Gloviczki	1992	1980–1989	214	97	45
Ernst	1992	1980–1989	91	41	45
Total			1731	845	49

Adapted from Ernst [85]

Most endovascular devices usually require surgical exposure of the proximal common femoral or distal external iliac arteries for access. Large access (typically >18 Fr) is typically required to deliver endografts for EVAR procedures. Recently, lower profile endovascular graft delivery devices have been developed which allow available percutaneous placement of these endografts with percutaneous arterial closure devices in lieu of direct arterial exposure [92]. This is made possible by the advent of newer percutaneous closure devices (e.g. new Prostar XL closure device, Abbott Vascular, Santa Clara, CA) that allow closure of the larger access sites as a completely percutaneous procedure [93, 94]. Percutaneous EVAR has been tauted to offer several advantages over surgical cut-down procedures, such as decrease in operative blood loss, length of hospital stay, wound infections and femoral neuropathy. Several studies attest to the fact that both approaches produce nearly equivalent clinical outcomes in selected patients [95–97].

Infrarenal versus suprarenal fixation devices: EVAR requires adequate nonaneurysmal proximal and distal attachment sites. Proximal fixation may be obtained through infrarenal or suprarenal fixation. Typical endografts providing infrarenal fixation approved by FDA are Medtronic AneuRx [Santa Rosa, Calif], Gore Excluder [Flagstaff, Ariz], and Endologix PowerLink [Irvine, Calif]. For the use of endografts with infrarenal fixation, an infrarenal neck at least 15 mm in length and less than 32 mm in diameter with an angulation <60° is required for optimal sealing. Pooled data from these devices have established their safety and efficacy [98, 99]. Overall 30-day mortality rates range from 1% with Gore Excluder to 4.2% for the Guidant Ancure endograft. Major complications range from 13.6% in FDA reports with the Gore Excluder to 35.6% with Guidant Ancure [100]. The incidence of Type I endoleaks within 30 days following EVAR with endografts with infrarenal fixation was 4.2% and ranged from 0.9 to 11% [100].

Suprarenal fixation has been proposed to be a more effective means of endograft fixation in the presence of a hostile proximal neck including: short length, severe angulation, reverse taper, a barrel-shaped neck, circumferential mural thrombosis, or extensive calcification. Several endografts in

Table 26.4 Results after endovascular repair of abdominal aortic aneurysm

Series	Patients	Conversion to open repair	30-Day mortality	Persistent endoleak	Other complications
Blum (1997)	154	3 (2%)	1 (1%)	9 (6%)	15 (10%)
Moore (1996)	46	7 (15%)	0	7 (15%)	27 (rate not stated)
Balm (1996)	31	1 (3%)	1 (3%)	3 (10%)	34 in 23 patients
Zarins (1999)	190	0 (0%)	5 (2.6%)	17 (9%)	23 (12%)
Beebe (2001)	258	5 (2%)	3 (1.2%)	44 (1.6%)	Minor 110 (47%)
					Severe 10 (3.9%)
Criado (2003)	70	5 (7%)	1 (1.4%)	5 (7%)	Not stated

Adapted from May et al. [166]

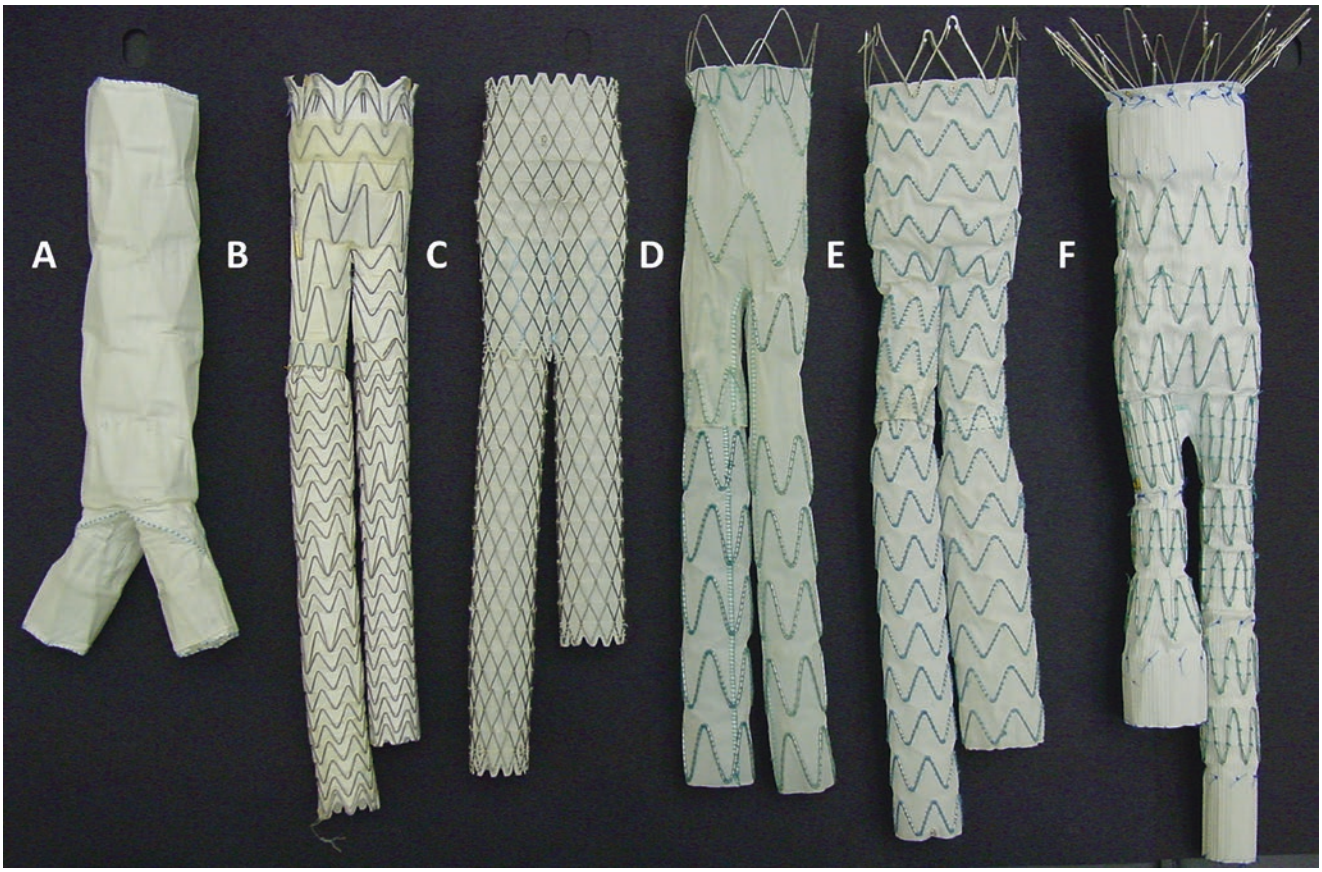

Fig. 26.8 U.S. Food and Drug Administration–approved devices for endovascular treatment of abdominal aortic aneurysms. The main body grafts without iliac limbs are shown. From left to right: (**a**) the Endologix Powerlink unibody endograft, (**b**) the W.L. Gore Excluder modular endograft, (**c**) the Medtronic AAA Advantage modular endograft, (**d**) the Medtronic Talent modular endograft, (**e**) the Medtronic Endurant modular endograft, and (**f**) Cook Zenith modular endograft

the market today employ suprarenal fixation including the Cook Zenith and Medtronic Talent and Endurant endografts. Almost 50% and 87% of endografts used in the DREAM and EVAR-1 trials, respectively, were endografts that used suprarenal fixation. Several studies have reported the efficacy and safety of suprarenal endograft fixation [101–105]. Despite concerns for increased risks of renal or mesenteric artery embolization and occlusion with suprarenal fixation, published data do not provide evidence in support of this concern [101].

Endograft sizing and selection: Great care is needed in selecting the length, diameter, and taper of the stent graft to match the aorta and iliac arteries. The diameter of these endografts are typically up-sized 10–20% in comparison to the native aorta and iliac arteries in order to seal and prevent blood flow into the AAA. Many current devices and delivery sheaths are relatively rigid. Therefore, it is important to envision how the prosthesis will sit in the target vessels. Angulation of the proximal and distal infrarenal aortic segments, as well as the iliac arteries, may make graft deployment and fixation difficult or even impossible. Sizing the aorta or other artery by angiography alone can be difficult, even with specially constructed calibration catheters or intravascular US. Lastly, covering the lumbar and inferior mesenteric arteries with the device may lead to failure or repair because of continued perfusion of the aneurysm by retrograde blood flow from one of these aortic branches (type II endoleak).

Branched and Fenestrated endografts: It is estimated that half of those patients with AAA are not candidates for EVAR using the currently commercially available devices because of unfavorable aortic anatomy. Technological advances and customization of endografts has extended the application of EVAR in these patients. Fenestrated grafts were first introduced in 1996 by Park et al. [106].

In patient's with inadequate infrarenal aortic neck length for a standard endograft device and whose renal arteries, celiac, and superior mesenteric arteries arise from normal aorta, a fenestrated endograft device is an option. Since the visceral segment of the aorta is normal and nonaneurysmal, simple fenestrations and scallops can be used to maintain patency of the renal, superior mesenteric, and celiac arteries

while using the normal diameter visceral aorta as a proximal landing zone for the endograft. Many times, bare metal or covered stents can be placed into the involved visceral vessels through the fenstrations to assure proper alignment of the stent graft with the visceral branches.

Branched EVAR involves using the distal descending aorta as the proximal landing zone in patients with aneurysmal or dilated visceral aortic segment. Either branch artery stenting with covered stents based in fenestrations with in the mainbody endograft are reinforced with a nitinol ring (fenestrated-branched stent grafts), or the main body of the endograft is constructed with cuffs that function as directional branches and serve as attachment sites for each branch artery stent (cuffed-branched stent grafts). Again, with branched EVAR, the visceral segment of the aorta is not normal in diameter and proximal seal with normal aorta is generally above the visceral segment and in the descending thoracic aorta. Stent grafts are placed through fenestration or cuffs in the main body graft to bridge the gap between aneurysmal aorta and the mainbody graft while maintain blood flow to the target vessels.

Midterm results for treatment of paravisceral, thoracoabdominal, and aortoiliac aneurysms with fenestrated and branched grafts are acceptable and demonstrate the benefits of avoiding extensive surgical exposure and maintaining visceral perfusion during the repair, particularly in high-risk patients [107–110]. Long-term results and larger series are still needed to further delineate the safety and efficacy of these devices.

Delayed FDA release of fenestrated and branch graft technology has resulted in the development of other arterial endovascular techniques for the management of the juxtarenal AAA. Placement of perigrafts to visceral arteries between the aortic main body graft and the aortic wall (so called chimney grafts or snorkle) has been used with success (Fig. 26.9) [111, 112].

Internal iliac artery occlusion as an adjunct to EVAR: This procedure is performed prior to EVAR to prevent type II endoleak when the AAA extends to internal iliac artery itself or distal common iliac artery [113–116]. It is typically performed on one side; rarely bilateral embolization is necessary in high risk candidates when aneurysm involves bilateral distal common iliac or internal iliac arteries. Such embolization can safely be performed during EVAR rather than as a staged procedure [115]. Risks associated with this procedure are buttock claudication, colon ischemia, and impotence. In one of the largest series, by Mehta et al., persistent buttock claudication developed in 12% of unilateral and 11% of bilateral internal iliac artery embolizations, whereas impotence occurred in 9% of unilateral and 13% of bilateral embolizations [117]. These potential risks in general are acceptable to patients who are otherwise not suitable candidates for open surgical repair and EVAR is the only reliable treatment option.

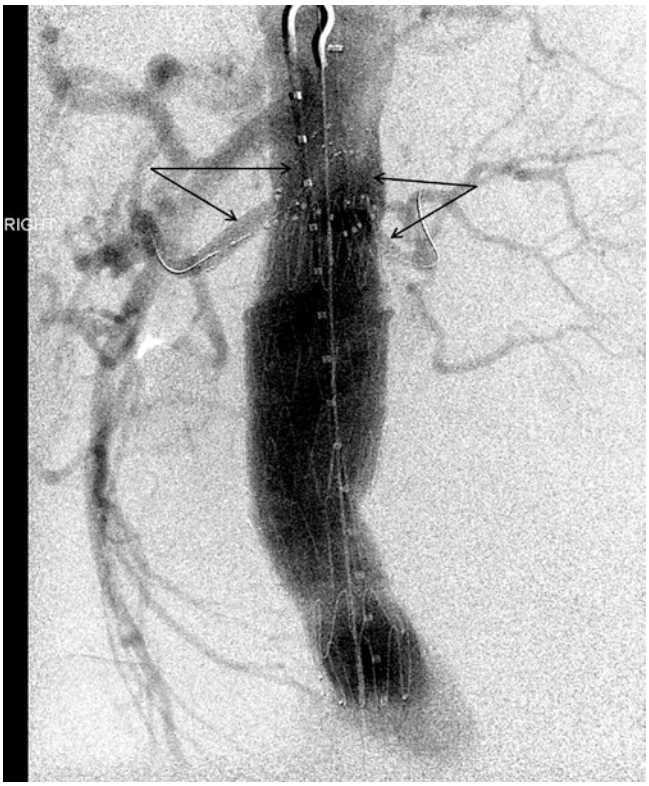

Fig. 26.9 An intraoperative angiogram showing placement of an endograft over the renal arteries with bilateral renal artery stents (snorkle or chimney grafts, denoted with arrows) extended into the aorta between the aortic wall and aortic endograft to maintain patency of the renal arteries and treat a juxtarenal AAA endovascularly in a patients unfit for open AAA repair

Branched Stent Grafting of the Internal Iliac Artery: This approach is one of the several techniques of preserving flow to the internal iliac arteries during EVAR such as surgical transposition or bypass of the internal iliac artery, external to internal iliac endografting, EVAR with a bifurcated stent graft where the contralateral limb is extended into the contralateral internal iliac artery while a femoral-femoral crossover bypass maintains perfusion to the lower limb, "bell-bottom" stent grafts, and branched stent grafts [118]. Branch stent grafting has the advantage of being performed entirely via an endovascular approach, providing antegrade flow into the internal iliac artery and not requiring additional incisions or suturing of bypass grafts. Three internal iliac artery branched endograft devices now exist: a modular multibranched system, the Zenith bifurcated iliac side branch, and the helical branch design [119–121]. A large multicenter trial has documented good preservation of flow in internal iliac artery, no perioperative mortality, a high rate of technical success, a low endoleak rate, and an excellent rate of aneurysm size shrinkage [120].

EVAR of Symptomatic and Ruptured AAA: Utilization of EVAR in the setting of AAA rupture remains somewhat controversial [122–127]. Nevertheless, there is an increasing trend in the utilization of EVAR for ruptured AAA with decreasing mortality [45, 46]. Published literature document less than 40% of patients have aortic anatomy suitable for EVAR in ruptured AAA [128, 129] due to unfavorable neck/proximal graft landing zone. Establishing an institution-based protocol for urgent or emergent EVAR for ruptured AAAs is essential if this approach is to be pursued [124]. Such protocols require that emergency room personnel alert the endovascular team and operating room staff as soon as a ruptured AAA is suspected. A CT angiogram is obtained in hemodynamically stable patients, with all other patients transferred directly to the operating room. With appropriate preparation, planning, and immediate availability of suitable endografts, many patients with ruptured aneurysms can be treated successfully with endovascular grafts.

EVAR Versus Open Repair: Comparision of Outcomes

Early (in-hospital and 30 day) mortality: Elective EVAR, when compared to open AAA repair, is associated with lower in-hospital and 30-day mortality rates in both non-randomized and randomized controlled trials [89, 130–132]. Specifically, in-hospital mortality rates in the EVAR-1 and the DREAM trials were 1.7% and 1.2% for EVAR and 6% and 4.6% for open repair, respectively [64, 133].

Analysis of a high risk cohort from the Veteran Affairs (VA) National Surgical Quality Improvement Program (NSQIP) also revealed those patients who underwent elective EVAR (n = 788) had a significantly lower 30-day mortality than those treated by open repair (n = 1580) (3.4% vs 5.2%, $P < 0.047$) [134]. Analysis of 45,000 propensity score-matched Medicare beneficiaries treated by EVAR and open repair also reported lower mortality with EVAR (1.2% vs 4.8%; $P < .001$), with the reduction in mortality most pronounced for those of advanced age (80–84 years:1.6% vs 7.2%; > 85 years:2.7% vs 11.2%; $P < .001$) [62].

Major medical adverse events: A meta-analysis of observational studies of EVAR performed prior to 2002 demonstrated lower incidence of major cardio-pulmonary events with EVAR compare to open repair (9% vs. 22%) [135]. The DREAM trial also reported lower major medical adverse events after EVAR as compared with open repair (12% vs 27%), although all cardiac morbidity (EVAR 5.3% vs open repair 5.7%) and severe cardiac complications (EVAR 1.8% vs open repair1.1%) were comparable in both groups [64]. An analysis of Medicare beneficiaries comparing EVAR and open repair also reported a reduction in the incidence of pneumonia (9.3% vs 17.4%, $P < .001$), acute renal failure (5.5% vs 10.9%, $P < .001$), and need for dialysis (0.4% vs 0.5%, $P = .047$) among those treated by EVAR [62].

Primary conversion of EVAR to open surgical repair: In the initial experience with EVAR, early conversion to an open repair was necessary in as many as 18% of patients [136, 137]. However, published data from randomized trials such as the DREAM and EVAR-1 studies report a primary conversion to open repair in 1.8% of patients [64, 133]. Analysis of the primary conversion rates by type of graft, as reported to FDA, showed rates ranged from 0% for Excluder and Zenith endografts to 1.6% for Endologix type [100]. In the analysis of 45,000 Medicare beneficiaries treated with EVAR between 2001 and 2004, Schermerhorn et al. reported primary conversion to open repair in 1.6% [62]. Thus EVAR has emerged to be a highly technically successful procedure in patients undergoing elective treatment of AAA.

Endoleak: Endoleak is the most frequent complication after EVAR and is defined as persistent blood flow in the aneurysm sac outside of the endograft [138]. Endoleaks are seen in almost 25% of patients at sometime during follow up after EVAR [139, 140]. The diagnosis of endoleak is most commonly made by CT imaging, although Duplex scanning can be effective [141, 142]. Endoleaks are one of the most common abnormalities identified on delayed imaging and used to justify lifelong followup of these patients. There are five different types of endoleaks.

Type I endoleak results from lack or loss of complete sealing at the proximal (**Type IA**) or distal (**Type IB**) end of the stent graft are generally due to difficult anatomy, such as short or angulated infrarenal aortic neck, calcified landing zones, tortuosity, or nonuniform aortic neck diameters along the proximal seal zone. Due to a direct communication the aortic aneurysm sac with in-line aortic blood flow, Type I endoleaks are associated with significant pressure elevation in the sac, posing a continued risk of rupture [143, 144]. Therefore they should be treated as soon as they are recognized. Type I endoleaks are commonly treated by endograft expansion with compliant balloons, endograft extension if a better landing zone exists proximally or distally, or placement of large balloon expandable stents [145]. Should a Type I endoleak persist, conversion to open repair may be appropriate, especially in patients with large aneurysms.

Type II endoleaks are the most frequently encountered type of endoleak and arise from retrograde filling of the sac by lumbar branches or the inferior mesenteric artery [139, 140]. Management of Type II endoleaks remains controversial as AAA rupture secondary to a type II endoleak is rare. Generally, when a type II endoleak is detected at the time of EVAR, further treatment is not indicated, since spontaneous resolution is possible and occurs approxi-

mately 50% of the time [146, 147]. Even those noted during follow up on imaging, the majority will show no change in sac size, and many will spontaneously resolve. Endoleaks arising from the inferior mesenteric artery are thought to resolve less frequently than those from lumbar vessels and they may be associated with a greater risk of sac expansion [148]. The principle of treatment is to eliminate the branches at their junction with the AAA. Typically the feeding branches are embolized with coils or other embolic agents following transarterial retrograde catheterization. Occasionally, translumbar direct puncture of the sac and embolization, laparoscopic ligation, or even endograft explant may become necessary [149, 150].

Type III endoleaks arise from poorly seated modular connections or more commonly from disconnection and separation of components [143, 144]. Less frequently these endoleaks result from erosion of the fabric. Type III endoleaks result in high sac pressure and therefore should be treated, typically with additional endograft limb components, as they represent a lack of exclusion of the aneurysm.

Type IV endoleaks are due to porosity of fabric resulting in self-limiting blood transmigration into the sac. This is generally a self limited process and treatment is not usually necessary. This endoleak is only noted at the time of repair on post-implantation intra-operative angiography and therefore, an endoleak noted on follow-up imaging should not be considered a Type IV endoleak.

Type V endoleaks (also called **Endotension**), results in continued enlargement of the aneurysm in the absence of demonstrable endoleak (Type I–IV) [151, 152]. Possible explanations include a type IV endoleak at a rate below the sensitivity of current imaging tools, transmigration of serous ultrafiltrate across fabric or pressure transmission through thrombus. It is difficult to treat endotension. Some treatment options include: relining with endografts of a low porosity fabric, endograft explanation, and open surgical repair.

Local complications: A higher incidence of local vascular or device related complications was reported after EVAR (9–16%) compared to open repair (less than 10%) [64, 100]. Groin and wound complications are the most frequent among local complications after EVAR. Access site vascular injuries, distal atheroembolization and endograft limb occlusion after EVAR are less frequent. Graft limb occlusion was observed more frequently in patients with associated aortoiliac occlusive disease, a small (<14 mm) distal aorta and tortuous vessels and when unsupported endografts are used. A 30-day re-intervention rate of 15.6% was reported from a pooled analysis that included pivotal data from the Ancure, AneuRx, Excluder, Powerlink, and Zenith studies reported to FDA [100]. In the EVAR-1 and EVAR-2 trials, reintervention within 30 days of EVAR was reported in 9.8% and 18% of patients, respectively [133, 153]. The EVAR-1 trial in particular reported that almost 75% more secondary interventions were undertaken within 30 days of the procedure or within the same admission after EVAR as compared with open repair.

Long-term outcomes–EVAR vs. Open repair: There is strong evidence that benefits of open repair of AAA are durable [154, 155]. The three principal randomized trials and large registry data comparing EVAR and open repair of AAA have all shown a marked benefit of EVAR with respect to 30-day operative mortality [62, 64, 133, 156]. Therefore, endovascular repair has become a common treatment option. However long-term outcome benefits of EVAR have only recently become available [157, 158].

EVAR 1 trial compared EVAR versus open repair of AAA in 1252 patients with large abdominal aortic aneurysms (≥5.5 cm) between 1999 through 2004 at 37 hospitals in the United Kingdom [158]. Patients were followed (minimum, 5 years; maximum, 10 years) for rates of death, graft-related complications, reinterventions, and resource utilization until the end of 2009. The EVAR patients had an early benefit with respect to aneurysm-related mortality, but the benefit was lost by the end of the study, at least partially because of fatal endograft ruptures (adjusted hazard ratio, 0.92; 95% CI, 0.57–1.49; P = 0.73). When follow up was completed, there was no significant difference between the two groups mortality rate from any cause (adjusted hazard ratio, 1.03; 95% CI, 0.86–1.23; P = 0.72). Thus among patients who were considered to be suitable candidates for either EVAR or open repair of AAA, eventhough EVAR was associated with a significantly lower operative mortality, no significant differences were seen in total mortality or aneurysm-related mortality in the long term. The rates of graft-related complications were higher in EVAR compared to open repair (adjusted hazard ratio, 4.39; 95% CI, 3.38–5.70; P = <0.001). The reintervention rates were also higher in EVAR group compared to open repair (adjusted hazard ratio, 2.86; 95% CI, 2.08–3.94; P = <.001). Both graft related complications and reinterventions were highest in the first 6 months after randomization. New complications occurred up to 8 years after randomization in EVAR group, contributing to higher overall costs. During the 8 years of follow-up, the total average cost of aneurysm-related procedures in the EVAR group was $4568 more than in the open-repair group (mean costs, $23,153 and $18,586, respectively).

EVAR-2 trial [157] reported long term outcome of EVAR in 404 patients who were physically ineligible to undergo open repair during the same period as EVAR 1 trial. One hundred and ninety-seven patients underwent EVAR and 207 patients were assigned to have no internvention. Among the two groups, Aneurysm-related mortality was lower in the EVAR group (adjusted hazard ratio, 0.53; 95% CI, 0.32–0.89; P = 0.02), but all-cause mortality was not significantly different (adjusted hazard ratio, 0.99; 95% CI, 0.78–1.27; P = 0.97). A total of 48% of patients who survived EVAR

had graft-related complications, and 27% required reintervention within the first 6 years. Similar to EVAR 1 trial, EVAR was considerably more expensive than open AAA repair.

Follow Up After Treatment of AAA

Follow up after EVAR: Late aneurysm rupture is still considered a potential risk with EVAR. Therefore, continued surveillance is recommended in these patients to detect aneurysm growth, due to endoleak, device migration, or structural failure of endograft. Typical protocol for EVAR surveillance consists of contrast enhanced CT imaging at 1 and 12 months after initial repair [159, 160]. If a Type II endoleak or other abnormality of concern is observed on contrast enhanced CT imaging at 1-month after EVAR, postoperative imaging at 6 months is recommended.

CT based follow up protocols have raised concerns related to the added costs of these studies, as well as cumulative radiation exposure and potential lifetime cancer risk [161]. Meta-analysis of CT scan data documented a sensitivity and specificity of 69% and 91%, respectively, with greater sensitivity in detecting Type I and III endoleaks than Type II endoleaks [162, 163]. Alternatively color Doppler US has been proposed as the tool for surveillance. If neither endoleak nor AAA enlargement is documented during first year after EVAR, Color Duplex ultrasonography is suggested as an alternative to CT imaging for annual postoperative surveillance. Color Duplex US and a non-contrast CT scan are recommended as a substitute for contrast enhanced CT imaging for post-EVAR surveillance of patients with renal insufficiency. The utility of US is primarily limited in obese patients or those presenting with substantial bowel gas or a large ventral hernia.

Open repair: In contrast to EVAR, open repair is durable and is not associated with a risk of persistent sac enlargement. Rarely, late paranastomotic aneurysm formation (1%, and 5%, at 5 and 10 years) can be seen during follow up [164, 165]. Therefore, a follow-up CT imaging at 5 year intervals after open repair is recommended.

Summary

AAA is a major cause of death in the United States, affecting 3–9% of the population. Diagnosis of AAA by US is efficient and cost effective, whereas physical examination alone is often unreliable in establishing the presence of an AAA. One-time ultrasound screening for AAA is recommended for all men at or older than 65 years. Screening men as early as 55 years is appropriate for those with a family history of AAA.

Repair is recommended for patients that present with an AAA and abdominal or back pain. Elective repair is recommended for patients presenting with a fusiform AAA >5.5 cm in maximum diameter, in the absence of significant comorbidities. Smoking cessation is recommended to reduce the risk of AAA growth and rupture.

Patients with active cardiac conditions (e.g., unstable angina, decompensated heart failure, severe valvular disease, significant arrhythmia) should be evaluated and treated per American College of Cardiology (ACC)/American Heart Association (AHA) guidelines before aneurysm treatment. Coronary revascularization is recommended prior to aneurysm repair in patients with acute ST elevation MI, unstable angina, or stable angina with left main coronary artery or three-vessel disease. Beta blockers should be continued in patients undergoing aneurysm surgery who are currently receiving beta blockers to treat angina, symptomatic arrhythmias, or hypertension. Diastolic hypertension and COPD are independent variables contributing to a greater risk of rupture of smaller AAAs.

Elective open repair of AAA carries an overall 4.3% mortality rate, and women fare worse than men. Emergency repair of ruptured AAAs carries an operative mortality rate of nearly 50%. The overall rate of mortality from AAA rupture, including patients who die before reaching a hospital, is 80%. Open surgical repair offers durable benefit. The EVAR of selected aneurysms of the abdominal aorta is safe and feasible with a mortality of approximately 1%.

Although early mortality benefits are noted in patients undergoing EVAR, EVAR-1 trial did not show any durable benefits in total mortality or aneurysm related mortality in the long-term. EVAR is associated with increased rates of graft-related complications and reinterventions, and is more expensive. Despite this, the early mortality benefit for EVAR and similar longer-term aneurysm-related mortality rates have made EVAR first-line treatment for AAA in recent years. Emergent EVAR should be considered for treatment of a ruptured AAA, if anatomically feasible.

Practical Points

- Aortic disease is the 14th leading cause of death in the United States and affects 3–9% of the population.
- Diagnosis of AAA by US is most efficient and cost effective.
- Large AAAs greater than 5.5 cm are life-threatening.
- Small AAAs, 3–5 cm, rupture with unpredictable frequency. Diastolic hypertension and COPD are independent variables contributing to AAA rupture.

- Elective repair of AAA carries an overall 4.3% mortality rate. Women fare worse than men do.
- Emergency repair of ruptured AAA carries a mortality rate of nearly 50%. Women fare worse than men do.
- The overall rate of mortality for ruptured AAA, including patients who die before reaching a hospital, is 80%.
- Preoperative planning and attention to technical detail during an expeditious operation are key factors in improving overall surgical results after AAA repair.
- Endovascular treatment of AAA is safe and feasible.
- Widespread application of endovascular technology has occurred; however, patients with endovascular grafts must be monitored indefinitely until the problem of endoleaks is thoroughly understood and resolved.

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Acute Aortic Dissection

27

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Usual Causes

Acute aortic dissection is the most common acute process involving the aorta and requires urgent intervention. Although dissection may develop within an aortic aneurysm and rupture may occur as a complication of dissection, aneurysm and dissection are separate entities that must be clearly distinguished [1, 2].

Acute dissection of the aorta is classified as Stanford Type A (proximal) if the ascending aorta is involved or Stanford Type B (distal) if only the aorta distal to the left subclavian is dissected (Fig. 27.1). Separation of the layers of the aortic wall is characteristic and results in the development of a false lumen or channel. Blood enters the intima media space, and further propagation of the dissection may occur in an antegrade or retrograde manner or both [3]. Communication between the true and false lumina may occur via one or more intimal tears. Intramural hematoma (IMH) without an intimal tear is now recognized as a distinct pathologic lesion that is believed to result from hemorrhage of the vasa vasorum and occurs more frequently in the distal aorta [4]. IMH may be the initiating event in certain patients with aortas that are intrinsically weakened and therefore more prone to complications. Atherosclerotic plaque may ulcerate, which leads to intramural hemorrhage or classic dissection. Typically, penetrating aortic ulcer is a localized lesion of the descending thoracic and abdominal aorta, but can propagate to become a more classic dissection [5].

Several predisposing factors have been noted in patients who present with aortic dissection (Table 27.1). A history of hypertension is documented in the majority of patients and is present in more than 70% of patients with Type B dissection [6]. Men are more commonly affected than women in a ratio of approximately 2:1, and the incidence of aortic dissection increases with advancing age.

Abnormal connective tissue within the aortic wall predisposes patients with the Marfan syndrome and other connective tissue disorders to aneurysm formation and dissection at a much younger age. Dissection should always be suspected in any patient with Marfan syndrome who has chest, back, or abdominal pain. Similarly, many patients with bicuspid aortic valve have abnormal connective tissue in the aortic wall and may also have an increased risk of aneurysm and dissection [7, 8].

As many as one in five patients presenting with acute dissection may have a history of prior or recent cardiac surgery [6]. Aortic dissection in these cases may result from shared risk factors (advanced age, hypertension, cigarette smoking, vascular disease) or rarely from trauma due to surgical instrumentation or prior catheterization of the aorta. Dissection or disruption of the aorta secondary to chest trauma or acceleration/deceleration injury is most often located in the region of the left subclavian artery, where the aorta is relatively fixed by the ligamentum arteriosum [9]. Acute aortic dissection has been reported to occur in rare instances during pregnancy, in certain inflammatory and infectious disorders, and as a result of cocaine or amphetamine use.

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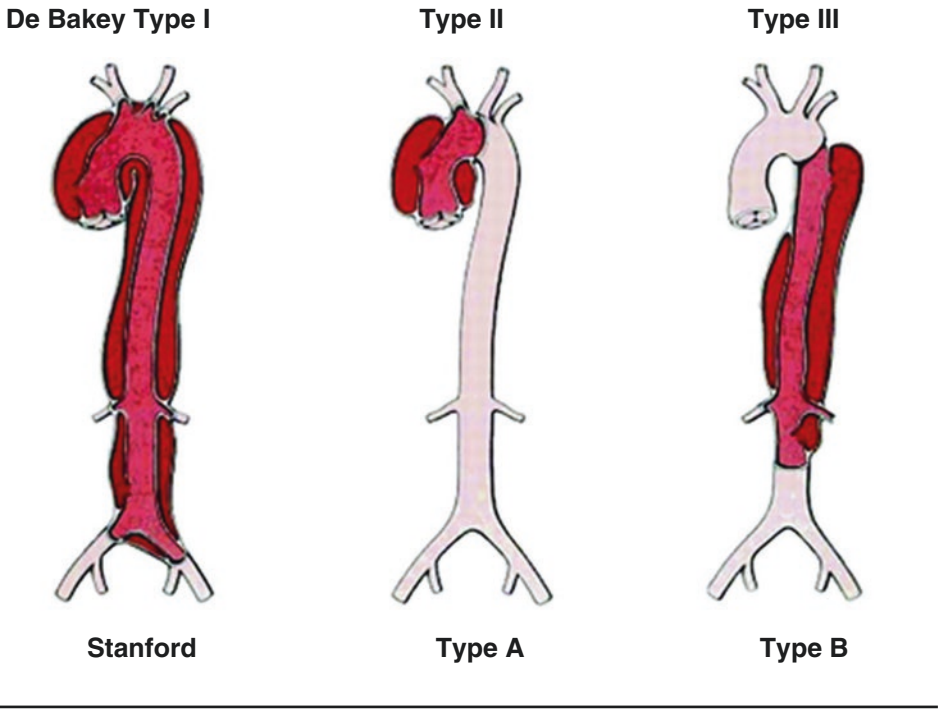

Fig. 27.1 Schematic of Type A dissection

De Bakey	
Type I	Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally.
Type II	Originates in and as confined to the ascending aorta.
Type III	Originates in the descending aorta and extends distally down the aorta or, rarely retrograde into the aortic arch and ascending aorta.
Stanford	
Type A	All dissections involving the ascending aorta, regardless of the site of origin.
Type B	All dissections not involving the ascending aorta.

Presenting Symptoms and Signs

Acute aortic dissection is a dynamic process that may occur throughout the course of the aorta. Therefore, perfusion to any organ system may be compromised and patients present with a broad range of symptoms (Table 27.2). The characteristic feature of acute aortic dissection is the abrupt onset of severe pain, typically in the chest, back, or both. Often the patient can pinpoint the onset of symptoms with "freeze-frame" accuracy. Although a tearing or ripping sensation is an obvious clue, patients are more likely to describe the quality of the pain of aortic dissection as sharp in nature [6]. Pain is most often located in the upper back, anterior chest, or upper abdomen. Often, pain resolves for a period shortly after the initial presentation, which creates a false sense of the patient's stability. Recurrent pain may herald propagation or extension of dissection. Conversely, pain may not be part of the acute presentation at all, particularly in patients presenting with neurologic deficits secondary to stroke [10, 11].

Syncope is a less common, but well-described, presenting symptom of aortic dissection. Most patients with aortic dissection and syncope have other neurologic or clinical findings, which are useful in suggesting the diagnosis. However, a small percentage of patients present with syncope alone [12]. This implies that aortic dissection should be considered in the differential diagnosis of unexplained syncope, especially in the population at increased risk: the elderly and those with a history of hypertension. Patients may present with clinical features of shock if dissection has resulted in cardiac tamponade or blood loss. Congestive heart failure

Table 27.1 Risk factors associated with acute aortic syndrome

Risk factor	Details
Historical features	• Cocaine use • Hypertension/pheochromocytoma • Weight lifting • Trauma/deceleration injury • Prior cardiac surgery • Advanced age • Pregnancy • Oral corticosteroid use (chronic) • Polycystic kidney disease
Atherosclerosis	• More common in Type B dissection
Bicuspid aortic valve	• >50% may have tubular/ascending aneurysm while 20% have sinus of valsalva enlargement • Estimated tenfold increased risk of dissection and irrespective of extent of valvular dysfunction
Genetically triggered conditions	
Marfan syndrome	• Most common inherited connective tissue disease • Mutation in Fibrillin1 gene leads to decreased tensile strength of the aorta • An estimated 75% of patients will have a dilated aortic root • Marked increased risk for dissection
Loeys-Dietz syndrome	• Aggressive vasculopathy linked to TGFBR 1 or 2 mutation • Dissection occurs at small aortic size • Early detection and intervention is important
Vascular Ehlers-Danlos syndrome	• Vascular rupture or dissection and gastrointestinal perforation or organ rupture can occur in 70% of adult patients • COL3A1 mutation
Familial aortic dissection syndrome	• Dilated aorta • Absence of other connective tissue disease • Family history dissection/aneurysm
Aortitis (rare)	
Infectious	• Syphilis (historical) • Salmonella • Staphylococcal species • Mycobacterium
Non infections/inflammatory	• More common: – Giant cell – Takayasu arteritis • Less common: – Behcets arteritis – Cogans syndrome – Relapsing polychondritis • Rare: – Rheumatoid arthritis – Spondyloarthropathies

may be the predominant clinical feature, especially in the presence of aortic regurgitation or myocardial ischemia.

Aortic branch vessel compromise may be caused by direct obstruction by the dissection flap, displacement of the true lumen by the false lumen, or thromboembolic occlusion. This may result in the clinical presentation of gastrointestinal, renal, limb, or spinal cord ischemia. In rare cases, extrinsic compression from an enlarged aorta or aneurysm results in hoarseness, dysphagia, or superior vena cava syndrome.

Classic physical findings include a pulse deficit or aortic regurgitation murmur; however, these helpful clues are usually absent [10]. A pulse deficit is recorded in fewer than 20% of all patients and may be transient if the dissection flap obstructs the arterial ostium intermittently. The murmur of aortic regurgitation is noted in fewer than half of patients with type A dissection [6] The murmur of acute aortic regurgitation may be faint, and other peripheral findings of chronic severe regurgitation, such as wide pulse pressure, are frequently absent. Pleural effusions may be present as a reactive phenomenon or as a result of hemorrhage into the pleural space.

Blood pressure at presentation is highly variable. Hypertension is more common in patients with Type B dissection. Hypotension or shock suggests a serious complication such as rupture or pericardial tamponade and carries a poor prognosis. Presenting features of IMH and penetrating aortic ulcer appear to be similar to those of classic aortic dissection, and progression to classic dissection with intimal tear may occur [5, 13].

Table 27.2 Comparison of clinical features between patients with proximal (type A) and distal (type B) acute aortic dissection

Category	Type A: % present of A	Type B: % present of B	*p* (A vs. B)
Total patients	289 (62.3%)	175 (37.7%)	–
Mean age (years)	61.2	66.3	<0.0001
Prior history of hypertension	69.3%	76.7%	0.086
Prior cardiac surgery	15.9%	21.1%	0.16
Presenting history			
Anterior chest pain	71.0%	44.1%	<0.001
Back pain	46.6%	63.8%	<0.001
Abdominal pain	21.6%	42.7%	<0.001
Syncope	12.7%	4.1%	0.002
Hypertensive (SBP ≥ 150 mmHg)	35.7%	70.1%	<0.001
Mean length of hospital stay (days)	24.1	22.0	0.19

SPB systolic blood pressure
Adapted from Hagan et al. [6]

Table 27.3 Role of imaging

Confirmation
Diagnosis: dissection, IMH, penetrating ulcer
Location
Extent
Intimal tear/communication
Identification
True lumen
False lumen thrombosis
Branch vessel involvement
Extraaortic extension
Pericardial effusion
Assessment
Aortic valve
LV function

IMH intramural hematoma, *LV* left ventricular

Helpful Tests

Immediate confirmation of the diagnosis and urgent institution of appropriate therapy are essential (Table 27.3). In addition to being the most frequently encountered acute aortic pathologic process, rapid recognition of aortic dissection is important because serious complications can develop rapidly. The chest radiograph has traditionally been considered helpful in the initial evaluation of suspected aortic dissection. Although a widened mediastinum and an abnormal aortic contour may be suggestive of the diagnosis, they are nonspecific and absent in more than 10% of patients [11]. With the widespread availability of safe, rapid, and accurate noninvasive imaging techniques, chest radiography should have a limited role in the evaluation of suspected acute dissection. A normal chest radiograph should not dissuade the clinician from further investigation.

Differentiating the pain of aortic dissection from myocardial ischemia is a common clinical dilemma. The presence of a normal ECG in the setting of acute chest pain may lead clinicians away from a diagnosis of myocardial ischemia and toward one of dissection. However, dissection and myocardial ischemia may occur together, and the electrocardiogram at presentation most often shows nonspecific ST/T wave abnormalities. Thus, the electrocardiogram is frequently unhelpful in the differential diagnosis [6, 14].

Routine laboratory studies are often nonspecific in the differentiating aortic dissection from other causes of chest pain. Several immunoassays have been evaluated to see if they can improve detection and facilitate early treatment of acute dissection. A monoclonal antibody to smooth muscle myosin was reported to be a rapid and accurate marker in a small number of Japanese patients with acute dissection [15]. Additionally, D-dimer may also be helpful in differentiating acute dissection from other causes of chest discomfort. However, further investigation is needed to determine the role of these studies in larger populations of patients [16].

Several imaging modalities are widely available to confirm the presence of aortic dissection (Table 27.4). The method of choice in any given center depends on the individual patient, local expertise, and availability. Computed tomography and angiography (CT) and magnetic resonance imaging (MRI) along with echocardiography (trans thoracic or trans esophageal) can give detailed information about the presence of a dissection, its location and involvement of branch vessels or aortic valve/root. These modalities are non invasive or minimally invasive. For these reasons, the role of invasive aortography has diminished. Previously the gold standard, aortography is now performed in fewer than 5% of patients and mainly as a second- or third-line evaluation or in conjunction with percutaneous therapy [17].

Although the overall sensitivity and specificity of computed tomography (CT), transesophageal echocardiography (TEE), and magnetic resonance imaging (MRI) are excellent, there are advantages and drawbacks to each modality in any given situation; therefore, no technique is uniformly superior to the others. Knowledge of the limitations of each method and local expertise is important so that the appropriate imaging study may be obtained expeditiously (Table 27.4).

CT is accurate, is widely available, allows visualization of the entire aorta, and is the most commonly used initial imaging modality [18, 19]. The sensitivity of CT in detection of aortic dissection is greater than 95%, and its specificity approaches 100%, particularly with ECG gating to limit motion artifact in the aortic root. Location, extent, and branch vessel involvement can be determined. Location of intimal tears, false lumen thrombus, or periaortic hemorrhage, which may be important for percutaneous treatment of complicated dissection, can be demonstrated. However, cardiac and aortic valve function are often not evaluated fully in the initial study.

Table 27.4 Imaging modalities used in the diagnosis of aortic dissection

Modality	Advantages	Disadvantages
MDCT angiography	• Rapid image acquisition (20–30 s) • Can use in unstable patients • 3 D reconstruction allows multiple views/ orientations • Ability for post image processing • Allows assessment of perfusion below the diaphragm	• Need for iodinated contrast • Radiation exposure (10–20 mSv)– – Of concern in young patients requiring serial imaging • Image artifacts—particularly in aortic root – May be improved by ECG gating • Aortic size can be overestimated on axial images due to oblique cuts through lumen – 3d rendering allows accurate measurements
MRI/MR angiography	• No radiation • No iodinated contrast • 3 D, multi planar and high resolution • Dynamic and functional information available • May be appropriate for serial imaging over many years	• Caution with use of gadolinium in renal failure • Need for breath hold • Time consuming (10–30 min at minimum) depending on center • Not for use in unstable patients (distance of equipment/staff for resuscitation from patient)
Transesophageal echocardiography	• No radiation • No iodinated contrast • Can be performed at the bedside • Immediate information availability • Excellent evaluation of valve function, pericardial effusion and LV function • Can visualize aorta from root to GE junction • Doppler interrogation of true and false lumen	• Cannot visualize entire aorta, and state of perfusion to abdominal organs is indeterminate • May be limited by technical difficulties • Semi-invasive • Requires conscious sedation and patent/secure airway

The sensitivity and specificity of TEE are similar to those of CT, and TEE can be performed quickly at the bedside with minimal risk to the patient [20]. Sensitivity and specificity for multiplane TEE are greater than 90%. Diagnostic difficulty typically occurs in the distal ascending aorta, where there may be a "blind spot" or reverberation artifact that may mimic a dissection flap. Information regarding the location and extent of dissection, false lumen patency, sites of intimal tear(s), valvular regurgitation, pericardial hemorrhage, and ventricular function can be obtained. Relative cost is low, and risk to the patient is minimal. However, conscious sedation is required and may be difficult to manage in a hemodynamically unstable patient. Additionally, imaging below the gastroesophageal junction is limited, as is accurate delineation of arch vessel involvement. Alternatively, TEE can be, and often is, performed in the operating room to evaluate aortic valve function and LV function once the decision to pursue operative intervention has been made [21]. A limited transthoracic echocardiogram may be helpful in the unstable patient to evaluate for the presence of pericardial fluid, left ventricular function, and aortic regurgitation. Occasionally, the dissection flap may be visualized on a transthoracic echocardiogram if the aortic root is involved.

Despite the high sensitivity and specificity of MRI it is rarely used (<2%) as an initial diagnostic modality [20, 22]. Relative lack of availability, time delay to perform the study, restricted ability to monitor unstable patients during imaging, and incompatibility with metallic devices are likely explanations for its limited use. Images may be reformatted in any plane to assess location of intimal tears as well as branch vessel involvement. MRI may be more appropriately used in the follow up of patients with stable or repaired aortic disease.

In summary, advanced diagnostic imaging test of choice for aortic dissection is CT scanning, particularly with visualization to the level of the iliac artery for surgical planning. If unavailable or iodinated contrast is contraindicated, then TEE or MRI can offer a reasonable alternative in the stable patient.

Differential Diagnosis

Because clinical manifestations are diverse and classical signs are often absent, a high clinical index of suspicion is necessary in order to diagnose aortic dissection. The differential diagnosis is extremely broad, and the diagnosis is frequently delayed or missed at presentation. Aortic dissection should be considered in the differential diagnosis of sudden unexplained hypoperfusion to any organ system.

Symptoms may result from several pathophysiologic mechanisms. Separation of the aortic layers typically results in pain that may be felt throughout the chest or abdomen and even to the neck and arms. Some patients develop symptoms of a vasovagal response. Perfusion to any organ may be compromised by hypotension, static or dynamic obstruction by the dissection flap, or distal embolization of thrombus. Aortic dissection may mimic a variety of more common but serious conditions such as myocardial ischemia, stroke, pulmonary embolism, and cardiac tamponade. A common clinical dilemma is distinguishing aortic dissection from an acute coronary syndrome. Because appropriate therapy for the

latter (thrombolysis/antiplatelet agents) may be catastrophic in a patient with dissection, accurate diagnosis is essential. Dissection and myocardial infarction may occur together, as the dissection flap obstructs the coronary ostia, more commonly the right coronary artery.

Complications

Due to difficulties in making a clinical diagnosis described above, coupled with the threat of potential catastrophic complications, aortic dissection is among the most challenging emergencies encountered in clinical practice. Serious complications develop quickly, and the early mortality rate is up to 1% per hour in the first 24 h [2]. Early death is commonly due to aortic rupture, often prior to hospital presentation. Rupture may extend into the pericardial sac, causing tamponade, or into the mediastinum or pleural space, resulting in exsanguination [23]. The tear may occlude any of the branches of the aorta at their origins. This may result in coronary ischemia or cerebral malperfusion if the carotid artery is involved. Other branch vessels may be involved, leading to celiac and mesenteric ischemia, lower extremity ischemia, or renal artery occlusion; less commonly, spinal arteries may be compromised. Multiorgan system failure and acute aortic rupture are the most common acute causes of death [6].

Therapy

Initial Medical Therapy

Whenever acute aortic dissection is suspected, rapid confirmation of the diagnosis, institution of therapy, and urgent referral to a center with expertise in aortic disease are essential. Patient preference should be addressed early in the evaluation. Some patients may choose not to pursue further therapy, especially if invasive in nature, because of advanced age or significant comorbidity.

The goal of initial medical therapy is to control blood pressure and the rate of change of pressure over time (dP/dT) while maintaining peripheral perfusion. A short-acting beta blocker such as esmolol in combination with sodium nitroprusside is typically administered in an intensive care setting. Intraarterial blood pressure monitoring is recommended, and blood pressure should be checked in both arms, to avoid misguided therapy. Endotracheal intubation and mechanical ventilation may be necessary in the unstable patient. Hypotension suggests a serious complication such as cardiac tamponade or rupture. Appropriate volume resuscitation should be administered in a monitored setting. Pericardiocentesis may be harmful in the presence of tamponade caused by Type A dissection and should not be performed without on site cardiac surgery expertise [24].

Surgical Therapy

Patients with Type A dissection should be referred for emergent surgical evaluation. The type of surgery performed depends on the size of the aorta, the condition of the aortic valve, and the presence of coronary artery involvement. Of the International Registry of Acute Aortic Dissection (IRAD) patients with type A dissection, 28% did not undergo surgery, mostly because of advanced age, comorbid medical conditions, patient refusal, IMH, and death before the planned date of surgery [6]. Patients who survive several days after onset of dissection, the initial extremely high-risk period, may undergo semielective surgery if visceral malperfusion or other high risk features for initial operation are resolving [25, 26]. IMH and penetrating ulcer disease are typically treated as an acute dissection with urgent operative intervention warranted if there is involvement of the ascending aorta, similar to a Type A dissection.

Patients with Type B dissection can be successfully treated with medical therapy which includes strict BP control in the majority of cases. Features that failure of medical therapy in type B dissection include increase in aortic diameter, organ malperfusion, progression of dissection, subacute rupture or leak, persistent pain, and persistent hypertension [24]. In these cases, endovascular therapy, or rarely open surgical therapy, may be considered.

Endovascular Therapy

Traditional open surgical therapy in Type B dissection is associated with high morbidity (including spinal cord ischemia) and mortality rates of up to 30% [27]. Therefore, endovascular therapy has developed into an alternative for patients with type B dissection who fail initial medical management. Additionally, endovascular therapy can be used in the temporization of Type A dissection patients with malperfusion and prohibitively high early operative risk [25, 28]. Endovascular therapy includes fenestration of the dissection flap to improve true lumen flow and end organ perfusion, stenting of statically obstructed branch vessels or stent graft placement in the descending thoracic aorta.

Endovascular fenestration involves perforating the intimal flap that divides the true and false lumina in one or more areas, thereby equalizing pressure and potentially restoring blood flow to arteries being supplied by a compromised lumen. The rate of complications from percutaneous fenestration procedures appears to be low [28]. Many patients show hemodynamic and symptomatic response, which may obviate the need for immediate surgery or improve the clinical status sufficiently to stabilize the patient and reduce the operative risk to an acceptable level. In some cases, a repeat procedure or stent implantation may be necessary for complete relief of obstruction.

The objective of endovascular stent graft placement is to stabilize the aorta by sealing the entry tear and promoting thrombosis of the false lumen. An endovascular stent is placed across the primary entry tear in dissections originating in the descending aorta with or without extension to the ascending aorta [29, 30]. Stent graft placement is often associated with thrombosis of the false lumen, which may translate into a lower risk of subsequent aneurysm formation, a common long-term complication of dissection [31, 32]. However, the use of thoracic endovascular aortic repair (TEVAR) in stable patients with Type B dissection who survive their initial hospitalization, does not seem to be more effective than medical therapy in recent trials [33]. In longer term followup studies, mean survival was reported as 47 months with 9.6% of patients requiring re-intervention for endoleak, a common complication [34].

Prognosis

Despite the widespread availability of accurate imaging modalities and advances in surgical and percutaneous therapies, the overall rate of in-hospital mortality from acute aortic dissection is high.

The in-hospital mortality rate among patients in the IRAD registry with Type A dissection not undergoing surgical therapy (due to patient preference, age or comorbidities) was 58%, as opposed to 26% among those undergoing surgical therapy [6, 35]. Death is most often due to aortic rupture and/or multiorgan system failure resulting from malperfusion and cardiac tamponade. Patients with type B dissection who do not require surgical therapy have an in-hospital mortality rate of approximately 10% with effective medical therapy. The mortality rate is approximately 30% among type B patients who require surgery, usually for extension of dissection or organ malperfusion. Three-year survival for patients treated medically, surgically, or with endovascular therapy has been reported to be 77.6 ± 6.6%, 82.8 ± 18.9%, and 76.2 ± 25.2%, respectively [36].

Follow-Up

Management of the post-acute phase should include stringent blood pressure monitoring and control with a target of less than 120/80 mmHg and heart rate near 60 bpm or as tolerated by the patient. Routine follow-up imaging of all patients, typically at 1-, 3-, 6-, and then 12-month intervals, depending on the situation and status of surgical repair is recommended because of the risk of recurrence or progression of dissection and aortic enlargement [24]. This is typically best accomplished at a center with expertise in aortic disease.

Most patients with uncomplicated Type B aortic dissection do well when maximally treated through medical control of blood pressure and heart rate along with close follow-up. However, the optimal long-term management is debated. Most clinicians monitor for symptoms that suggest progression and for enlargement of the aorta (typically in the proximal descending thoracic aorta) by serial imaging (>0.5–1 cm per year or to a maximum diameter of >5.5 cm in the affected aorta). Unfortunately, operation in the chronic phase of dissection is often complicated by extended surgery because of the need to reconstruct vessels and the narrowed true lumen along with frequently encountered adhesions to surrounding tissue.

Beta blocker therapy has been shown to decrease the rate of aortic enlargement and the incidence of cardiovascular events in Marfan's syndrome [37]. Angiotension receptor antagonists are also favored in long term management of aortic disease based on several recent studies in the Marfan population and in Marfan murine models [38, 39]. Statin therapy may also be helpful in preventing disease progression in certain patients with aortic disease who also have traditional indications for statin therapy [40, 41]. Smoking cessation is also critically important in these patients.

Late death after dissection is often caused by an additional aortic event such as rupture or extension, but it also may result from other associated cardiovascular diseases. This highlights the need for coronary risk factor assessment and modification in all patients. A multidisciplinary approach is necessary from the time of presentation because comorbidity is common, and the role of medical, surgical, and percutaneous therapy needs to be considered for each patient.

Practical Points

- Presentation is variable; a high clinical index of suspicion is necessary.
- Classic symptoms and signs are often absent.
- The diagnosis should be confirmed and therapy instituted rapidly.
- The majority of patients with type B dissection may be managed medically or with percutaneous therapy.
- Strict blood pressure control is necessary during the acute and chronic phases.
- Cardiovascular risk factors must be controlled in all patients.

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Lower Extremity Ischemia

28

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Epidemiology and Usual Causes

Lower extremity limb pain is a common complaint among patients, particularly the elderly. The first step is to define the cause of the lower extremity pain and, in reference to the topic at hand, determine whether ischemic arterial vascular disease is the causal factor. Once other common causes of limb pain such as arthritis, low back pain, and musculoskeletal and neurologic causes are eliminated, the workup for ischemic vascular disease should commence. Peripheral arterial disease (PAD) is by far the most common disease manifestation of systemic atherosclerosis in patients, apart from coronary heart disease, and is estimated to occur in up to 15% of persons older than 55 years [1]. Risk factors for PAD are the same as those for coronary heart disease and include increasing age, tobacco use, hypertension, hyperlipidemia, male gender, hyperhomocystinemia, and diabetes. Other less common causes of lower extremity vascular occlusive disease symptoms include Buerger's disease (primary small-vessel obliterative arteriopathy associated with tobacco use) and systemic arteritides such as Takayasu's arteritis.

The pathophysiologic process of ischemic PAD is critical reduction of blood flow secondary to encroachment of the lumen by atherosclerotic plaque. If the vessel lumen cross-sectional area is narrowed by more than 75%, functionally significant stenosis results, as a consequence of the dramatic impact that alterations in diameter can have on flow. This relationship is approximated by Poiseuille's law [2]. The degree of vessel stenosis and whether the stenosis or occlusions are in series or parallel are the most important determinants of the severity of the symptoms and presentation. As muscle activity increases (such as with ambulation), tissue oxygen demand increases, which is compensated for by increased cardiac output, local vasodilation, and increased limb blood flow. In a patient with critical limb ischemia, tissue oxygen demand exceeds delivery even at rest, with anaerobic glycolysis and lactate production, resulting in the sensation of pain. The most common anatomic location for infrainguinal atherosclerotic occlusive disease is at the adductor canal (Hunter's canal) in the distal superior femoral artery (SFA)/proximal popliteal artery, followed by iliac artery lesions. Tibial arterial occlusive vascular disease is more common in diabetic patients and often occurs at a younger age, although the basic pathophysiologic process is thought to be the same.

Presenting Symptoms and Signs

Many asymptomatic patients have underlying PAD evident on arteriography. However, because the occlusion/stenosis occurs slowly, collateral vessels develop, and muscle units physiologically adapt. Thus, ischemic pain is minimized. In the pelvis and lower extremity, the importance of internal iliac and profunda femoris collateral vessels in maintaining lower limb blood flow cannot be overstated. In general, most patients with cardiovascular disease have PAD of the lower extremities, but whether it needs to be addressed beyond general risk factor modification and exercise depends on the signs and symptoms (of which a full spectrum exists). A detailed and useful set of guidelines for reporting the degree of lower extremity ischemia has been published [3].

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The most common and least limb-threatening condition is claudication. This is described typically as limb pain, a sensation of heaviness, or numbness that occurs with ambulation, usually for a reproducibly defined distance, and is relieved by rest. It is important to mention the term *disabling claudication,* because this is the most *subjective indication* for an invasive intervention. The decision to perform an intervention should not be done without critical assessment of the patient's symptoms and living situation. The degree of lower extremity ischemic pain that a patient tolerates is individualized and often dependent on age and occupation. Thus, two-block claudication for a sedentary person would not generally warrant intervention. Conversely, a person who ambulates several miles a day for a living may be significantly impaired by the same degree of claudication. The opposite end of the spectrum is rest pain, described as persistent unremitting pain that occurs without any definite preceding lower limb activity. This often occurs at night when the patient is recumbent and the cardiac output is decreased. The pain is often relieved by limb dependency. Other physical findings with significant ischemic disease include hair loss, muscle atrophy, and marked rubor in the foot. The patient in whom rest pain is diagnosed certainly needs intervention, not only for relief of pain but also to prevent limb loss.

Ulceration is a common manifestation of PAD and often accompanies severe claudication and rest pain. It is important to distinguish ischemic ulceration from venous ulcers (usually medial malleolar in the setting of chronic edema and hyperpigmentation) and neuropathic ulcers (secondary to degeneration of sensory nerves with resultant abnormal pressure distribution on the feet with ambulation). These two types of ulcers may coexist within one patient. Isolated ischemic ulcers are painful and usually occur distally on the foot and toes. These ulcers may progress to frank tissue gangrene and necessitate an urgent amputation if infection supervenes. From a therapeutic standpoint, tissue loss is a definite indication for an intervention to improve blood flow. An endovascular or surgical intervention should precede the débridement or amputation to maximize the chances of tissue salvage, unless the patient has systemic signs of infection.

Overall, any intervention must be judged according to whether the risk entailed by the procedure is less than the benefit derived from the intervention and judged against the possible outcome of severe lifestyle disability and limb loss without the intervention.

A clinical scenario that mandates a slightly different workup is the "blue toe syndrome", usually caused by atheroembolism. The typical presentation is a single toe or several toes that have a purplish/black appearance, is usually unilateral, and the toes are quite painful. It is important to treat the pain with analgesics, to make sure that the patient is taking antiplatelet therapy, and to initiate a workup that defines the embolic source. In general, this includes an echocardiogram (surface or transesophageal); abdominal, femoral, and popliteal ultrasonography to evaluate for aneurysmal disease; and then either arch-to-outflow aortography (to evaluate for ulcerative atherosclerotic lesions), or CTA of the thoracic and abdominal-pelvic aorta.

Another important differentiation is whether the patient is presenting with chronic or acute lower extremity ischemia. Acute limb-threatening ischemia (ALI) may or may just be related to PAD, and represents a true emergency, in which the physician must determine the magnitude of the ischemia to prevent limb loss. Limb-threatening ischemia is suggested by the "six Ps": limb pulselessness, pain, pallor, paraesthesias, paralysis, and poikilothermia. The presentation is usually quite dramatic. The most common cause of ALI is a cardiac thromboembolism; the next most common cause is arterial thrombosis *in situ.* For example, a left atrial thrombus in a patient with atrial fibrillation or left ventricular aneurysm after a myocardial infarction are typical sources of lower extremity emboli. Less common embolic sources are aortic arch plaques or cardiac tumors. Another common diagnostic consideration is thrombosis *in situ,* such as in a patient with severe PAD with a significant collateral branch occlusion or a popliteal artery occlusion in the setting of an undiagnosed popliteal artery aneurysm. History and physical examination alone can often enable the physician to distinguish these two scenarios, and the therapeutic approach that follows is slightly different, as discussed later.

Helpful Tests

The history and physical examination of any patient with cardiovascular disease should include evaluation for peripheral manifestations of atherosclerotic occlusive vascular disease. Thorough inquiries of claudication, rest pain, stroke, and neurologic and cardiac symptoms should be obtained. On physical examination, particular attention should be paid to all pulses, both in character and in quality. Loss of hair, shiny dry skin, and trophic nail changes should also be looked for and described. Careful evaluation for any evidence of foot ulcers or deep cracks in the skin between the toes should be noted as well. A physician should be able to determine whether the lower extremity arterial occlusive disease is primarily inflow (e.g. aortoiliac, above the inguinal ligament), outflow (e.g. common femoral artery and distally, below the inguinal ligament), or both, primarily on the basis of the presence or absence of femoral pulses.

Once the history and physical examination suggest the presence of PAD, the patient's segmental limb pressures/Doppler waveforms and ankle/brachial indices (ABIs) should be measured. The 2011 AHA guidelines recommend that a resting ABI be obtained in all patients with PAD,

defined as individual with one or more of the following: exertional leg symptoms, nonhealing wounds, age >65, >50 and smoking history, or diabetic. Additionally, definitions of normal and abnormal ABI values have been modified based on publication of the results of the Ankle Brachial Index Collaboration [4]. These state that a normal ABI is defined as 1.00–1.40, abnormal values are <.9, and values >1.40 are non-compressible arteries [1, 5, 6] Importantly, the ABI should be measured in both lower extremities in new PAD patients to establish a baseline [7–9]. The ABI is based on the differential blood pressure between the highest brachial systolic pressure and the best ankle systolic pressure and indeed, an ABI <.9 is an accepted objective definition of PAD [10]. The 2005 AHA guidelines specifically recommend segmental measurements, where the revised 2011 guidelines recognize that segmental pressures, Doppler wave form analysis, pulse volume recordings or ABI with duplex ultrasonography can all be used to document lower extremity PAD.

Much practical and important information is obtained through these simple tests for estimating the anatomic level and magnitude of arterial insufficiency. They also allow serial assessment of the patient for progression of disease. Typical ranges of ABI that correlate with symptoms are shown in Fig. 28.1. Full lower extremity duplex arterial examination is not routinely performed at our institution because it is quite time consuming and has not replaced arteriography as the "gold standard" for determining further intervention, though some institutions utilize this fully. Again, the most important determinant for intervention is sensitivity of patient's symptoms or the presence of tissue loss in the setting of PAD. The absolute ABI values are not to be used solely as a basis for any intervention, and arteriography, including CTA, is discouraged as a screening test. However, patients with an absolute toe pressure of less than 40 mmHg do have an increased risk of tissue loss and may benefit from an intervention, in comparison with patients with higher pressures but similar claudication symptoms [11]. The recommended diagnostic algorithm is shown in Fig. 28.2.

Two situations bear further discussion: noninvasive testing in diabetic patients and in patients with classical ischemic vascular symptoms but nearly normal ABIs. Diabetic patients have a propensity for arterial medial calcification, which results in non-compressible arteries and, thus, invalid ABIs. In patients with unreliable ABI's, due to incompressible vessels, the toe-brachial index should be used [12–16]. Some surgeons opt directly for arteriography in diabetic patients with tissue loss and without palpable pulses. In patients with suspected significant PAD but normal ABIs, exercise ABIs may be useful for unmasking and confirming a significant occlusive lesion A baseline ABI is measured, and the patient is then put on a treadmill for 5 min of ambulation. The ABIs are obtained every minute thereafter to determine magnitude of pressure drop and recovery duration. Both of these are proportional to the degree of stenosis and can help clarify an ischemic cause from other causes of limb pain when the history, physical examination, and resting ABIs do not fully correlate.

Arteriography remains the "gold standard" for determining the anatomic site, severity, and extent of atherosclerotic occlusive disease although, CTA is approaching severity and specifically for larger arterial beds [17, 18]. It must again be emphasized that patients with stable claudication but without tissue loss should not undergo invasive testing unless interventions are planned because definite risk of complications exist. The angiographic images are most often performed in the angiography suite with digital subtraction angiographic techniques. These techniques produce high-resolution images and minimize contrast volume. Some institutions have adopted intraoperative angiography, which is immediately followed by an operative procedure, if indicated [19]. The standard aorta and outflow arteriogram is used to examine the infrarenal aorta, including the renal arteries and

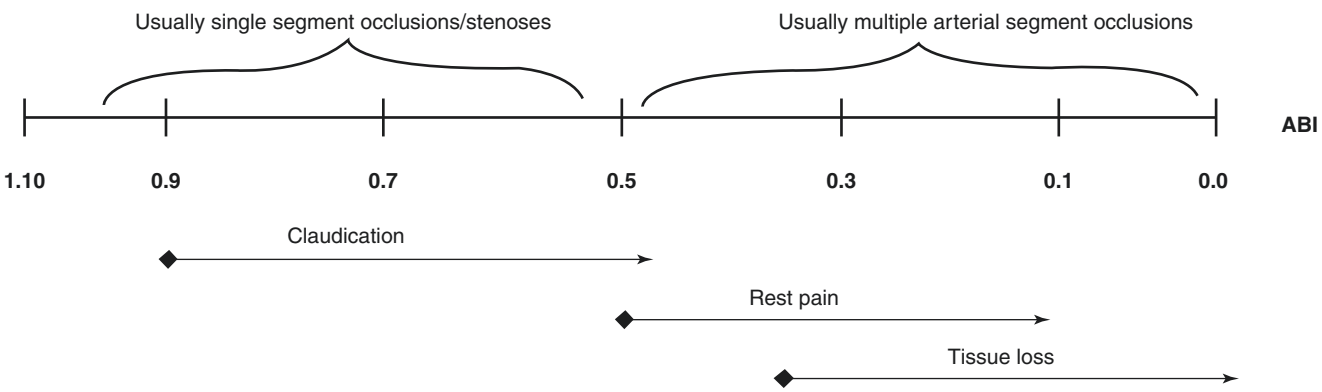


Fig. 28.1 Schematic of generalized ankle/brachial index, symptoms, and anatomic interrelation in patients with peripheral arterial vascular occlusive disease

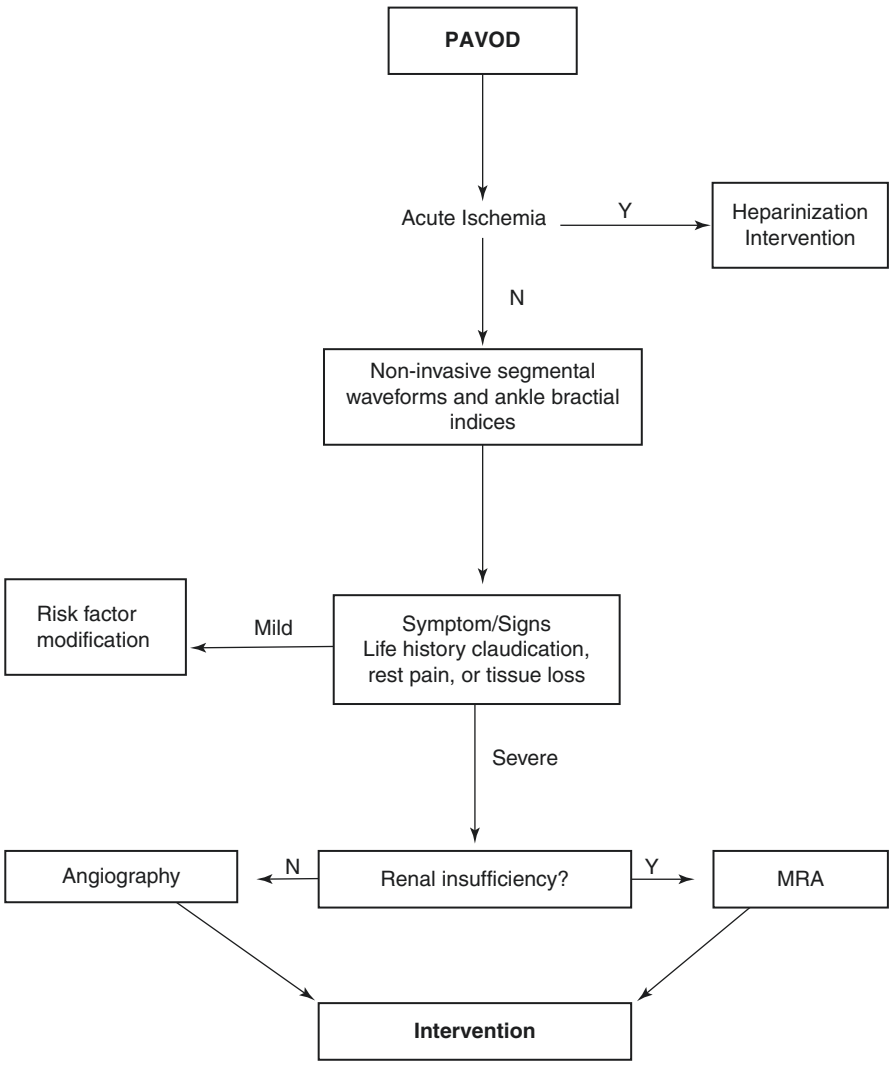


Fig. 28.2 Suggested algorithm for diagnostic evaluation of patients with peripheral arterial disease

oblique views of the pelvis and groin, to define the internal/external iliac and deep/superficial femoral artery bifurcations, respectively. Contrast runoff is performed to assess popliteal and tibial vessels. Foot films are very important for defining suitable targets for a very distal bypass. Of note, in the patient with chronic renal insufficiency in whom contrast-induced nephropathy is a significant risk, gadolinium can be used with good resolution and less risk of impairment of renal function [20]. In addition, preprocedural administration of acetylcysteine and bicarbonate infusion may decrease the incidence of nephrotoxicity [21].

Magnetic resonance angiography has emerged as a useful test for arterial anatomy with very good results. In comparison trials with conventional angiography, sensitivity and specificity for MRA was found to be essentially equivalent with arteriography [22, 23]. Advantages include no contrast-induced nephropathy risk and the noninvasive nature of the procedure. Furthermore, tissue abnormalities can be determined at the same time, and in at least one study, greater sensitivity for very distal run-off vessels was observed [24]. However, the specialized magnetic resonance expertise is not widely available at many hospitals and thus has not replaced arteriography as the "gold standard."

Therapy

All patients with PAD require medical and risk factor reduction therapy regardless of whether they will undergo an invasive procedure. Indeed, a comprehensive consensus statement regarding the diagnosis and treatment has been published [10]. The priority in the treatment of the patient with PAD is the correction of underlying risk factors that not only may contribute to the progression of disease but also may increase the risk of dying from cardiovascular causes. Of equal importance are reassuring the patient that exercise is excellent therapy for claudication and instituting antiplatelet, hypertension control, and a HMG CoA reduction inhibitor.

Therapy for overall cardiovascular protection is important. Only a minority of patients require some intervention, in the form of pharmacotherapy, surgery, or angioplasty.

Risk Factor Modification/Medical Therapy

Exercise Rehabilitation

There is unequivocal evidence that exercise rehabilitation reduces symptom severity and prolongs claudication distance substantially. A meta-analysis of several prospective controlled studies indicates that the maximal walking distance increases by more than 100% (two blocks or more) [25]. The predictors of response appear to be supervised training, high levels of claudication pain during the rehabilitation session, and at least 3 months or more of training. Treadmill exercise appears to be far more effective than strength training. Figure 28.3 provides some guidelines for initiation of exercise therapy in the patient with claudication.

Smoking Cessation

All tobacco-using patients with claudication should be referred to a smoking cessation program. Observational studies have found that the risk of death, MI, and amputation is substantially greater in PAD patients who smoke [26, 27]. Additionally, patency rates for both open and endovascular treatments are significantly lower in smokers [28]. For those unable to quit, the use of nicotine replacement therapies in the form of gum, spray, or patch may be considered with intensive counseling. The various nicotine replacement therapies significantly decrease symptoms of the withdrawal syndrome as smokers abruptly stop smoking. The different formulations of these therapies provide alternative methods for delivery and have slightly different onsets of action and durations. In meta-analyses, cessation rates with transdermal nicotine range from 15 to 31%, with a trend toward decreased efficacy in the most highly dependent smokers. Nicotine gum studies demonstrate a similar range of cessation rates; the greatest efficacy is seen with the 4-mg gum in highly dependent smokers. Nasal spray cessation rates range from 26 to 28%, also with greatest efficacy in the most dependent smokers [29]. Limited inhaler studies report cessation rates similar to those for the nasal spray. Bupropion was initially developed and marketed as an antidepressant medication (Wellbutrin). Although bupropion also aids in smoking cessation, the mechanism by which it does so is unknown. The recommended dosage schedule includes a starting dose of 150 mg per day for 3 days, then increasing to twice per day, with an approximately 25% efficacy rate for tobacco use cessation. In one published clinical trial [30], "treatment with sustained-release bupropion alone or in combination with a nicotine patch resulted in significantly higher long-term rates of smoking cessation than use of either the nicotine patch alone or placebo." Several randomized control trials have shown that Varenicline, a nicotine receptor partial agonist, has demonstrated improved quit rates when compared with bupropion or nicotine quit rates [31–33]. Abstinence rates were higher with combination therapy than with bupropion alone, but the difference was not statistically significant.

Weight Loss

It is generally believed that obesity may contribute to reduction in claudication distance, and weight loss may alleviate this reduction. All obese patients with symptomatic claudication should be encouraged to lose weight. More importantly, obesity contributes to the risk of hypertension, dyslipidemia, and metabolic syndrome as well as frank diabetes. As an important risk factor modification, weight loss is an essential part of medical therapy for claudication.

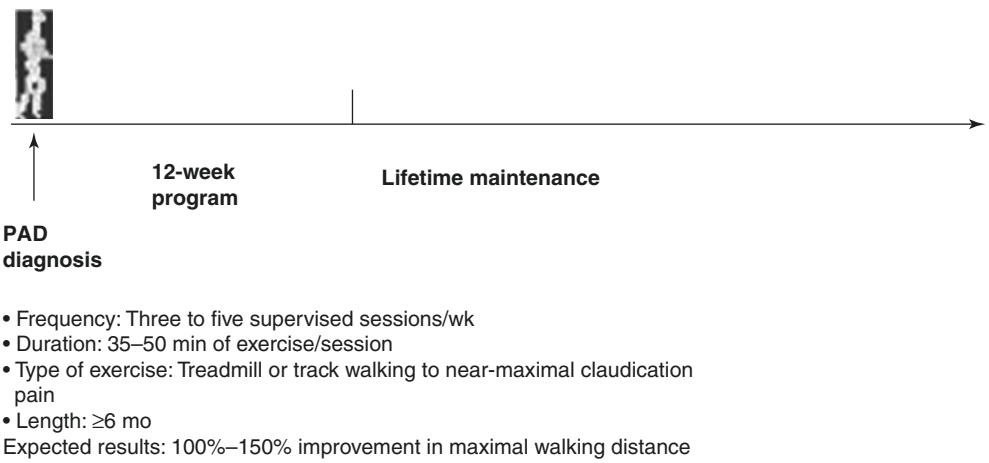


Fig. 28.3 A prescription for exercise. *PAD* peripheral arterial disease. (Adapted from Stewart et al. [93])

Glycemic Control

There is a strong correlation between duration of diabetes and risk of claudication and chronic critical limb ischemia. However, the data on strict diabetes control and amelioration of symptoms of claudication are conflicting. The United Kingdom Prospective Diabetes Study (UKPDS) examined a variety of end points, including peripheral vascular complications with aggressive glycemic control, using a variety of measures including insulin, sulfonylureas, and metformin in patients with type II diabetes. Tight glycemic control in the study was not associated with improvement in risk for macrovascular events, including peripheral vascular events [34]. Because patients with peripheral vascular disease are at risk for the development of foot complications, they should be advised to inspect their feet regularly, avoid pressure points with specially designed footwear, and pay immediate attention to minor cracks and fissures in the skin.

Treatment of Hyperlipidemia

Lipid-lowering therapy is among the most effective interventions for the reduction of mortality and morbidity from cardiovascular disease of all kinds. This applies to patients with PAD, too. The greatest risk to life for PAD patients is the risk of heart attack and stroke, which are both reduced substantially by lipid-lowering therapy. The best studied agent is the use of HMG-CoA reductase inhibitors or statins. The study most pertinent for PAD patients specifically, is the Heart Protection Study. This study showed that patients with any known cardiovascular disease, included those in whom PAD is their only known manifestation of disease, had a significant reduction in death and MI with the use of pravastatin [35]. For PAD patients specifically, there was a 24% reduction in cardiovascular events [36].

For the patient with peripheral arterial disease (PAD), the National Cholesterol Education Program guidelines for the patient with established coronary artery disease are applicable. For these high risk patients, low-density lipoprotein cholesterol levels above 100 mg/dL should be treated aggressively with statins. The goal of therapy should be an LDL level of <100 mg/dL, with strong consideration given to even lower LDL levels, such as LDL <70 mg/dL in those with severe or premature disease [37].

As for treatment of high-density lipoprotein (HDL) levels, both the efficacy data and treatment options are currently limited. Exercise and moderate alcohol consumption have been associated with higher HDL levels, and exercise is clearly of benefit in patients with all forms of cardiovascular disease. It is not clear that the benefit of exercise is related to HDL level, however. Data from the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) suggest that therapy with gemfibrozil can raise HDL levels and is associated with improved cardiovascular prognosis [38]. This is especially relevant to the diabetic patient population, whose metabolic profile often comprises low levels of high-density lipoprotein and elevated triglyceride levels [39]. These patients would benefit from fibrate therapy.

Hypertension Control

Hypertension is a very strong risk factor for the development of all forms of cardiovascular disease, and PAD is no exception. Although there are no data linking blood pressure control to improvements in the natural history of PAD, the overall cardiovascular protective effects are so overwhelming that hypertension control is of great importance. (Due consideration should also be given to a search for secondary causes of hypertension, especially renal artery stenosis). According to the UKPDS data and the Hypertension Optimal Treatment (HOT) study results, control of blood pressure appears to be far more important than tight glycemic control in diabetic patients [34].

The choices for antihypertensive therapies should be guided by Joint National Committee VII guidelines [40]. In this regard, it must be emphasized that there is no evidence that beta blockers adversely affect mild to moderate claudication, and they should be considered strongly, especially for the patient with concomitant coronary artery disease. For diabetic hypertensive patients, angiotensin-converting enzyme inhibitors should be first choice, due to the renoprotective effects of these medications in diabetic patients. On the basis of the benefit of angiotensin-converting enzyme inhibitors in patients with established atherosclerosis, these drugs may be preferred over calcium channel blockers in the initial therapy of uncomplicated hypertension in the patient with PAD [41].

Correction of Hyperhomocystinemia

Although hyperhomocystinemia is a strong risk factor for PAD, the correction of elevated homocysteine levels with B vitamins and folic acid results has not proven to be of clinical benefit. Several randomized trials have tested the use of B vitamins for the treatment of cardiovascular disease. Most recent studies have shown no benefit for the duration of the trials [42–44].

Pharmacotherapy for Claudication

Pharmacotherapy for claudication is not meant to replace risk factor modification or exercise rehabilitation but rather to complement it. The drugs that are currently in use are mentioned as follows.

Cilostazol

Cilostazol is a type III phosphodiesterase inhibitor that is both a vasodilator and an antiplatelet agent. It also has favorable effects on the lipoprotein profile, including a 15%

reduction in triglyceride levels and a 10% increase in high-density lipoprotein levels. Two randomized controlled trials showed distinct improvements in walking distance with cilostazol in addition to exercise [45, 46]. A meta-analysis that was composed of eight separate double-blinded trials involving more than 2000 patients confirmed the efficacy of cilostazol in improving treadmill walking time and quality of life [47]. Initial benefit may not be seen for up to 3 months after initiation of the drug, and the drug effect wanes within a month of discontinuation. Cilostazol is metabolized to a large extent by the CYP3A4 pathway but has no effect on the activity of this enzyme system. Drugs that inhibit these pathways may result in an increase in drug levels (see Table 28.1). Because of concerns about the use of phosphodiesterase inhibitors in patients with depressed left ventricular systolic function, the use of cilostazol is contraindicated in patients with congestive heart failure and a left ventricular ejection fraction of less than 40%.

Pentoxifylline

Pentoxifylline is a substituted xanthine derivative that, unlike theophylline, has hemorheologic properties (i.e., it is an agent that alters blood viscosity). In early clinical trials, pentoxifylline was shown to improve initial claudication distance and peak walking time, but subsequent studies have failed to demonstrate any improvement in these parameters [45].

Agents Under Investigation

Carnitine

Metabolic abnormalities in the lower extremity muscles have been demonstrated in patients with PAD. There has been a direct correlation between metabolic intermediates of carnitine metabolism and impaired exercise performance, and therefore studies have investigated the role of supplementing L-carnitine or its potent analogue, propionyl-L-carnitine. Two phase II double-blinded placebo-controlled trials have demonstrated improvements in peak walking times with propionyl-L-carnitine in comparison with placebo in select subgroups of patients who have more severe symptoms at baseline [48, 49]. To achieve a benefit, the drug must to be taken at doses of 1 g twice a day for a duration of 1 year.

L-Arginine

L-Arginine, the precursor for nitric oxide synthesis has been demonstrated to have favorable effects in improving peak walking time and pain-free claudication time in small trials [50]. The precise mechanism may be more complex than a simple restoration of L-arginine stores in the body. The dose of this drug, which is available in the form of a snack bar, is 1 g orally twice a day. Because of the biologic plausibility of increased NO synthesis, and the suggestion of benefit from small trials, a recently completed trial to examine the effect of L-arginine was reported, with completely negative results, and even the possibility of some harm [51].

Surgical and Endovascular Therapy

Surgical and interventional options are available for patients in whom medical/exercise therapy has failed and those with ALI (classified as threatened limb, category IIa or IIb [3]) (Fig. 28.4). If limb-threatening ischemia exists, the first order the physician should convey is full heparinization (100–150 U/kg, intravenous bolus). The history and physical examination are crucial in determining the next step: namely, whether to proceed directly to the operating room, or the angiography suite (Table 28.2). If evidence suggests that the process is embolic in the setting of nonsignificant underlying PAD, the patient should proceed directly to the operating room for open embolectomy [52]. Conversely, if there is any question of whether the process is embolic or thrombotic, arteriography with the option for catheter based intervention is the best course. In two well-controlled trials comparing thrombolysis with direct surgery [53, 54], the outcomes of 6-month amputation and death rate were not significantly different, although major bleeding complications were more numerous in patients receiving thrombolytics. Furthermore, long-term revascularization durability after thrombolysis is also not as good in comparison with surgical therapy. Thus, thrombolysis can be recommended for semiacute ischemia (less than 14 days) with reasonable results, although often as a prelude to a surgical bypass.

Table 28.1 Drugs used in treatment of claudication

Drug	Dosage	Strength of evidence in trials[a]	Side effects	Interactions
Cilostazol	50–100 mg b.i.d.	Class I	Headache, diarrhea, palpitations, and dizziness	Substances that inhibit CYPA4 or CYP2C19, including macrolide antibiotics, ketoconazole, grapefruit juice, and omeprazole
Pentoxifylline	400 mg t.i.d.	Class II	Nausea, bloating, and dizziness	Theophylline (increases levels)

[a]Class I: General agreement that the therapy is efficacious. Class II: Conflicting/diverging opinions on efficacy. Class III: Not useful/harmful

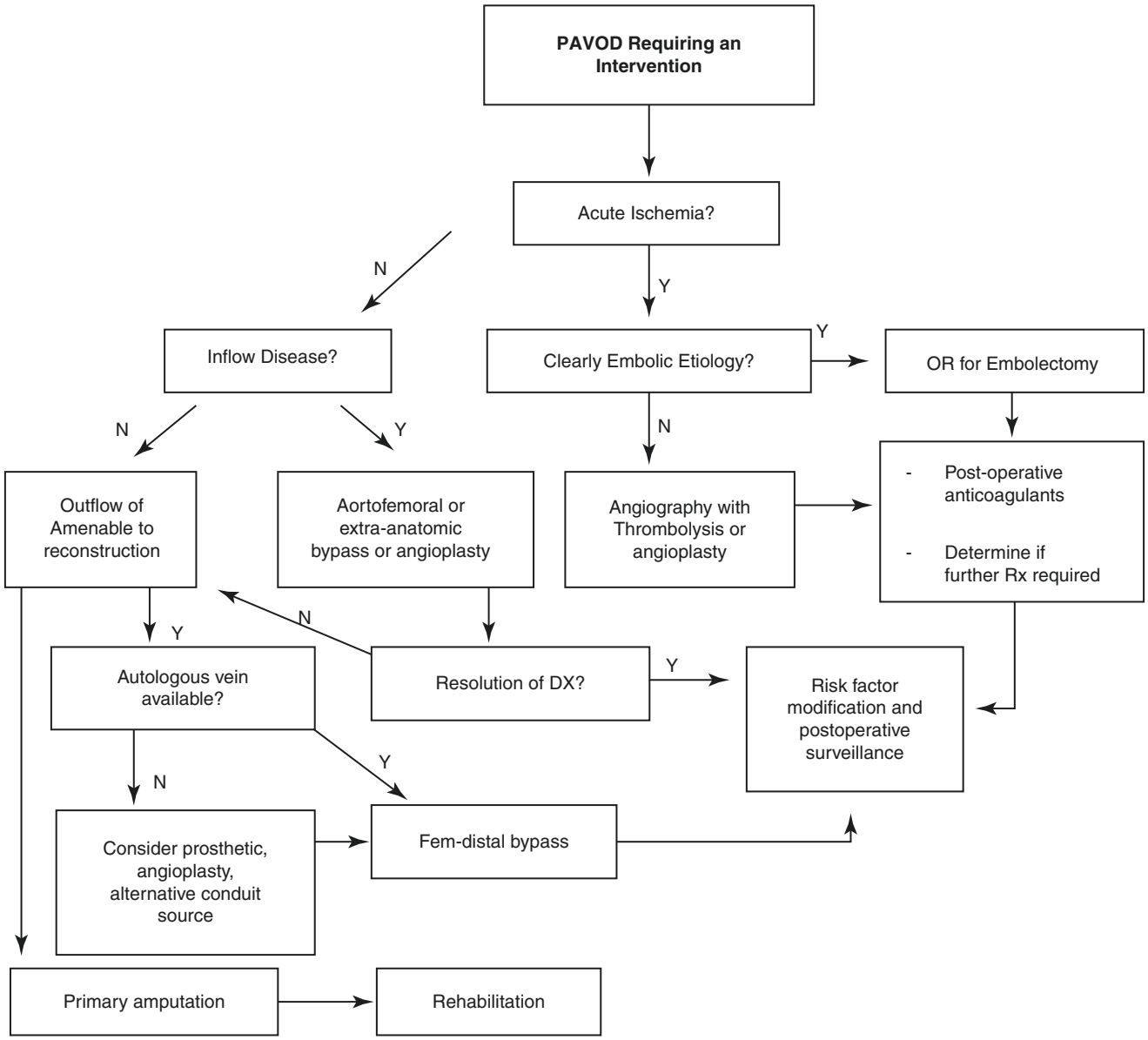


Fig. 28.4 Suggested algorithm for therapeutic approach to patients with peripheral arterial vascular occlusive disease deemed suitable for an intervention

Endovascular therapies are becoming more commonplace, with the number of practitioners willing to perform this type of intervention increasing. At present, lesser symptoms, such as modest claudication, do not warrant this less invasive approach (with the endovascular techniques described), because they have not proved to be more efficacious than exercise and risk factor modification alone [55]. The endovascular approach is appealing, because it is less invasive, is less physiologically stressful, offers decreased hospital length of stay, and possibly reduces cost in comparison with open operative therapy [56]. The arterial lesions best treated with angioplasty, stent implantation, or both are those in larger arteries such as the aorta or common iliac artery with short concentric stenotic lesions and unobstructed runoff, for which 5-year patency rates are nearly equivalent to those after surgical repair (Fig. 28.5) [57]. Restenosis rates with iliac intervention tend to be low, and stent implantation in conjunction with angioplasty in this situation has not been shown to decrease recurrent stenosis or increase patency rates although is now commonly practiced [58, 59]. Longer segment external iliac, SFA, and popliteal or distal lesions can, technically, be successfully repaired by endovascular approaches; however, long-term patency rates are lower than at other sites and significantly lower than those for open operative bypass [60] and PTA is now first line therapy for may infrainguinal lesions. Recanalization of short occlusions

Table 28.2 Comparison of operative embolectomy with angiography and lysis for acute lower extremity ischemia

Presumed diagnosis	Thromboembolism	Thromboses *in situ*
Procedure	Operative embolectomy	Angioplasty with lysis
Pertinent history and physical examination findings	Acute onset of symptoms	Slower onset of symptoms
	No prior PAD diagnosis	History of PAD
	Recent cardiac event	No cardiac history
	Timing well documented	Older patient
	Normal findings on contralateral limb examination	Abnormal findings on contralateral limb examination
Anatomic conditions	Aortic bifurcation	May be diffuse/ occlusive or distal arteries
	Femoral bifurcation	
	Popliteal artery disease	
Advantages	Rapid restoration of blood flow	Define anatomy for bypass
	Simple	Lyse small artery thrombi
	Minimal hemorrhagic risk	No anesthesia risk
	Possible lower cost	
Disadvantages	Anesthetic	Hemorrhagic risk
	Wound infection potential	Failed lysis
		Contrast risk
		Slower restoration of blood flow

PAD peripheral arterial disease

in the iliac artery or SFA is also being more commonly pursued with the endovascular route, with reasonable patency rates (Fig. 28.6). However, morbidity and mortality rates are not significantly lower than those with open repair, as documented in one study [59, 61].

The disadvantages of endovascular techniques for infrainguinal disease primarily concern the durability and long-term patency, as well as the increased need for further interventions that often increase cost and patient discomfort. In younger patients with long segment iliac or femoral artery disease, operative bypass provides better long-term durability with low morbidity and mortality rates. However, all physicians who treat peripheral vascular disease must individualize these options and tools.

The surgical options for bypass are briefly reviewed. It is imperative that inflow arterial disease be addressed first. Oftentimes, in combined inflow and outflow disease, improving inflow alone suffices in relieving most of the patients' symptoms, and more distal arterial disease necessitates no further intervention. In general, inflow or aortoiliac disease is treated with an aortobifemoral prosthetic bypass. Inflow reconstruction yields a good result prior to further infrainguinal reconstructions if needed [62]. In patients in whom this procedure is not feasible (e.g. those with hostile conditions in the abdomen), an axillofemoral or thoracobifemoral bypass may be performed. Infrainguinal or outflow disease presents more options and more controversy. The proximal artery is most often the common femoral artery, and the distal artery is that which arteriographically provides the best anatomic target for outflow to and across the foot. For example, a patient with a nonhealing ulcer on the great toe with an SFA occlusion, a diseased popliteal artery, and a patent anterior tibial artery, should undergo a femoral-to-anterior tibial bypass (Fig. 28.7).

The options for bypass conduit are an autologous vein (usually the ipsilateral greater saphenous vein), prosthetic material, the umbilical vein, or a cryopreserved vein. The latter two options are much less commonly used and are not discussed here. Several large trials have detailed the comparative efficacy between prosthetic and autologous tissue as an infrainguinal bypass conduit [63, 64]. These studies suggest the following: (a) In any below-knee bypass in which a vein is available (arm or leg), an autologous conduit should be used, and (b) an above-knee bypass should be performed with the ipsilateral greater saphenous vein, if available; however, the use of prosthetic material as an initial conduit is not unreasonable, inasmuch as long-term patency results are not appreciably different over 2–3 years of follow-up between these two conduit types. However, reports concerning the divergence of prosthetic graft patency and autologous vein are concerning. Our current practice is to use an autologous vein if available and a prosthetic as a distant second choice. In the patient in whom no autologous vein is available and the patient's limb is in jeopardy, good efficacy has been reported with the use of a prosthetic conduit with a distal vein patch in limited series [65]. However, aggressive endovascular approaches may be a letter first choice before prosthetic. The debate between *in situ,* reversed, and nonreversed translocated vein bypasses can be summarized as saying that current studies suggest clinical equipoise and should be based on the surgeon's own preference and best outcomes [66–68].

Postoperatively, patients who receive an endovascular stent or angioplasty are usually prescribed a combined antiplatelet regimen of aspirin and clopidogrel for 6 weeks, on the empirical basis of coronary stent trials [69]. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial demonstrated a benefit in patients taking clopidogrel. On the basis of this study, as well as the CHARISMA (Clopidogrel for High Athero-Thrombotic Risk and Ischemic Stabilization Management and Avoidance trial), aspirin plus clopidogrel are recommended for PAD patients without increased risk of bleeding [70–72]. Aspirin is recommended based on data from the CLIPS trial (Critical Leg Ischemia Prevention Study) where PAD patients demonstrated a

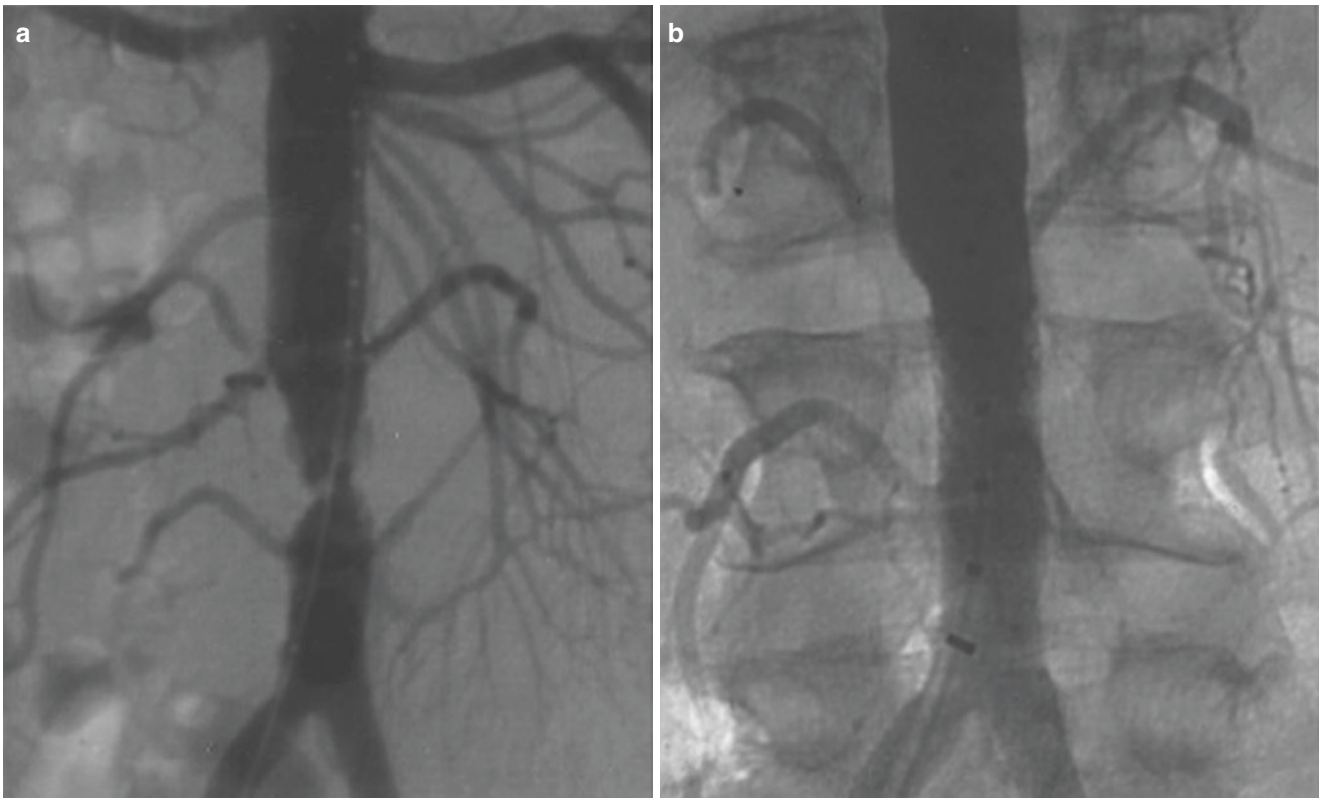


Fig. 28.5 Angiograms of a patient who had a history of lifestyle-limiting claudication and a high-grade aortic focal stenosis. Although his resting ankle/brachial indices (ABIs) were approximately 0.8, his exercise ABIs dropped dramatically to 0.4. A high-grade focal infrarenal aortic stenosis (more than 80%) (**a**) is seen with a 45–mm HG pressure gradient (**b**). A balloon angioplasty and stent implantation procedure was done; the resultant post-procedural angiogram showed an excellent technical result. No appreciable pressure gradient was measured after the procedure. The postoperatively, his pedal pulses were palpable and he had full relief of his symptoms

significant reduction in cardiovascular ischemic events when receiving aspirin versus placebo [73]. The recommended dose of aspirin is 75 mg based on the dose studied in this and other trials. A study comparing infrainguinal autologous bypass with and without adjunctive ticlopidine has shown superior graft patency rates in those receiving this antiplatelet agent, but further trials are needed to fully evaluate this adjunct [74]. It may be beneficial for patients to receive anticoagulation with a vitamin K antagonist, such as warfarin (Coumadin), in high-risk grafts prone to thrombosis, such as those with prosthetic below-knee and composite grafts [65]. However, the recent WAVE trial provided evidence that anticoagulation for prevention of cardiovascular events in PAD patients is not indicated [75]. Similarly, graft patency may be improved with statin use [76, 77].

Prognosis/Outcomes

Medical therapy with risk factor modification and an exercise program has been shown to very effective in increasing walking distance for patients who are compliant with the regimen. This has already been emphasized. Overall, 5-year assisted patency rates in infrainguinal bypass grafts and 10-year rates in aortoiliac grafts approach 80%, and the limb salvage rate is even higher [62–65, 67, 68]. Endovascular therapeutic outcomes are more dependent on the anatomic location and runoff beyond the occlusive lesion; for example, in one large prospective trial, common iliac angioplasty was associated with a 5-year patency rate of 60%, whereas that for femoral/popliteal angioplasty was only 40% [57]. In other smaller studies, the 2-year assisted patency rate for iliac angioplasty was between 45 and 90%, depending on anatomic factors [58, 60], whereas that for SFA angioplasty at 1 year was 46% patency [59]. Perioperative mortality rates are in the range of 1–3% [62–64]. The presence of PAD itself is the harbinger of severe generalized atherosclerotic disease, and approximately 30–50% of these patients die over a 5-year span after their intervention [78]. In fact, patients with multivessel coronary artery disease have a fivefold greater mortality rate if coexistent PAD is present [79]. Regarding treatment for critical limb ischemia (CLI) the BASIL trial (Bypass Versus Angioplasty in Severe Ischaemia of the Leg) examined whether endovascular therapy or open bypass was the preferable first-line treatment. Results from these trials have

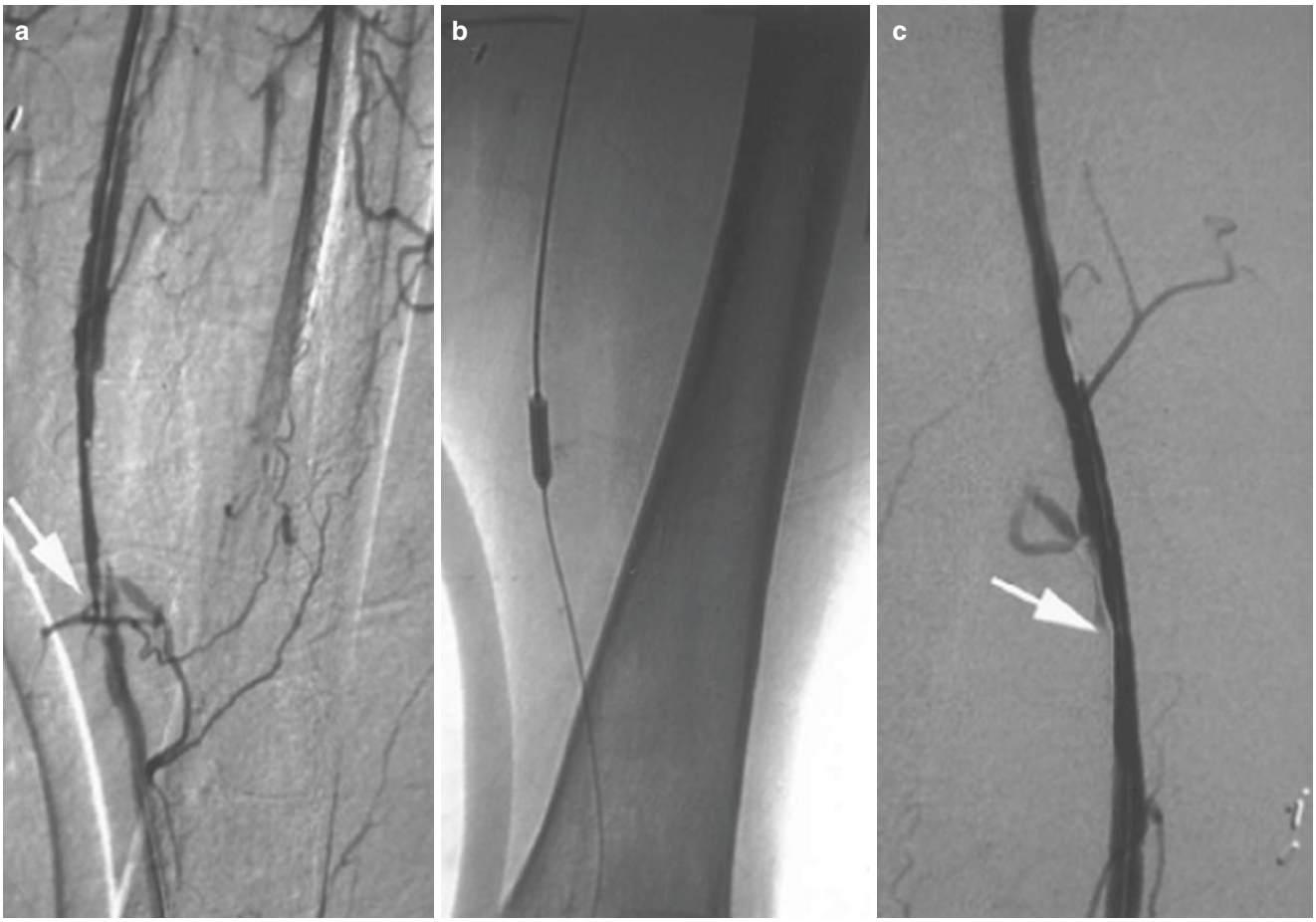


Fig. 28.6 Views in a patient with severe claudication and no available autologous conduit. (**a**) A short segment superior femoral artery (SFA) occlusion was the main anatomic finding (*arrow*). (**b**) The balloon has followed the wire across the occluded segment, probably in the subintimal plane. (**c**) Recanalization of the SFA was successful, with a good angiographic result (*arrow*). After the procedure, the patient experienced full relief of his symptoms

shown that bypass first surgery was associated with a significant increase in overall survival of 7.3 months and improved amputation free survival of 5.9 months for patients who survived for at least 2 years post-treatment [56, 80]. The study further confirmed the poor outcomes following prosthetic bypass and balloon angioplasty, and concluded if feasible, balloon angioplasty may be preferable to prosthetic bypass even if patients are expected to live greater than 2 years [80].

Early operative failure (within 30 days), such as stent or bypass occlusion, does occur in a minority of patients (less than 10%). These patients usually require an aggressive revascularization attempt, whether it is with thrombolytic agents, angioplasty, and stent implantation or with graft thrombectomy and correction of the technical problem (or repeat grafting). Late angioplasty failures may be treated with repeat angioplasty or conversion to open operation and late bypass graft failures should usually be treated with a new bypass, preferable avoiding the previously operated fields.

Overall, an aggressive approach to limb salvage with surgical and endovascular approaches results in decreased amputation rates, increased survival rates, and an improved quality of life [81, 82]. Only about 5% of patients have no distal outflow artery target and are candidates for primary amputation if rest pain or tissue loss persists. Amputation is associated with decreased long-term survival, particularly in patients with end-stage renal disease [83].

Follow-Up

Several long-term care issues of PAD patients need to be emphasized. First, once the bypass or intervention has been completed successfully, these patients may require further surgery for limb infection or amputation. Occasionally, a patient with a functioning bypass may require an amputation for persistent infection. This scenario is more common in diabetic and renal failure patients. More commonly, chronic limb pain and swelling with decreased mobility plagues a

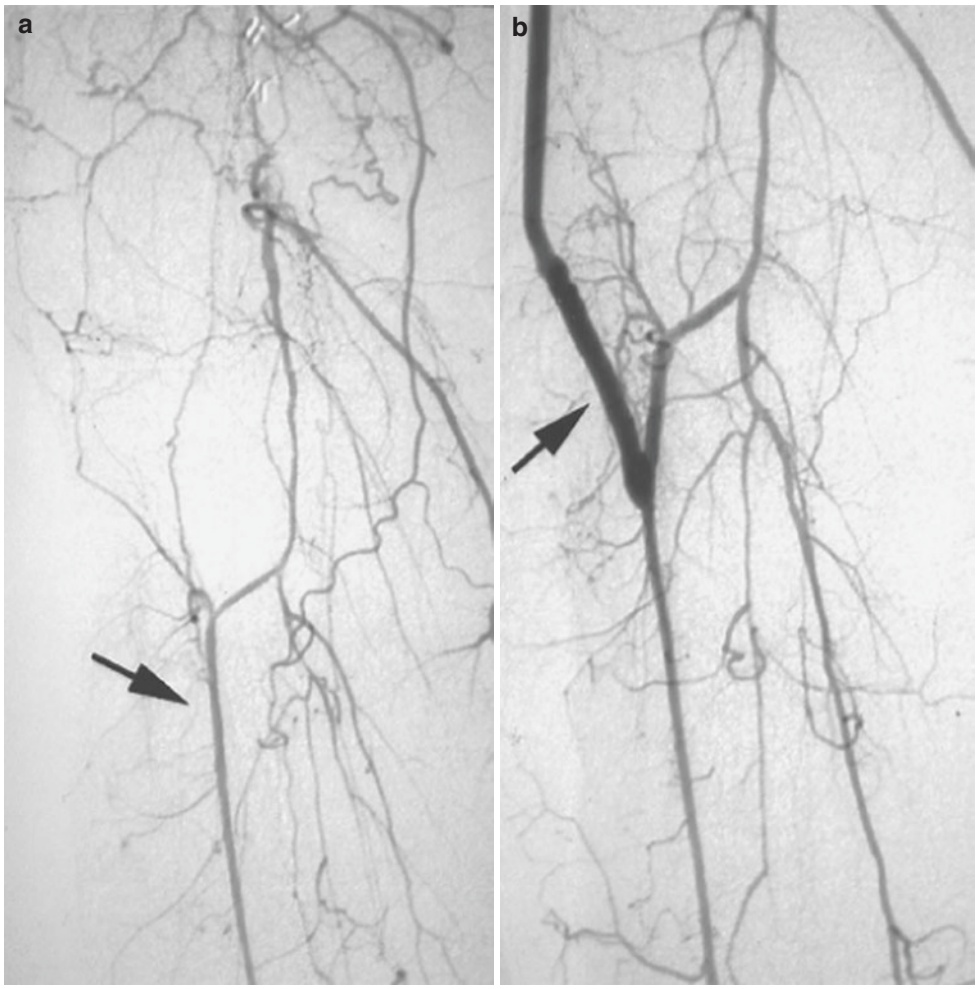
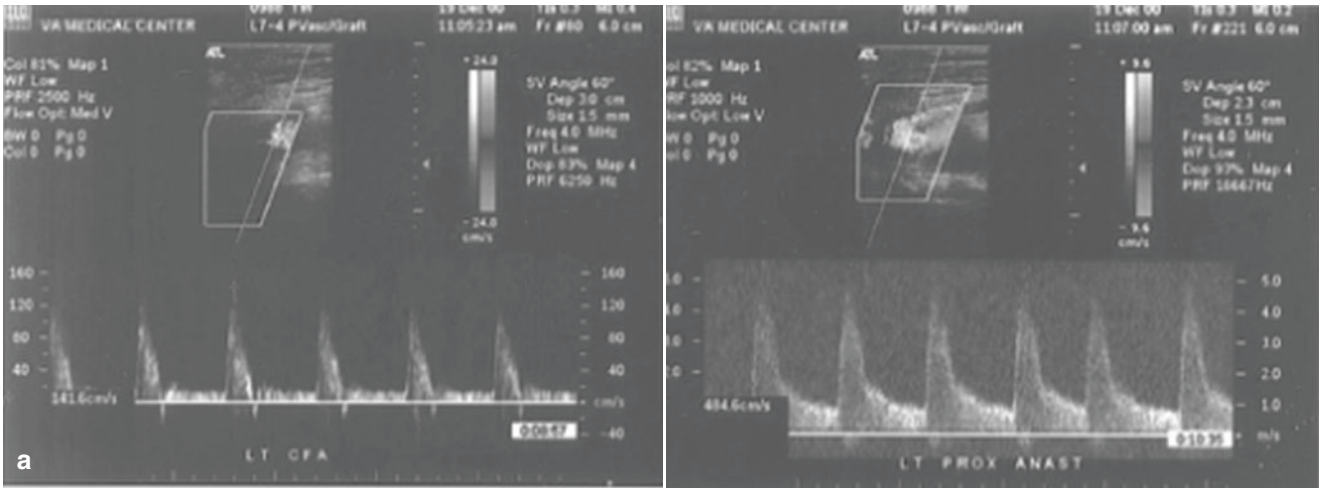


Fig. 28.7 Example of peripheral arterial vascular occlusive disease affecting the popliteal-tibial arteries, with rest pain and a nonhealing ulcer. The patient had an adequate ipsilateral autologous conduit and underwent a femoral–to–dorsalis pedis bypass with reversed GSV (greater saphenous vein). (**a**) The preoperative angiogram shows an adequate anterior tibial artery target (*arrow*). (**b**) The postoperative angiogram shows a patent graft (*arrow*) with no evidence of any technical defects

significant number of these patients. Postoperative physical therapy, with structured exercise programs and compression stockings to reduce edema that inevitably occurs after most bypasses, is useful. The cause of postoperative edema has not been fully defined but is probably a combination of lymphatic disruption, reperfusion injury, and, in some instances, venous insufficiency [84]. An important study by Abou-Zamzam et al. showed that preoperative ambulatory functional status was the best predictor of postoperative ambulatory status and that mortality was due mostly to comorbid diseases, not to the surgery itself [85]. Because a majority of operative patients require further procedures related to PAD, the decision for intervention is not to be taken lightly; it should be discussed with the patient and their family, to affirm realistic outcome expectations [86]. These outcome issues are now prominent in studies examining the functional patient outcome rather than just technical aspects [85–87].

Another important issue in follow-up is that after the intervention, whether percutaneous or operative, these patients need to be monitored for their lifetime by a vascular specialist. As part of the follow-up in patients after angioplasty, especially for infrainguinal lesions, high-risk lesions (e.g., those in the long segment of the external iliac artery) or individuals at high risk (those who continue to smoke), it is recommended that ABIs be obtained every 3 months for 1 year and every 6 months thereafter. In patients with an infrainguinal autologous vein bypass, duplex graft surveillance has proven efficacy for prolonging graft patency and limb salvage and is cost effective [88–90]. Intraoperatively, a duplex scan is performed along the whole graft, and abnormalities and flow velocity are noted and corrected [91]. Graft abnormalities tend to occur at the proximal and distal anastomotic sites in reversed grafts and at sites of retained valves or injury in the *in situ* grafts. The detection of significant graft stenosis before thrombosis (for which later graft salvage is nearly impossible) is imperative. For example, a peak systolic velocity ratio of greater than 3.5 (at the point of stenosis in comparison with the proximal flow) and a mean graft velocity of less than 50 cm/s are the currently recommended criteria for critical stenosis that should be operatively corrected (Fig. 28.8) [92]. Our protocol is an intraoperative scan



HISTORY:
THIS IS A FOLLOW-UP EVALUATION POST GRAFT PLACEMENT.
PERIPHERAL ARTERIAL DUPLEX SCAN:

LEFT:

COMMON FEMORAL ARTERY:	141	CM/SEC
PROXIMAL ANASTAMOSIS:	484	CM/SEC
PROXIMAL GRAFT:	162	CM/SEC
DISTAL GRAFT:	76	CM/SEC

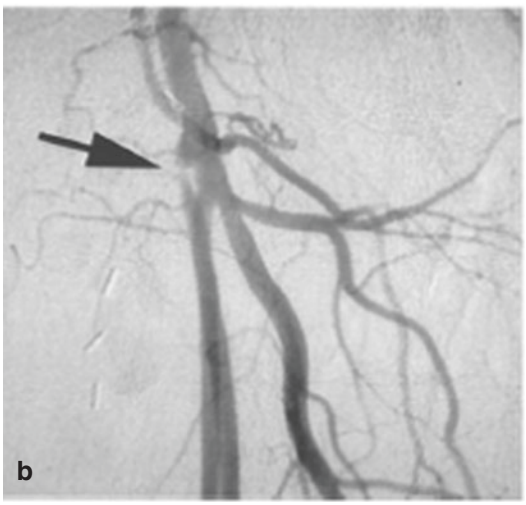


Fig. 28.8 (**a**) Example of 3-month graft surveillance duplex scans of left femoral–to–below-knee popliteal bypass, showing a high-grade focal lesion at the proximal vein graft anastomosis. Velocities are as shown with a PSV ratio of 3.4. (**b**) A confirmatory angiogram reveals a high-grade focal stenosis (*arrow*). The patient underwent a successful vein patch angioplasty with intraoperative normalization of graft flows and more than a 0.15 increase in the ankle/brachial index. The likely pathophysiologic process was neointimal hyperplasia, as judged at surgery

(with or without angiogram), followed by scans every 3 months for 1 year and then every 6 months for the next year, and then yearly throughout life of the graft, although the most cost-effective algorithm has not yet been fully determined. Last, development of significant symptoms of PAD in the contralateral limb occurs in approximately 25% of patients. Again, risk factor modification and exercise can often stave off the need for any further interventional treatment on the contralateral limb and should be the goals. The setting of an operative or endovascular intervention is a prime time to emphasize the lifestyle changes that are critical in these patients to ensure a longer life.

Practical Points

- Peripheral arterial disease is prevalent in patients with coronary heart disease and should be actively identified from the history and physical examination.
- Noninvasive testing should be an extension of the physical examination and allows quantification of arterial ischemia.
- Risk factor reduction, establishment of an exercise program, and cessation of tobacco use are top management priorities, whether an invasive procedure is performed or not.
- Endovascular angioplasty/stent implantation therapy has the best outcomes in short, focal large-artery stenosis, and is reasonable first/one therapy for many peripheral lesions.
- Surgical therapy for PAD is durable, with excellent long-term patency, but is morbid.
- PAD is a marker of severe generalized atherosclerosis, and the 5-year mortality rate is significant.
- Patients with PAD need lifelong cardiovascular care.

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Pulmonary Embolism

29

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Epidemiology and Usual Causes

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are two manifestations of one disease, venous thromboembolism (VTE). DVT is confirmed by venography in more than 80% of patient with PE that is proven by angiography [1]. However, on average, only 35–45% of patients with PE demonstrate DVT by ultrasonography or impedance plethysmography [2], and even fewer (about 15%) show clinical evidence of DVT [3].

The incidence of PE in the United States is estimated to be about 600,000 per year [4]. This may well be an underestimate, because PEs are not clinically diagnosed in a majority of patients with PE at autopsy [5]. Mortality due to pulmonary embolism is not insignificant. All-cause mortality following the PE ranges from 8.6 to 17% at 3 months [6], and in a longitudinal study of 1023 patients followed for a mean of 4 years mortality was 36% and only 3% died in the hospital from the index event. About 2–4% of patients with a PE will develop chronic thromboembolic pulmonary hypertension defined as a mean pulmonary artery pressure greater than 25 mmHg 6 months after the acute event [6] (see Chap. 30).

Diagnosis and treatment of this condition poses a significant health care burden in the United States. In a retrospective analysis of the Integrated Health Care Information Services National Managed Care Database, of hospital claims using DVT or PE as a primary or secondary discharge diagnosis, total health care costs for a single VTE ranged from $7594 to $16,644 depending on the type of event (PE vs. DVT) and whether it was a primary or secondary diagnosis (associated with other comorbidities). The costs of a VTE are not limited to diagnosis and treatment. A history of VTE is a strong independent risk factor for recurrence and recurrent DVT was associated with 21% greater costs ($2057) when compared with an initial DVT event [6].

VTE occurs in the milieu of stasis of blood flow, damage to the vascular wall, and activation of the clotting system, particularly in the presence of acquired or inherited thrombophilic factors. It is classified as idiopathic and primary or provoked and secondary when associated with a specific disease (e.g. cancer) or trigger (immobilization). Approximately 80–90% of PEs originate in the veins of the lower extremity, the initial thrombi originating in the calf veins. They may, however, originate in more proximal sites, particularly in patients undergoing gynecologic surgery, parturition, and prostate surgery. Upper extremity DVTs are an increasing cause of PE, associated with the placement of central venous catheters (often with sepsis), malignancy, thrombophilic states, prior leg vein thrombosis, and malignancy [7].

Recognition of the predisposing factors for VTE forms the cornerstone of diagnosis. These may be acquired or congenital. Acquired causes include: (1) surgery, including major hip and knee and cancer surgery, (2) previous trauma of the hip leg or pelvis within the last 3–6 months, (3) previous VTE including superficial vein thrombosis [8], (4) leg paralysis or immobilization and casting, (5) heart conditions such as congestive heart failure and myocardial infarction in the past 3 months [9], (6) hospitalization or nursing home confinement [10, 11] (7) central venous catheter or pacemaker placement [12], (8) cancer, with approximately 20% of all new VTE associated with active malignancy [12], (9) travel lasting 4 h or more or of greater than 5000 km [13], (the "economy class syndrome"). Other risk factors include: myeloproliferative disorders, air pollution, metabolic syn-

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drome, paroxysmal nocturnal hemoglobinuria, pregnancy, estrogen containing oral contraceptives and cigarette smoking [3, 14–17].

The annual incidence of idiopathic VTE is about 0.04% in the general population and increases to 0.1–0.4% in family members of symptomatic carriers of prothrombotic mutations. One or more markers of hypercoagulability can be identified in more than 60% of patients with VTE, particularly when it is idiopathic (no associated triggers or risk factors). Features suggesting the presence of a thrombophilia include age below 50 years, family history of VTE, VTE in unusual locations, recurrence, idiopathic VTE, fatal VTE and warfarin induced skin necrosis [18]. The most common are factor V Leiden and activated protein C resistance (APCR), which are found in 11–21% of VTE. Factor V Leiden heterozygosity is present in 5% of Caucasians, 2.2% of Hispanics and 1.2% of African Americans [19]. APCR may be congenital or acquired. Protein C heterozygosity is found in 0.2% of the general population. (Table 29.1). The estimated risk of DVT is sevenfold in factor V Leiden carriers and increased further by pregnancy and the use of birth control pills. Heterozygosity for the prothrombin G20210A mutation is present in 1.1% of Caucasians and Hispanics but only in 0.3% of African Americans [20] and carries a three- to four-fold risk of VTE. There is a 15-fold relative risk of VTE during pregnancy with this mutation, and when the mutation is combined with factor V-Leiden, the risk is greater than 100-fold. Hyperhomocysteinemia is found in about 25% of patients with idiopathic VTE. A plasma homocysteine level above the 95th percentile (more than 17 μmol/L) increases the risk of DVT by two- to three-fold and is associated with a nearly threefold risk of recurrence (Table 29.1). However, there is no evidence that folic acid or other treatment beyond anti-coagulants is of value. The relative contribution of lower levels of homocysteine is not established. In men with hyperhomocysteinemia and factor V-Leiden, there is a 20-fold increase in VTE. High levels of factor XI are also a risk factor for DVT; at high levels, which are present in 10% of the population, the risk doubles. Other, less common genetic causes of hypercoagulability that increase the risk for VTE include elevated factor VIII level, deficiencies of antithrombin III, deficiencies of proteins C and S, and abnormal plasminogen levels. Antiphospholipid antibodies, including anticardiolipin, associated with the lupus anticoagulant and ovarian stimulation for *in vitro* fertilization are acquired risk factors. Duration of treatment of idiopathic VTE should not be influenced by the finding of genetic factors associated with thrombosis, thus screening for hypercoagulabilty can be done primarily to provide family counseling. The following tests are suggested by some in patients with idiopathic VTE: factor V Leiden and APCR, prothrombin mutation G20210, VTE in a patient younger than 45 years, recurrent VTE, or a patient with a family history of VTE if oral contraceptives or pregnancy are being considered [17, 21].

Presenting Signs and Symptoms

Combinations of clinical findings in patients with PE are both extremely sensitive and extremely nonspecific. Dyspnea or tachypnea (respiratory rate, more than 20 breaths/min) occurred in 90% of patients with PE in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study; dyspnea or tachypnea or signs of DVT (despite their inaccuracy) occurred in 91%; dyspnea or tachypnea or pleuritic pain occurred in 97%; and dyspnea or tachypnea or pleuritic pain, or radiographic evidence of atelectasis or parenchymal abnormality, occurred in 98%. The frequency of individual findings in PIOPED and the urokinase/streptokinase studies are shown in Table 29.2 [3, 14, 15]. In PIOPED, in patients without prior cardiopulmonary diseases, only tachypnea (70%), dyspnea (73%), chest pain (66%), and crackles were found in the majority of patients with PE, and only crackles showed a statistical difference

Table 29.1 Heritable and acquired thrombophilia and venous thromboembolism

Genetic trait	Prevalence in population	Prevalence in VTE subjects	Relative risk of VTE	Relative risk of recurrent VTE[a]
Homocysteinemia (above 17 μmol/L)	5%	25%	2–3	3
Factor V Leiden	5% of white people	11–21%	Heterozygous: 7	0–4
	2% of Hispanics	Not known for others	Homozygous: 80	
	0.3% of Asians			
	<1% of blacks			
Prothrombin 20,210	2%	<5%		0
Factor V Leiden and prothrombin 20,210	0.1%	3%	3–4	
			~20	~4
Homocysteine and factor V Leiden (men only)	0.3%	2.7%	10 for any VTE	
			20 for idiopathic VTE	Unknown

VTE venous thromboembolism
[a]After anticoagulants are discontinued

Table 29.2 Signs and symptoms in pulmonary embolism

Sign/symptom	PIOPED (no prior cardiopulmonary disease)		
	PE ($N = 117$) (%)	No PE ($N = 248$) (%)	UK/SK trials: PE ($N = 327$) (%)
In majority			
Respirations (>16/min)	–	–	92
Respirations (>20/min)	70	68	–
Dyspnea	73	72	84
Chest pain	66	59	88
Pleuritic pain	–	–	74
Apprehension	–	–	59
Crackles	51	40[a]	58
Cough	37	36	53
S2P	23	13[a]	53
Frequent			
Hemoptysis	13	8	30
Pulse >100	30	24	44
Sweats	11	8	27
Syncope	–	–	13
Leg pain	26	24	–
Temperature (>37.8 °C)	7	12	43
Diaphoresis	–	–	36
S4 Gallop	24	14[a]	34
Phlebitis	–	–	32
Edema	–	–	24
Murmur	–	–	23
Cyanosis	–	–	19
Uncommon			
Palpitations	10	18	–
Holman's sign	4	2	–
Wheezing	9	11	–
Angina-like pain	4	6	–
Right ventricular lift	4	2	–
Pleural friction rub	3	2	–
S3 Gallop	3	4	–

PE pulmonary embolism, *PIOPED* Prospective Investigation of Pulmonary Embolism Diagnosis, *SK* streptokinase, *UK* urokinase. Adapted from Weg [101]
[a]$p < 0.001$

from the findings in the patients without PE. These signs and symptoms are found in many diseases, are very common in sick patients, and are almost uniformly present in patients in intensive care units.

Clinical Model

Once suspicion of PE occurs based on the predisposing factors, symptoms and signs, we recommend an escalating approach starting with a validated clinical model followed by a D-dimer. We prefer the Wells model [22] (see Table 29.3), although others such as the Geneva score or empirical estimates may perform well [23, 24]. In a multicenter study of 930 patients in whom only 86 (15%) had PE, emergency department physicians using the Wells criteria reported a high pre-test probability in 64 (7%), moderate in 339 (36%) and low in 527 (57%) of patients. PE was found in 24 (40.6%) of high, 55 (16.2%) of moderate, and 7 (1.3%) of low probability patients [22]. More recently, this group reported on 1126 outpatients and inpatients with a prevalence of VTE of 15.2%. Utilizing a cut point of 4 (vs. 2 as in their prior study), 670 (60%) were categorized as low probability, and PE was diagnosed in 5% of them [25]. Fifty percent of inpatients had a low probability vs. 69% of outpatients. The prevalence of PE was 20% among inpatients vs. 11% among outpatients.

Table 29.3 Model for determining the clinical probability of pulmonary embolism, according to the Wells score[a]

Clinical feature	Score
Clinical signs and symptoms of DVT (objectively measured leg swelling and pain with palpation in the deep-vein system)	3.0
Heart rate > 100 beats/min	1.5
Immobilization for ≥3 consecutive days (bed rest except to go to bathroom) or surgery in previous 4 weeks	1.5
Previous objectively diagnosed pulmonary embolism or DVT	1.5
Hemoptysis	1.0
Cancer (with treatment within past 6 mo or palliative treatment)	1.0
Pulmonary embolism likely or more likely than alternative diagnoses (on the basis of history, physical examination, chest radiography, ECG, and blood tests)	3.0

<2.0 low probability, 2.0–6.0 moderate probability, >6.0 high probability, *DVT* deep venous thrombosis, *ECG* echocardiography
[a]See Wells et al. [22]

D-Dimer

The quantitative rapid enzyme-linked immunosorbent assay (ELISA) generally provides the most satisfactory likelihood ratio's (abnormal value >500 ng/mL): DVT, positive or sensitivity −0.96 and negative −0.12 and for PE sensitivity of 0.96 and negative 0.09 [26]. There are alternative D-dimer assays that produce equivalent results. In isolation, however, the D-dimer may be misleading. In a study of 1177 patients with a prevalence of PE of 17%, a negative d-Dimer with a normal ventilation-perfusion (V/Q) scan had a post-test probability of PE of 0.4%. With a nondiagnostic V/Q scan the post-test probability of PE was 2.8% and if the V/Q scan was high probability the post-test probability of PE was 65.4%. *The d-Dimer should be used in association with other testing in everyone but those with low pretest probabilities.* A positive d-Dimer only indicates the need for additional testing. Unreliable positive d-dimer tests are often found in patients with cancer, atrial fibrillation, post-operative states, and pregnancy and sepsis or similar conditions.

Clinical Model and D-Dimer

The clinical model should be mated with a d-dimer assay as the initial paradigm for diagnosing PE. A low or intermediate clinical probability (see Table 29.3) with a negative D-dimer effectively excludes PE; the post-test probability of PE ranges from 0.7 to 2.0% [27]. We believe further testing is not necessary. However, some would also obtain a venous ultrasound of the lower extremities. If the clinical probability is high, a D-dimer need not be done since even if negative the likelihood of PE is greater than 15% [26]. If the D-dimer is positive then imaging studies are necessary.

Imaging Studies

The selection of the initial and subsequent imaging studies should be based on their rapid availability, institutional expertise/preference, risks such as radiation, allergy to iodinated contrast agents, renal status, costs and conditions of the patient (Fig. 29.1) [27].

Contrast-Enhanced Spiral Computed Tomography (CT)

The most commonly used initial imaging study for the evaluation of possible PE is CT of the pulmonary arteries (CTA) preferably combined with CT venography of the abdominal and femoral-popliteal veins (CTV). These studies are minimally invasive (injection of the dye) and are of additional value in identifying other lung lesions. A systematic review of single slice CTA outcome studies reported sensitivities of 53–100% and specificities of 81–100% [28]. The identification of sub-segmental clots has been 30% or less; however some 6–36% of PEs have been limited to sub-segmental vessels [29]. In a prospective study of 259 patients, the sensitivity of single slice CT angiography was only 70% (95% CI 62–78%) and specificity 91% (95% CI 86–95%). The likelihood ratio for a false negative CT was 0.3-close to that of a low probability scan in PIOPED. The false negative rate was reduced from 30 to 20% if ultrasonography was negative and to 5% if the lung scan was also non-diagnostic. The false positive rate was 15% in lobar arteries and 38% in segmental arteries [30].

The Prospective Investigation for Pulmonary Embolism Diagnosis II (PIOPED-II) was a multicenter prospective investigation of the accuracy of multidetector CTA in combination with CTV (additional venography) and the application of a validated clinic model (Wells) (see Table 29.3) [27]. PIOPED-II used a composite reference test to diagnose or exclude PE. PE was found in 192/824 (23%) of patients. The sensitivity of CTA was 83% and the specificity was 96%; 51 CTA studies were not adequate for interpretation. The likelihood ratio for a positive test was 19.6 (95% CI 13.3–29.0) and the likelihood ratio for a negative test was 0.18 (95% CI 0.13–0.24). A positive likelihood ratio of greater than 10 and a negative likelihood ratio of less than 0.1 provide a highly definitive change from pre-test to post-test [31]. The sensitivity of the CTA-CTV was 90% and the specificity was 95%; 87 CTA-CTV studies were inadequate for interpretation; the likelihood of a positive test was 16.5 and for a negative test 0.11 (see Table 29.4). Location of the PE has significant implications. The positive predictive values for PE in the main PA and primary branches were 97% (116 of 120), 68% (32 of 47) in a segmental vessel and 25% (2 of 8) in sub-segmental vessels. Table 29.4 emphasizes the effect of discordance between the test and the clinical impression. In the case of major discordance, both clinical and test impressions should be reevaluated with consideration of additional testing. The substantial number of inconclusive readings highlights the need to review the initial interpretation. Additionally, the study was conducted in centers with experience beyond that generally available. A negative CTA alone is insufficient to exclude the diagnosis of PE, but a low clinical score and a negative CTA confirms the exclusion of PE.

PIOPED II was an accuracy study. It compared its results to an independent gold standard. Such studies provide the understanding of test performance in both diagnosing and excluding disease [32]. In contrast, outcome studies provide guidance for clinical management. The recent outcome studies of Perrier, et al. [32, 33] and Christopher Study Investigators [24] support the validity of CTA. CTA is also the study of choice to screen for central and secondary branch occlusive disease in CTEPH. However, in patients with pulmonary hypertension the V/Q scan is necessary to exclude CTEPH (see Chap. 30).

Ventilation/Perfusion Lung Scanning

Ventilation/perfusion (V/Q) lung scans or perfusion lung scans was the usual initial imaging test for PE for more than 20 years prior to the evolution of CTA/CTV. The only ventilation/perfusion (V/Q) results that permit definitive, rational clinical decision making are those indicating high probability (more than one segmental or larger perfusion defect with normal ventilation—a mismatch) and those that are normal (no significant defects). In PIOPED, a high-probability V/Q scan had a positive predictive value of PE in 87% of patients, and the likelihood of PE was greater than 96% if the clinical suspicion was high. However, PE was found in only 74% of patients with this reading. If they had a history of prior PE, a PE was found in 4% of those with a normal or near normal V/Q scan. Only 27% of patients had high (13%) and normal

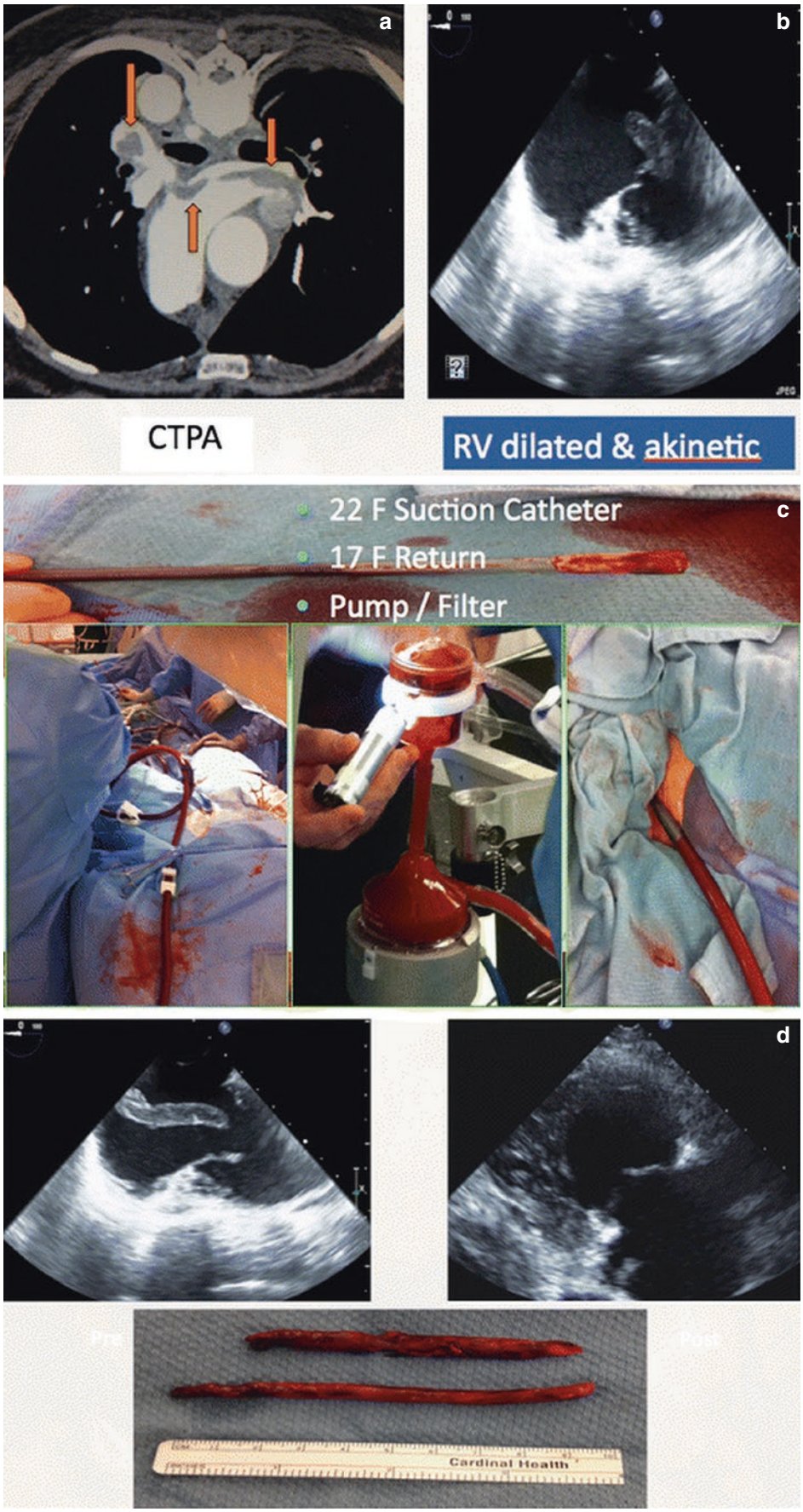

Fig. 29.1 (**a**) Chest CT pulmonary angiogram of a 76-year-old female with sickle cell anemia, acute shortness of breath and hypotensive/tachypneic in emergency department with SaO_2 = 86% on non-rebreather. Large thrombus burden in bilateral proximal pulmonary arteries. (**b**) Transthoracic echocardiogram demonstrating dilated and akinetic right ventricle with "clot-in-transit" from right atrium to ventricle. (**c**) Photograph of AngioVac Vortex mechanico-aspiration thrombectomy device, employed in this hemodynamically unstable woman with acute PE, deemed too high risk for operative embolectomy. (**d**) Transesophageal echocardiogram-guided Vortex thrombo-aspiration showing "tail" of thrombus in right ventricle (*left*), pre-Vortex, absent after Vortex (*right*), and representative samples of thrombus extracted by device. (From Rajachandran and Schainfeld [103]; with permission)

Table 29.4 Positive and negative predictive values from Prospective Investigation of Pulmonary Embolism II (PIOPED II)

	CTA			CTA or CTV			CTA			CTA and CTV		
	Positive predictive value						Negative predictive value					
	N	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI
Alone	150/175	86	79–90				567/598	95	92–96	524/543	97	94–97
Clinical												
High	22/23	96	78–99	27/28	96	81–99	9/15	60	32–83	9/11	82	48–97
Intermediate	93/101	92	84–96	100/111	90	82–94	121/136	89	82–93	114/124	92	85–96
Low	22/38	58	40–73	40/72	57	40–72	9/11	82	48–97	146/151	97	92–98

Data from Stein et al. [27]

(14%) readings. Intermediate- and low-probability V/Q scans should be reported and considered as nondiagnostic. PE was found in 33% of patients with intermediate-probability scans and 14% of patients with low-probability scans, an incidence too high to abandon the diagnosis of PE and too low to initiate treatment [34]. In patients with substantial chronic obstructive pulmonary disease, only 5% had high-probability scans, and they had PE; there were no normal scans [35]; lung scans are also of little value in patients with acute respiratory failure [36].

V/Q scans are more likely to provide clinically useful information when the chest roentgenogram is normal. In PIOPED (I 1990) only 33 patients (15%) had normal chest roentgenograms. However, 69 (52%) had V/Q scans that were either high probability or normal. In a retrospective review of 613 consecutive patients, the chest roentgenogram was normal in 220 (36%); 179 (81%) of these had a normal V/Q scan and 22 (10%) had high probability scans. Thus, the non-diagnostic scans were reduced to 19 (9%). In the 393 with abnormal scans, 98 (25%) had high probability readings and 188 (48%) had non-diagnostic readings (low and intermediate) [34, 37]. While the low probability V/Q scan alone is non-diagnostic, it is helpful in patients with a low clinical probability, particularly with a normal d-dimer.

Lower Extremity Studies

Noninvasive studies have all but replaced venography in the diagnosis of DVT. A positive study is sufficient to diagnose VTE, because there is no difference in the need for anticoagulation. However, because approximately 20% or more of patients with PE have nondiagnostic lower extremity studies, these studies are insufficient to exclude the diagnosis of PE. Real-time B-mode compression color (color duplex) ultrasonography is preferred and should include imaging of the calf and external iliac veins.

Pulmonary Angiography

Pulmonary angiography is the "gold standard" for the diagnosis or exclusion of PE. In the 1111 angiograms in PIOPED, the correct diagnosis was made in 96% of the patients on the basis of a 1-year outcome study; 4% of studies were nondiagnostic or incomplete. There were five deaths among patients with unstable severe cardiopulmonary disease. In comparison, one patient died after a V/Q scan. Major complications occurred in an additional nine patients, and less severe complications occurred in 60 patients. Complications did not correlate with pulmonary artery pressure but were more common in patients in a medical intensive care unit [38]. Since the introduction and validation of CTA-CTV, pulmonary angiography is used infrequently in the diagnosis of PE. It is reserved for the uncommon situation in which the previously described studies do not exclude or diagnose PE and the treatment decision important. The other exception is the patient with severe cardiopulmonary instability in whom angiography is used to document and localize PE followed by thrombus extraction. CTA can be used to select patients for emergent thrombectomy.

Magnetic Resonance Imaging

The sensitivity and specificity of magnetic resonance angiography with contrast enhancement shares with helical contrast enhanced CT the attributes of being minimally invasive and permits the interpretation at a work station which improves results. In small prospective studies, it has shown promise. In one study it had a sensitivity of 100% and a specificity of 87%, but all the clots were in main or segmental vessels [39]. In another small study, the sensitivity was 85% and the specificity was 96%; however it missed four subsegmental emboli [40]. In a much larger study or 300 patients, MRI had a sensitivity of 78.7–84.5% and a specificity of 99.1–100% respectively. Sensitivity was better for proximal (97.7–100%), than for segmental (68.0–91.7%) and sub-segmental PE (21.4–33.3%) [41]. Magnetic resonance venography is exceptionally accurate in upper and lower extremity iliac and pelvic (including ovarian) veins [42]. The recent reports of nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy (NSF/NFD) associated with the use of Gadolinium for MRA in patients with moderate to end-stage renal disease (the majority requiring dialysis) may limit the usefulness of MRA/MRV [43].

Echocardiography and Biomarkers

In patients with acute PE, transthoracic echocardiography may identify right ventricular dysfunction related to sudden increase in pulmonary pressure and or RV stunning/ ischemia/infarction. There is also substantial pulmonary hypertension in submassive and massive PE, which may be related to the clot burden, hypoxemia, and vasospasm, as well as reflect the contribution of left heart failure. These findings are nonspecific; they are not markers for PE and were found in only 56% of patients with PE in a prospective study [44]. However, persistent RV dysfunction is associated with increased risk of recurrent VTE. While CTEPH is relatively uncommon (2–4%), following sub massive or massive PE a repeat echo-Doppler should be performed at about 3 months since CTEPH is treatable with both medication and surgery (see Chap. 30). Transesophageal echocardiography has identified main pulmonary artery and intracardiac emboli in 12 of 24 patients in shock with neck vein distention [45]. In several small studies of patients with cor pulmonale, transesophageal echocardiography has had sensitivities of only 58% to 65% in identifying emboli [46]. Cardiac biomarkers including B-type natriuretic peptide (BNP), NT-proBNP, and cardiac troponin I and T have been evaluated in PE and identify higher risk cohorts. While they do not have adequate predictive value for the high risk patient, low risk can be defined by negative biomarkers and a normal echo-Doppler [47].

Nonspecific Tests

In PIOPED, some nonspecific abnormality was present in 80% of chest roentgenograms: atelectasis or consolidation in 65% and pleural effusion in 48%. The so-called classic findings of wedge-shaped infiltrates, prominent central pulmonary arteries and pulmonary artery cutoffs, and decreased peripheral vascularity occurred in less than 25% of those studies; these findings are particularly difficult to see on portable anterior-posterior chest roentgenograms. Similarly nonspecific electrocardiographic findings were seen in 70%: tachycardia and nonspecific ST-T wave changes were common; again, the so-called classic but nonspecific findings of S_1, S_2, S_3, complete right bundle branch block; and S_1, Q_3, T_3 patterns were seen in only about 10%. Left-axis deviation was more common than right-axis deviation. The nonspecific findings of hypoxemia, an increased alveolar-to-arterial oxygen [$P(A\text{-}a)O_2$] gradient, and hypocarbia were equally present in patients with and without PE. The absence of hypoxemia lowers the likelihood but does not exclude PE. The pathogenesis of hypoxemia in PE is not easily explained. In contrast to the classic perfusion of poorly ventilated areas in pneumonia, atelectasis, and pulmonary edema, the hypoxemia with PE is more readily responsive to supplemental oxygen. The chest x-ray, blood gases, and ECG may identify other conditions that simulate or occur with a PE [3].

A Recommended Diagnostic Algorithm

A reasonable approach for the diagnosis of PE is provided in Fig. 29.2 as adapted from Stein et al. [27]. It generally escalates from the simple and least expensive to the more complex and more expensive, while weighing these characteristics against the diagnostic yield, rapidity of availability and particular limits imposed by underlying problems in individual subjects. The application of a validated clinical model at no expense, coupled with a quantitative rapid ELISA D-dimer assay (or its equivalent D-dimer assay) with minimal expense is a logical starting point [27]; a low clinical score and negative D-dimer for all practical purposes eliminates the diagnosis of PE. If PE is not excluded, the next recommended test is the CTA; it performs as well as the CTA/CTV when used with a validated clinical model. However, negative CTA alone had a false negative rate of 17% in PIOPED-II vs. 11% with a negative CTA/CTV. *When there is discordance between the clinical probability and CTA or CTA/CTV, additional testing is required:* e.g. a negative CTA with a high clinical probability had a false negative rate of 48% and with a negative CTA/CTV it was 18% (see Table 29.4).

Alternative or Additional Testing

These tests are listed in Table 29.5. There is generally less evidence supporting a specific choice and often the selection is based on individual issues raised by each patient and local preferences. Venous ultrasound is relatively inexpensive and has no attendant risks. It has been reported as positive in patients with proven PE in some 30–45%. See Table 29.5.

Special Circumstances

Allergy to iodinated contrast material occurs commonly. If the clinical manifestations of allergy to contrast are not severe, pretreatment with corticosteroids and H-2 blockers may be adequate. If venous ultrasound is nondiagnostic, a V/Q perfusion scan is preferred. One can consider gadolinium enhanced MRI in centers that routinely perform it well and in individuals with a normal glomerular filtration rate [48]. Serial venous ultrasonography can also be considered.

Impaired renal function impacts the use of iodinated contrast material. With a creatinine <1.5 mg/dL there is minimal

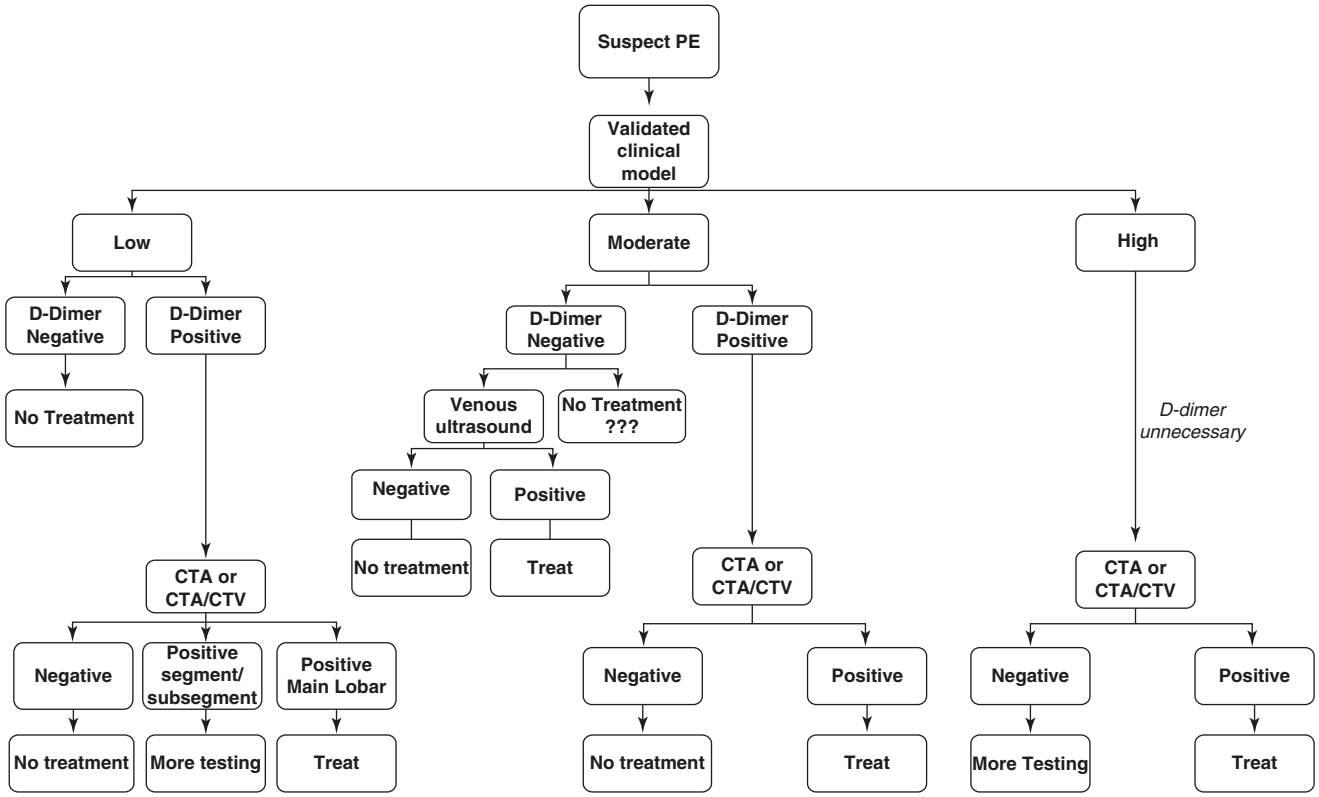

Fig. 29.2 An algorithm for the diagnosis of pulmonary embolism, starting with the application of a validated clinical model (Wells) and a D-dimer. Venous ultrasound of the lower extremities is an acceptable first test. When there is discordance between the validated clinical model and the test, the test should be reviewed and if the interpretation is unchanged, additional testing is warranted. *PE* pulmonary embolism, *CTA* multidetector computed tomography of the pulmonary arteries, *CTV* multidetector computed tomography of the thigh veins

Table 29.5 Alternative/additional testing

Venous ultrasound (color Doppler) of thighs
Perfusion, ventilation/perfusion of the lungs
Digital subtraction pulmonary angiography
Magnetic resonance angiography (MRA)
Magnetic resonance venography (MRV)
MRA/MRV
Review/repeat poor quality imaging studies

risk to contrast, and if <2 mg/dL renal failure (0.5 mg/dL increase post contrast) is relatively rare (<5%) with the following precautions: (1) nonionic contrast material; (2) pre and post procedure hydration; (3) discontinuation of nonsteroidal anti-inflammatory drugs (NSAIDS), metformin and possibly angiotensin-converting enzyme (ACE) inhibitors; (4) and pretreatment with acetylcysteine.

In pregnancy, a validated clinical model and a D-dimer test is a reasonable starting point, although pregnancy itself may result in a positive D-dimer without clinical VTE. Venous ultrasound should be the first exam (using the lateral decubitus position late in the second and third trimesters to avoid venous compression of the gravid uterus), and if necessary CTA. The estimated radiation dose to the fetus from CTA is about the same as a perfusion scan; some indicate the dose is lower with the CTA.

Differential Diagnosis

The alternative diagnoses in patients with symptoms of PE are extensive. Signs, symptoms, chest roentgenograms, electrocardiograms, and arterial blood gas measurements cannot easily differentiate the patient with PE from one with the other diagnostic possibilities in Table 29.6. A high index of suspicion is necessary, since many of these entities occur concomitantly with PE; examples being congestive heart failure, atelectasis, and pneumonia.

Therapy

The approach to treatment of acute VTE-PE requires risk stratification (low, intermediate, high) that includes hemodynamic stability, arterial oxygen saturation, and associated diseases. A simplified version of the Pulmonary Embolism Severity Index reported by Jimenez et al. provides such

Table 29.6 The differential diagnosis of pulmonary embolism

Cardiovascular
Acute myocardial infarction
Dissecting thoracic aortic aneurysm
Congestive heart failure
Pulmonary
Intrathoracic malignancy
Pneumonia
Exacerbation of chronic obstructive pulmonary disease
Exacerbation of diffuse infiltrative disease (e.g., idiopathic pulmonary fibrosis, sarcoidosis)
Atelectasis
Respiratory failure
Hypoxemia (etiology undetermined)
Pleuritis
Infectious
Sepsis
Urinary tract infection (chest, flank, back pain)
Extrapulmonary abscess
Peritonitis
Neurologic
Cerebral vascular accident
Others
Collagen vascular disease
Transplant rejection
Pancreatitis
Musculoskeletal pain
Hyperventilation
Sighing respiration

stratification [49, 50]. The presence of any of the following variables defines high risk: age >80 years, history of cancer, history of heart failure or COPD, heart rate ≥110 bpm, systolic BP <100 mmHg, or arterial oxygen saturation <90%. Low risk patients (short term mortality about 1%) can be discharged quickly or even treated as an outpatient. High risk patients (about 5% of symptomatic VTE-PE with 15% short term mortality) should be considered for thrombolytic therapy, or surgical or catheter thrombectomy [6].

The current preferred treatment for acute proven VTE-PE and DVT is low molecular weight heparin (LMWH) subcutaneously (SC) for 5–7 days and an inhibitor of the synthesis of vitamin K dependent coagulation factors such as warfarin for **at least** 3 months (see discussion below). Patients with cancer, patients who had unprovoked pulmonary emboli and patients who have had a previous pulmonary embolism, with low to moderate bleeding risk may require extended therapy. These recommendations are based on large randomized prospective consistent multicenter studies using objective validation and/or outcome; this is a 1A recommendation (1 benefit/risk clear, A methods strong) [49, 50]. LMWH is preferred throughout pregnancy and warfarin should not be used during pregnancy [17]. Patients with proximal DVT should also wear fitted compression stockings for at least 3 months to reduce the incidence of the post-phlebitic syndrome [51].

Table 29.7 Guidelines for low-molecular-weight heparins approved for use in the United States and Canada

Drug	Dose
Dalteparin sodium	200 IU/kg/d anti–factor Xa
	Should not exceed 18,000 IU/dose
Enoxaparin sodium	1 mg/kg q12 h SC *or* 1.5 mg/kg/d SC
	Single daily dose should not exceed 180 mg
Fondaparinux	5 mg (body weight < 50 kg), 7.5 mg (body weight 50–100 kg), or 10 mg (body weight > 100 kg) by SC once daily
Nadroparin calcium: Available in Canada	86 IU/kg anti–factor Xa b.i.d. SC × 10 d *or* 171 IU/kg/d SC anti–factor Xa. Should not exceed 17,100 IU/dose
Tinzaparin sodium	175 IU/kg/d SC anti–factor Xa

An appropriate anticoagulation regimen reduces the mortality due to PE ≤ 2.5% vs. a mortality of 25–35% in historical controls [52, 53]. If PE is strongly suspected 5000–10,000 IU of unfractionated heparin (UFH) should be given immediately intravenously unless there is a high risk or contraindication to anticoagulation [49, 50, 54].

Low Molecular Weight Heparin (LMWH)

LMWH has been shown to be at least as effective as UFH in preventing recurrence of thrombotic events, reducing mortality, and minimizing bleeding. In some studies and meta-analyses it has been found to be superior to UFH [55–60]. Its first major advantage is accurate effective dosing by body weight; the anti-Xa level is achieved by administering units/kg without laboratory monitoring for the anticoagulant effect vs. UFH (see Table 29.7). However, one should consider monitoring plasma anti-Xa activity in patients who are pregnant, have a creatinine clearance <30 mL/min (some recommend using unfractionated heparin for patients in renal failure [60]) or are very obese [49, 61]. Secondly, LMWH facilitates outpatient treatment of many patients with DVT and the early outpatient treatment of PE in the stable patient once a system is in place for outpatient care including: (1) administration of LMWH; (2) monitoring the patient for recurrence and complications of bleeding; and (3) monitoring warfarin therapy. The minimal patient criteria for outpatient treatment include: a stable patient, normal vital signs (pulse, respirations, blood pressure and temperature), a low bleeding risk, absence of severe renal disease, and good control of other disease processes [62]. Early discharge results in improved quality of life. The third major advantage is a substantial reduction in costs [62–67]. Cost reduction will result from decreased hospital stays, decreased costs of laboratory monitoring, and decreased recurrence of VTE that would occur in those patients who are inadequately anticoagulated with UFH in the first 24 h. Table 29.7 provides

guidelines for LMWH that are currently approved in the United States, Europe and Canada.

Unfractionated Heparin (UFH)

UFH intravenously is an effective alternative to LMWH. UFH requires initial monitoring every 4–6 h until a stable therapeutic level is obtained along with prompt and vigorous dose adjustment—see Table 29.8. The activated partial thromboplastin time (aPTT) is in general use. However, variations in reagents and clot detection systems occur and titration with protamine sulfate or an amidolytic assay to should be performed to assure that the aPTT of 1.5–2× control represents the therapeutic range of 0.2–0.4 heparin units [49]. The thrombin clotting time (TCT) is preferred. The target is 0.2–0.4 heparin units. The TCT is linear over a range of 0.2–0.6 heparin units (vs. the nonlinear aPTT with its frequent reports of >100× control). The TCT has better correlation with predicted heparin units and it is less altered by warfarin [68, 69]. If the aPTT is less than 1.5× control or TCT <0.2 heparin units, the risk of recurrence increases. Unfractionated heparin in a dose of 1300 IU/h or ≥ 30,000 U/24 h (186 × 70 kg × 24 h = 30,240 IU) is required to achieve and maintain a therapeutic range. If venous access is poor or absent, SC heparin can be considered; the usual SC dose of UFH is about 50,000/24 h.

Table 29.8 Body weight–based dosing of intravenous unfractionated heparin[a]

aPTT seconds[b]	Dose change (U/kg/h)	Addition action	Next aPTT (h)
<35 (<1.2 × mean normal)	+4	Bolus with 80 IU/kg	6
35–45 (1.2–1.5 × mean normal)	+2	Bolus with 40 IU/kg	6
46–70[c] (1.5–2.3 × mean normal)	0	0	6[d]
71–90 (2.3–3.0 × mean normal)	–2	0	6
>90 (>3 × mean normal)	–3	Stop infusion 1 hr	6

aPTT activated partial thromboplastin time
Adapted from Weg [50] and Raschke et al. [102]
[a]Initial dosing; loading 80 IU/kg; maintenance infusion; 18 IU/kg/h (aPTT in 6 h)
[b]The therapeutic range in seconds should correspond to a plasma heparin level of 0.2 to 0.4 IU/mL by protamine sulfate or 0.3 to 0.6 IU/mL by amidolytic assay. When aPTT is stable at 6 h or longer, steady-state kinetics can be assumed
[c]Heparin, 25,000 IU in 250 μL of 5% dextrose in water (D_5W). Infuse at rate dictated by body weight through an infusion apparatus calibrated for low flow rates
[d]During the first 24 h, repeat aPTT every 6 h Thereafter, monitor aPTT once every morning unless it is outside the therapeutic range

Recombinant hirudin and argatroban are direct thrombin inhibitors administered by continuous infusion and are approved in the United States for treatment of heparin-induced thrombocytopenia. They have been at least as effective as heparin in clinical trials.

Oral Anticoagulants

Oral anticoagulation should be started with warfarin 5 mg/day (2.5 mg tablets), in the evening of the first day and adjusted to obtain an international normalized ratio (INR) of 2–3. Warfarin should be continued to maintain this range for 3–6 months for the first VTE with a recognized cause. If the first VTE is idiopathic (no recognized cause) warfarin should be continued for *at least* 6 months with consideration given to long term based upon recent studies.

Whether prolonged anticoagulation is warranted in patients with a first and idiopathic VTE remains controversial. In a recent meta-analysis of controlled studies designed to assess the optimal duration of anticoagulation for VTE, long-term anticoagulation in patients with VTE does reduce the risk of recurrence [70]. The incremental benefit of prolonging anticoagulation decreases as the duration of anticoagulation increases, but persist for at least 6 months after stopping it. The bleeding risk, both in absolute and relative terms, is very low and fairly constant between populations. This suggests that physicians should focus on risk stratification and that in certain high-risk populations (significant residual DVT, obesity, COPD, congestive heart failure, cancer, relative immobility, thrombophilia, and persistent RV dysfunction) lifelong anticoagulation may be needed, while for low-risk populations a shorter course of therapy may be adequate. In a recent study, about 20% of patients with a PE (without CHF and COPD) had persistent right ventricular dysfunction at hospital discharge; this was associated with a nearly fourfold risk of recurrent VTE over the next 5 years [71]. The benefit of longer term anticoagulation was similar in patients with and without genetic thrombophilia. An abnormal D-dimer 1 month following the VTE or presence of residual thrombi in the leg veins identifies groups with higher risk for recurrence that has been shown to benefit from long term warfarin. A normal value has no prognostic value [52, 72].

If there is a recurrence of VTE or if there are risk factors such as unresolved cancer, or anticardiolipin antibody, the anticoagulation is maintained for lifetime. Long term LMWH has been shown to be more effective than warfarin in patients with cancer.

If the INR is elevated and bleeding is severe, fresh-frozen plasma can be used to reverse the effect of warfarin; with minor bleeding, oral vitamin K is effective; and with INR elevations without bleeding, the warfarin can be stopped for 1–3 days.

Novel Oral Anticoagulant Drugs

These drugs are inhibitors of factor II, Dabigatran, or factor X, Rivaroxaban, Apixaban and Edoxaban. They differ in their pharmacokinetics and are attractive alternatives to warfarin as they do not require monitoring and may have lower risk of bleeding than Coumadin [73] Dabigatran is ingested as the etexilate and is converted to the active form. Its bioavailability is 6.5% with an onset of action of 1–2 h and a half-life of 14–17 h. Eighty percent of the drug is excreted by the kidney with the rest being excreted by the biliary system after conjugation. It is contraindicated in severe renal failure.

Apixaban is a direct factor Xa inhibitor. Its bioavailability is about 50% and its onset of action is within 3–4 h. Its half-life is within 8–15 h. Fifty to fifty-five percent is excreted in the feces with 25% by the kidneys and the rest by the intestines and oxidative metabolism. Its metabolism is affected by CYP P450 inhibitors.

Rivaroxaban is also a factor Xa inhibitor with a bioavailability of about 80%. Its onset of action is within 2–3 h and its half-life is between 4 and 9 h. Sixty-five percent of the drug is excreted by the liver and the rest is excreted unchanged in the urine.

Edoxaban is also a factor Xa inhibitor with a bioavailability of 62%. Its onset of action is within 1–2 h with a half-life of approximately 12 h. Fifty percent of the drug is excreted in the kidney.

In a recent met analysis of different treatment strategies including UFH-vitamin K antagonist, LMWH-vitamin K antagonist, LMWH-dabigatran, LMWH-edoxaban combinations with Rivaroxaban, Apixaban or LMWH alone. Using LMWH-Vitamin K antagonist combination as a comparator, treatment with UFH-vitamin K combination was associated with a higher risk of recurrent venous thromboembolism during the follow up period and management strategies using Rivaroxaban or Apixaban without preceding parenteral anticoagulation were associated with a reduction in risk of major bleeding episodes compared with the LMWH-vitamin K antagonist combination.

Thrombolytic Agents

Thrombolytic agents activate plasminogen to form plasmin, and result in the accelerated lysis of clots; however, the role of thrombolytic agents (urokinase, streptokinase, tissue plasminogen activator, alteplase, and reteplase) remains unclear. Despite multiple randomized controlled studies of over 1000 patients since 1970, no clinically important reduction in morbidity, including objectively proven recurrent VTE, or in mortality rates has been demonstrated [14, 15, 74]. Over the first 2–24 h, thrombolytics produce a greater reduction in pulmonary vascular pressures, pulmonary vascular resistance, V/Q scan findings, and angiographically evident extent of clot than does heparin alone. However, there is no difference in lung scans at 1, 5–7, and 14–30 days [14, 15, 74]. Thrombolytic therapy carries an 8% risk of major hemorrhage in some studies; fatal hemorrhage occurred in slightly more than 2% of patients and intracranial bleeding in a similar percentage. The risk is fourfold in patients older than 70 years. It also carries incremental costs of about $1160 (streptokinase) to $2750 (recombinant tissue plasminogen activator), in addition to the costs of heparin, warfarin, and complications.

In a recent randomized trial of 256 patients with PE and pulmonary hypertension or right ventricular dysfunction, there was no reduction in hospital mortality between those receiving alteplase and heparin (3.4%) vs. heparin alone (2.2%) [75]. In a recent follow-up of the International Cooperative Pulmonary Embolism Registry (ICOPER), massive PE defined as a systolic blood pressure of <90 mmHg was found in 4.5%. Thrombolytics or surgical intervention was *not* given to 74%. Mortality amongst those receiving thrombolytics was not different from those who did not [76].

Thrombolytic therapy is generally reserved for patients with proven massive or sub-massive PE with hemodynamic instability (shock) and hypoxemia despite heparin and inotropes [74, 77, 78]. Although reduction in mortality rates among such patients has not been documented in a randomized trial, this group does represent patients with a mortality rate of 20–30%. Right ventricular dysfunction is common in PE, and is a marker of increased risk, but because the mortality due to PE is only about 2%, thrombolytics would not appear warranted [79].The benefit of thrombolytic therapy in PE with severe hypoxemia, elevated cTnI and BNP (markers of high risk), and echocardiographic evidence of right ventricular dysfunction needs to be assessed in a controlled trial.

Inferior Vena Caval Interruption

Inferior Cava Interruption

Inferior vena cava interruption is recommended for: (1) a contraindication or complications (e.g. major bleeding) of anticoagulant therapy in a patient with or at high risk of VTE; (2) documented recurrent VTE despite adequate anticoagulation; (3) chronic or recurrent PE with pulmonary hypertension; (4) following transvenous extraction of PE; pulmonary embolectomy; and pulmonary thromboendarterectomy of major central PE [50, 77, 80]. It has also been used in patients with massive PE and upper extremity PE. The largest experience is with the Greenfield filters; they have a 20 year efficacy rate of 95% and a patency of about 96% [81]. A recent randomized study of 106 patients comparing

IVC filters with anticoagulation vs. anticoagulation alone in patients with proximal DVT (not with the recommended indications cited above) showed a reduction in PE at 12 days, but an increased recurrence of DVTs at 2 years [82]. This small study does not reflect clinical experience. The filters were of various undocumented types and were inserted by many individuals at multiple sites. The bird's nest filter is also effective, but is associated with a higher rate of vena caval occlusion [83]. Filters are also used for primary prophylaxis in patients with a high risk of bleeding such as visceral cancer, extensive trauma, bariatric surgery, and hip or knee surgery [84, 85].

Pulmonary Embolectomy and Transvenous Catheter Extraction

These procedures are reserved for patients in shock despite heparin and resuscitative efforts with fluids and vasopressors who also usually have a contraindication to thrombolytic therapy [49, 50, 74, 77]. Operative mortality has been reported as 10–75% in retrospective case series [86, 87]. Transvenous catheter pulmonary embolectomy has been reported to have a 70% 30 day survival [88]. The approach to massive PE requires a team effort between specialists including cardiopulmonary, radiology/interventional and thoracic surgery.

Prevention of Venous Thromboembolism

Primary prophylaxis of VTE should be a major focus of every physician who cares for patients at risk. The many risk factors for VTE and the efficacy of prevention are well established [89].

Important reductions in VTE can be achieved with the use of LMWH, low dose UFH (5000 IU every 8 or 12 h), adjusted-dose UFH, and low-dose warfarin. Specific recommendations are available [78]. A recent systematic review of randomized trials of VTE prophylaxis in non-surgical patients found that heparin prophylaxis reduced the incidence of PE but not overall mortality and led to more bleeding events [90]. As a result of this, the American College of Physicians (ACP) recommends assessment of the risk for thromboembolism and bleeding in medical patients prior to initiation of VTE prophylaxis, with subsequent initiation of pharmacological therapy unless the risk of bleeding outweighs the benefits of therapy. The ACP also recommends against the use of graduated compression stockings in medical patients and did not support the use of performance measures that promote universal venous thromboembolism regardless of risk [91].

Recurrence

The risk of recurrent VTE varies widely, ranging from 0.6 to 5.0% at 90 days and from 13 to 25% at 25 years [92]. This risk is greatest in the first 6–12 months after the initial event and never falls to zero. In a population based cohort study in Olmstead County, Minnesota, Independent predictors of first overall VTE recurrence included; increasing age and body mass, neurologic disease with paresis, malignant neoplasm and neurosurgery. VTE patients with transient or reversible factors were at less risk [92]. Recurrence may also be associated with greater costs, up to 21% greater with DVT's but not PE [6] and is associated with a higher likelihood of the post-thrombotic syndrome [93], chronic thromboembolic pulmonary hypertension [94] and may be fatal [53]. This brings up the dilemma of when to stop anticoagulation in certain patients. There is increasing evidence that a normal D-dimer level and absence of residual venous thrombosis after discontinuation of oral anticoagulation are associated with a lower risk of recurrence [95]. Vigilance in monitoring these patients may be lifelong. Extended therapy with warfarin and oral rivaroxaban reduces the risk of recurrent venous thromboembolism by up to 60–90% [96, 97]. The risk of major bleeding in the rivaroxaban group was 0.7% [98, 99] Surprisingly, aspirin is an alternative to anti-coagulants. In the WARFASA study, aspirin when compared to placebo in patients who stopped their warfarin and began aspirin,the rate of recurrent unprovoked venous thromboembolism was reduced by 40% with no increase in bleeding risk [100]. This may be of particular benefit to that subset of patients with a high risk of bleeding.

Practical Points

- A consideration of VTE must include the predisposing causes, both acquired (e.g., stasis, surgery, trauma) and inherited (prothrombotic factors), and the signs and symptoms.
- The diagnosis of VTE can be excluded if a *validated clinical score* e.g. Wells is low *and* (1) a D-dimer by quantitative rapid enzyme-linked immunosorbent assay (ELISA) (or its equivalent is low or (2) if a CTA or CTA/CTV is negative or (3) ventilation/perfusion or perfusion scan is normal. The diagnosis of VTE can be confirmed if the *validated clinical score* is high or intermediate and (1) CTA or CTA/CTV is positive or (2) the ventilation/perfusion or perfusion is high probability or (3) ultrasound of the thigh is positive. A diagnosis of VTE can be confirmed if the CTA or CTA/CTV

shows a clot in the main or lobar pulmonary arteries or if the pulmonary angiogram is positive. If there is a disparity between the clinical model and the test, the test should be carefully reviewed. If this does not resolve the problem, further tests are necessary.

- Standard treatment includes LMWH subcutaneously for 5–7 days and warfarin for 6 months or longer, starting on the first day, maintaining an international normalized ratio (INR) of 2–3. The novel oral anticoagulants are increasingly being used instead of warfarin.
- Thrombolytic therapy is indicated if there is hemodynamic instability (shock) or severe RV impairment, and or refractory hypoxemia, despite resuscitative efforts with fluids, inotropic agents and vasopressors.
- Inferior vena caval interruption is indicated when there are (a) contraindications to or complications (e.g. major bleeding) of anticoagulants in patient with or at high risk of VTE; (b) documented recurrent VTE despite adequate anticoagulation; and (c) chronic or recurrent PE with pulmonary hypertension. It is also indicated for patients undergoing transvenous extraction, pulmonary embolectomy, or thromboembolectomy.
- Direct pulmonary embolectomy or transvenous extraction is indicated for patients in shock despite resuscitation, usually with contraindication to thrombolytic therapy.
- **Primary prophylaxis is the most efficient treatment of VTE**.

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Pulmonary Hypertension

30

Veronica Franco

Introduction

Pulmonary hypertension (PH) is an important medical condition affecting a significant number of patients with chronic heart and lung diseases, which significantly contributes to the development of dyspnea and fatigue. The diagnosis, assessment of severity and prognosis, and treatment strategies for PH can be made with a relatively high degree of certainty by experienced practitioners. Pulmonary hypertension is defined by a right heart catheterization, where the mean pulmonary arterial pressure is ≥25 mmHg at rest [1]. Pulmonary capillary wedge pressure (PCWP) of 15 mmHg is utilized to distinguish between pre-capillary (≤15) and post-capillary (>15) PH. The most common causes of PH and right-sided heart failure (HF) are postcapillary, such as left-sided HF and aortic and mitral valvular disease characterized by pulmonary venous hypertension and an elevated PCWP. Pulmonary arterial hypertension (PAH) is defined as PH with PCWP ≤15 mmHg, where significant cardiac and lung disease have been excluded. This chapter emphasis in evaluation of PAH.

Pulmonary hypertension is a challenging disease to diagnose accurately and treat. There is often a delay from first symptoms to diagnosis of up to 2–3 years [2]. Identifying patients with PH earlier in the disease process would be beneficial, allowing targeted therapies to be started before development of significant right-sided HF [3]. The subgroup of patients with PAH usually have an insidious onset but often rapidly progressive disease and it is important to have a high index of suspicion to achieve this diagnosis, particularly in persons at risk because of associated diseases and exposures. Patients at high risk to develop PAH include those with scleroderma-related disorders and lupus, congenital heart disease, cirrhosis with portal hypertension, human immunodeficiency virus (HIV) infection, and a family history of PAH; chronic cocaine users; and those using anorexigens [4].

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Common Signs and Symptoms in PH

The signs and symptoms associated with PH are summarized in Table 30.1 and they are common to all types of PH. Symptoms attributable to PH are similar to those in left-sided HF, valvular disease, and lung disease. The symptoms depend on the functional limitation and the degree of hemodynamic impairment.

1. **Dyspnea and fatigue** are correlated with decrease stroke volume (only with exercise initially but in severe disease also present at rest), cardiac output, and oxygen transport.
2. **Angina-like chest pain** on exertion is correlated with increased right ventricular (RV) myocardial oxygen demand and pulmonary artery pressures in excess of aortic pressure.
3. **Presyncope and syncope**: postural-, tussive-, and exercise-induced systemic hypotension are correlated with decreased left ventricular (LV) filling, and LV compression by the enlarged RV.
4. **Signs of right-sided HF:** Abdominal pain and distention, anorexia, edema, and ascites are correlated with gastric distention, hepatic congestion, increasing jugular venous pressure and tricuspid insufficiency.

Physical findings varied based on the cause and severity of PH. Patients with severe lung disease usually have moderate PH and it can be identified by decreased breath sounds, chest deformities, rales consistent with interstitial lung disease, abnormal jugular venous wave or pressure, a murmur of tricuspid insufficiency, and often clubbing of the fingers and toes and cyanosis.

Long-standing Eisenmenger's syndrome (severe PH associated with congenital intracardiac shunt at the atrial, ventricular, or pulmonary artery level) with predominant right-to-left shunting is characterized by cyanosis at rest or

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Table 30.1 Common presenting symptoms and signs in PH

Symptoms
General: fatigue, weakness, generalized swelling
Cardiac: chest pain consistent with angina, atypical chest pains, palpitations
Pulmonary: dyspnea
Gastrointestinal: nausea, anorexia, abdominal bloating and fullness (from ascites)
Neurologic: lightheadedness with positional change, pre-syncope and syncope with effort, cough, and at rest
Blood pressure: normal to low (occasionally hypertension)
Signs
Jugular venous pulse: distension with prominent V waves, elevated JVP, giant V waves with tricuspid regurgitation
Carotid pulse: normal or low amplitude
Lungs: usually normal, rales (rare in PAH, but may be present in pulmonary fibrosis and left-sided heart disease)
Cardiac: left parasternal RV lift, palpable pulmonic closure sound, increased P2, systolic murmur at left fourth ICS increasing with inspiration (tricuspid insufficiency), soft diastolic decrescendo murmur of pulmonic regurgitation in left third ICS, systolic ejection murmur at left second or third ICS, RV S4 and/or RV S3 gallop at lower left and/or right sternal border
Abdomen: pulsatile and enlarged liver, ascites, splenomegaly with portopulmonary hypertension and severe right-sided heart failure, distension
Extremities: peripheral edema, clubbing, Raynaud's phenomenon, sclerodactyly, loss of digital pulp (scleroderma related disorders)
Skin: pallor, plethora, cyanosis, telangectasias, livedo reticularis

ICS intercostal space, *JVP* jugular venous pressure, *RV* right ventricular

with exercise, clubbing of the fingers and toes, and often murmurs of tricuspid insufficiency and pulmonic insufficiency. Because the RV hypertrophies over a period of years, patients are often only mildly symptomatic until very late in the course. Patients with atrial septal defects and anomalous pulmonary venous drainage (about 2%) can rapidly develop severe PH that resembles PAH and manifests without clubbing of the fingers and toes or without cyanosis. Cyanosis can be due to intracardiac right-to-left shunting or to low cardiac output and decreased alveolar-capillary diffusion.

Classification of PH and Associated Triggers

Pulmonary hypertension is better understood if considered as a disease of triggers (Table 30.2). A clinical classification was established in order to individualize different categories of PH sharing similar pathological findings, similar hemodynamic characteristics and, similar therapeutic algorithms [4]. Pulmonary arterial hypertension is a diagnosis of exclusion and includes several diseases that produce common pathological findings in the pulmonary arteries, including medial hypertrophy, intimal proliferation and fibrotic changes, complex lesions (plexiform) and thrombotic lesions. Pulmonary veins are classically unaffected in PAH.

Table 30.2 Triggers in PH

Classification of PH	Trigger
Pulmonary arterial hypertension	Genetic polymorphisms, permissive phenotype
PH due to left-sided heart disease	Elevated left atrial pressure
PH due to lung disease	Hypoxia
Chronic thromboembolic PH	Obstruction/clot
PH due to unclear multifactorial mechanisms	Miscellaneous

The term secondary PH has been abandoned and not longer utilized. Five groups of disorders that cause PH were identified: PAH (WHO Group 1); PH due to left-sided heart disease (WHO Group 2); PH due to chronic lung disease and/or hypoxia (WHO Group 3); chronic thromboembolic PH (WHO Group 4); and PH due to unclear multifactorial mechanisms (WHO Group 5) (Table 30.3).

Algorithm for Assessment and Diagnosis of PH

The goal of PH evaluation is to determine if they have a diagnosis of PAH or not. If they do have PAH, patients would benefit of specific PAH vasodilators. Figure 30.1 provides an algorithm for assessment of PH. The algorithm provides a logical sequence to exclude conditions that are mostly associated with PH. The algorithm could be modified considering cost and therapeutic implications based on medical history and physical examination: for example, venous disease or pulmonary embolus, cirrhosis, evidence of sclerodactyly, telangiectasias, obesity or use of anorexigens, Raynaud's phenomenon, and cyanosis. The clinical presentations of diseases associated with precapillary PH overlap and PAH as well as PH related to hypoxia (WHO group 3) are both associated with a normal wedge. Diagnosis and management require a multidisciplinary approach and liberal referral to physicians experienced in evaluating and treating PH.

Testing to Determinate Appropriate Diagnosis in PH

Electrocardiogram

The electrocardiogram (ECG) has a high degree of sensitivity (more than 75–80%) for detecting RV hypertrophy in symptomatic patients with severe PH (Fig. 30.2). The sensitivity is less than 40% when the ECG is read without clinical information or when the ECG is unedited and computerized. Frequent misdiagnoses include inferior, anterior, and septal infarction; inferior and anterior ischemia; and left posterior fascicular block. The ECG is not an effective

Table 30.3 Classification of PH

Pulmonary arterial hypertension (PAH)—WHO group 1
Idiopathic PAH
Heritable PAH • BMPR2 • ALK-1, ENG, SMAD9, CAV1, KCNK3 • Unknown
Drug and toxin-induced
Associated with: • Connective tissue disease • HIV infection • Portal hypertension • Congenital heart disease • Schistosomiasis
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″ Persistent PH of the newborn (PPHN)
PH due to left heart disease—WHO group 2
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
PH due to lung disease and/or hypoxia—WHO group 3
Chronic obstructive pulmonary disease
Interstitial lung disease
Mixed restrictive and obstructive pattern disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental lung diseases
Chronic thromboembolic pulmonary hypertension (CTEPH)—WHO group 4
PH with unclear multifactorial mechanisms—WHO group 5
Hematological disorders: • Chronic hemolytic anemia • Myeloproliferative disorders • Splenectomy
Systemic disorders: • Sarcoidosis • Pulmonary histiocytosis • Lymphangioleiomyomatosis
Metabolic disorders: • Glycogen storage disease • Gaucher disease • Thyroid disorders
Others: • Tumoral obstruction • Fibrosing mediastinatis • Chronic renal failure • Segmental PH

screening tool in asymptomatic or mildly symptomatic persons.

The most common ECG patterns in PH include right axis deviation, qR in V_1, and increased voltage (> 2.5 mm) of the *p* wave in lead II (sometimes called *p pulmonale)*. The increased voltage is associated with a fourfold increase in mortality rate [4]. Atrial premature beats occur frequently,

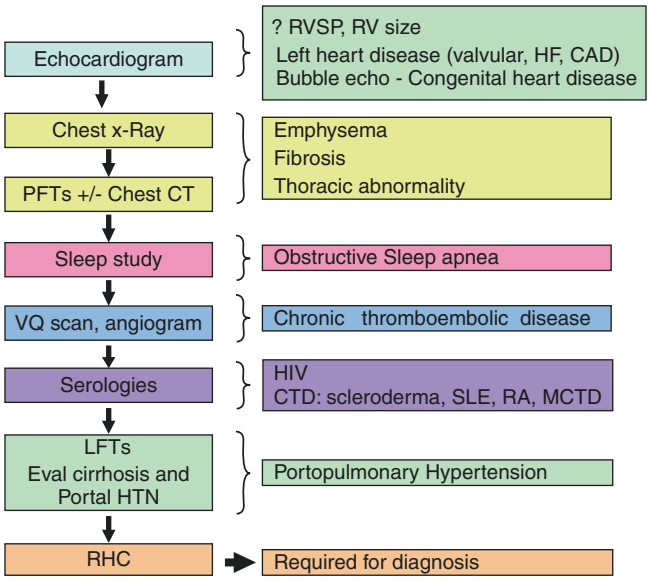

Fig. 30.1 Schema for patient evaluation

but atrial fibrillation, atrial flutter, and serious ventricular arrhythmias are not common.

Chest Radiograph

The magnitude of lung disease (emphysema, fibrosis, masses, and skeletal deformity) needed to induce significant PH is usually detectable on the chest radiograph. Chest radiographic indicators of PH include enlargement of the RV, the right atrium, the superior vena cava, and the main pulmonary artery and its major branches. The criteria for PH is found in 95% of patients with PPH and only 4% of controls matched for age, gender, and body surface area. Figure 30.3 represents typical chest x-ray findings in a patient with PAH.

Echocardiography

Doppler echocardiography is the most effective non-invasive screening tool for detecting PH and for monitoring progression of disease, particularly, the development of RV enlargement and failure [5, 6]. It is an essential test as it is the most useful noninvasive tool to evaluate RV function and estimate pulmonary pressure. The tricuspid regurgitant velocity (TRV) is proportional to the gradient between the RV and RA and is used to calculate the systolic RV pressure (RVSP, equivalent to systolic pulmonary arterial pressure) with Bernoulli's equation:

$$\mathrm{RVSP} = 4 \times \mathrm{TRV}^2 + \mathrm{estimated\,RA\,pressure}\left(\mathrm{mmHg}\right)$$

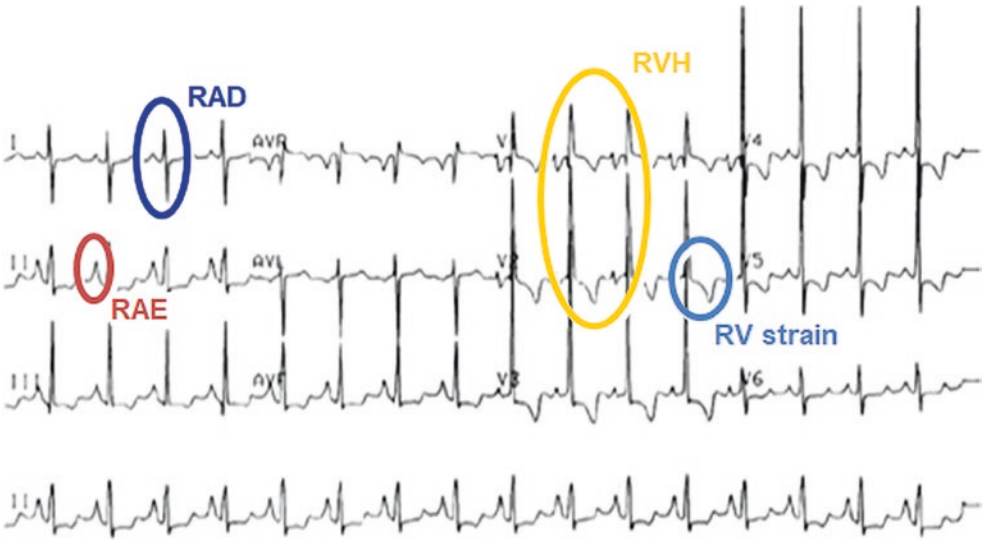

Fig. 30.2 ECG in PH. *RAD* right axis deviation, *RVH* right ventricular hypertrophy, *RV strain* right ventricular strain, *RAE* right atrial enlargement

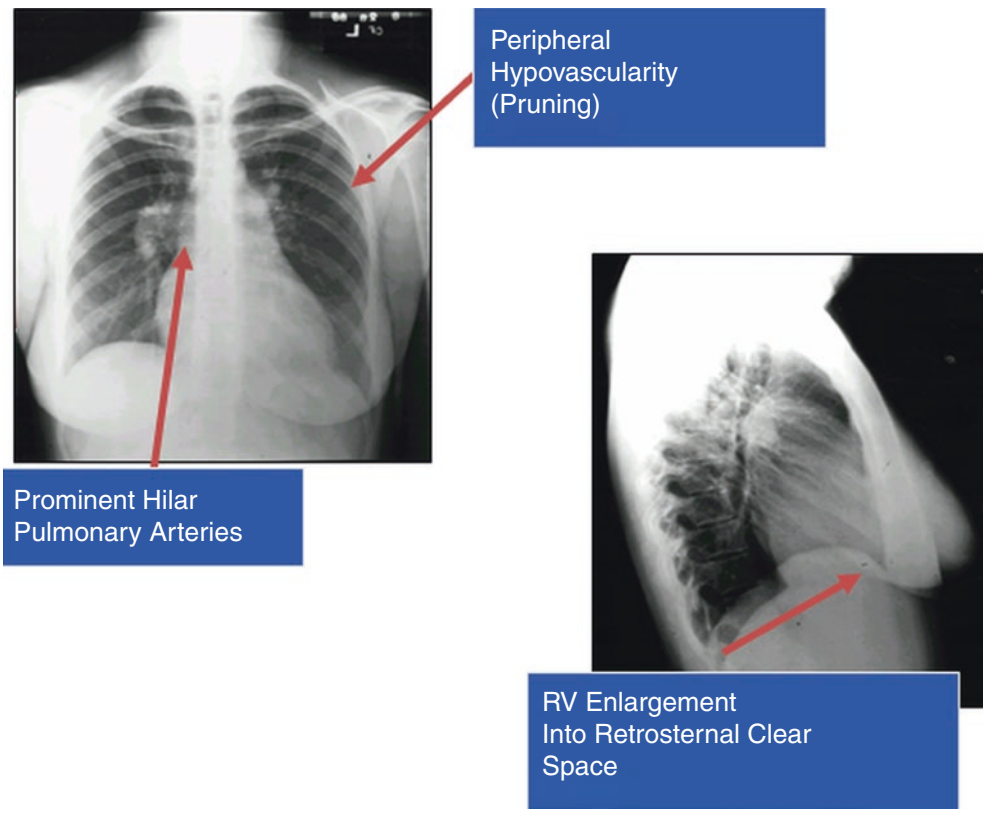

Fig. 30.3 Chest x-ray in PH. Typical changes include: prominent hilar pulmonary arteries, peripheral pruning or hypovascularity and RV enlargement into retrosternal clear space (lateral view)

Some authorities estimate the RA pressure from the size of the inferior vena cava and its response to respiration (collapse with inspiration), and others use a fixed value (range, 5–15 mmHg). The TRV (in meters per second) should be provided to allow the clinician to add an estimate of the RA. TRV should be carefully reviewed to assure the tricuspid regurgitation envelop is complete for an adequate estimation of RVSP, otherwise, echo-Doppler is less accurate and it can under- or over-estimate the true pressure compared to cardiac catheterization [7].

Echocardiography can also identified abnormal systolic and diastolic dysfunction of the left ventricle. An enlarged left atrium suggest left-sided heart failure. Agitated saline contrast material should be used to identify intracardiac (i.e. atrial septal defect) or intrapulmonary shunts. A patent foramen ovale or atrial septal defect can be the explanation for rest and exercise arterial desaturation. The common anatomic findings in severe PH include dilated right atrium and RV, flattened or D-shaped septum, and often a small, compressed left ventricle [6]. Pericardial effusions are not com-

mon but may be predictive of a poor outcome regardless of size [8]. Tricuspid annular plane systolic excursion (TAPSE) is a marker of RV function as its contraction is related to longitudinal axis shortening (thus drawing the tricuspid annular plane toward the apex). A TAPSE ≤18 mm was associated with lower cardiac index, more right heart remodeling, and poorer prognosis in PH patients [9].

The recommendations for Doppler echocardiography in persons at risk for PH are presented in Table 30.4 [1]. In the absence of other potential etiologies of PH, such as left heart disease or advanced lung disease, an estimated RVSP >40 mmHg generally warrants further evaluation in the patient with unexplained dyspnea. Although echocardiogram is a very effective screening tool and is useful for monitoring progress of RV size and function, it is less useful in monitoring pulmonary pressures, particularly in the setting of severe RV dysfunction. It is important to remember that echocardiography is not diagnostic in patients with PH and a catheterization is required for appropriate diagnosis.

Right Heart Catheterization (RHC)

The role of RHC in PH is to confirm the diagnosis and provide prognostic information when evaluating RV function [1]. Cardiac catheterization is required to make a diagnosis and fundamental to differentiate between PAH and cases of left-sided HF induced PH. An elevated wedge pressure (>15 mmHg) is indicative of left-sided HF and, if present, a left heart catheterization may also be considered for direct measurement of LV end-diastolic pressure as well as to perform angiography if coronary artery disease is suspected. The wedge pressures can be inaccurate in severe PH. The hypertrophied or occluded arteriole is not capable of transmitting the true left atrial pressure. Obtaining a LV end-diastolic pressure is recommended if there is not an appropriate accurate wedge tracing.

Experts now recommend the use of fluid challenge in the cath lab to unmask LV diastolic dysfunction based on clinical suspicion [1]. Studies in healthy individuals have shown that administration of 1 L of saline over 6–8 min raised the wedge pressure by a maximum of 3 mmHg but not to >11 mmHg. In contrast, in a population at high risk for diastolic dysfunction, administration of 500 mL of saline over 5 min was able to reveal patients in whom the wedge increased to >15 mmHg. Thus, fluid challenge may identify patients with left-sided HF but normal wedge at baseline and may help reduce the number of inappropriate diagnoses of PAH in patients with LV diastolic dysfunction. A fluid bolus of 500 mL administered over a period of 5–10 min appears to be safe and seems to discriminate patients with PAH from those with LV diastolic dysfunction.

The importance of the progression of RV failure on the outcome of PAH patients is confirmed by the prognostic impact of RA pressures and CI [10]. Patients are considered stable and with better prognosis if there have a RA < 8 mmHg and CI < 2.5 L/min/m^2 [6, 8]. RA >15 mmHg and CI ≤2.0 L/min/m^2 are harbingers of poor outcomes in PAH even with effective therapies. A PVR >32 Wood units foresees a fourfold increased in the risk of death [8]. In contrast, the level of pulmonary arterial pressure has only modest prognostic significance, in part as pulmonary pressures drop as the RV approaches end-stage.

Vasoreactivity testing is also be useful to assess reactivity and reversibility of pulmonary pressures. It is important to choose the appropriate vasodilator agent and a list of effects is detailed in Table 30.5. Inhaled nitric oxide (iNO), intravenous adenosine, or intravenous epoprostenol can be used to assess pulmonary vasodilator reserve if there is a normal wedge pressure. Most PH centers use iNO given that is better tolerated, onset of action is rapid, the half-life is less than

Table 30.4 High risk groups to develop PH: recommended echocardiography

High risk conditions	Schedule
Idiopathic PAH first-degree relatives	At diagnosis of index patient and subsequently, if symptoms appear
Scleroderma spectrum of diseases	Annually (even if asymptomatic)
Other collagen vascular diseases (not scleroderma)	When symptomatic
Liver disease/portal hypertension	When symptoms appear or at time of liver transplant evaluation
HIV disease	When symptomatic
Previous cocaine or anorexigens use	When symptomatic

HIV human immunodeficiency virus, *PAH* pulmonary arterial hypertension

Table 30.5 Vasoreactivity agents used in pulmonary hypertension

Agent	PVR	mPAP	PWCP	CI	SVR	Uses	Notes
Nitroprusside	↓↓↓	↓↓	↓↓	↑↑	↓↓↓	L-sided HF	0.5–5.0 μg/k/m
Milrinone	↓↓↓	↓	↓	↑↑↑	↓↓↓	L-sided HF	50 μg/k IV bolus
Nitric oxide	↓↓↓↓	↓↔	↑↑	↔	↔	PAH	20 (80) ppm in 10 min
Prostacyclin (Epo)	↓↓↓↓	↓↓	↑ ↓	↑↑	↓↓↓	PAH	2–10 ng/k/min
Adenosine	↓↓↓↓	↓↔	↑	↑	↔	PAH	100 μg/k/m

PVR pulmonary vascular resistance, *mPAP* mean pulmonary arterial pressures, *PWCP* pulmonary wedge capillary pressure, *CI* cardiac index, *SVR* systemic vascular resistance, *HF* heart failure, *PAH* pulmonary arterial hypertension

60 s, the test requires only 5–7 min, and, because iNO has no effect on systemic pressures, it is extremely safe. Nitric oxide is not widely available in all centers and the absence of it, should not be a limitation for performing a RHC and delaying diagnosis. Vasoreactivity testing to evaluate if a patient will respond to calcium channel blockers is only indicated in patients that have idiopathic PAH [1].

Computed Tomography and the Ventilation/Perfusion Lung Scan

The ventilation/perfusion (V/Q) lung scan is the "gold standard" for the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH), and a normal or low-probability V/Q scan can be used to exclude chronic thromboemboli [10]. Despite recent advantages in computed tomographic (CT) and magnetic resonance imaging (MRI), the V/Q scan remains the preferred test for screening and should be viewed as an initial step in the diagnosis of CTEPH. The limitations of using computed tomography pulmonary angiogram (CTPA) for detecting chronic thromboembolic disease were highlighted in the report from Tunariu et al. [11]. They reported a sensitivity rate of detecting chronic thromboembolic disease of just 51% with CTPA vs. >96% with V/Q scan. Further, V/Q scan remains the preferred test for screening given less radiation exposure, no risk of contrast-induced renal disease and cost benefits with less likelihood for detection of incidental findings. Underutilization of V/Q scans in screening PH could lead to potential misdiagnosis of PAH, and there have been up to 43% of patients with PAH that never had a V/Q scan [10]. When considering the lower sensitivity of CTPA in detecting CTEPH, some of these patients presumed to have PAH may in fact could have CTEPH.

Despite these advances in CT and MRI scans, catheter-based selective pulmonary angiography (particularly incorporating digital subtraction angiography to improve vessel contrast) remains the gold standard for diagnosis and confirmation of chronic thromboembolic disease, and it is the reference technique by which other imaging modalities are compared in CTEPH [12]. A major advantage with catheter-based pulmonary angiogram is the ability to combine the imaging with assessment of hemodynamic parameters by using right heart catheterization. It is fundamental to thoroughly evaluate patients for CTEPH, given that PH is potentially curable with surgery in those cases, in contrast with PAH, which can not be cured.

A high-resolution CT scan is recommended for patients with PH associated with collagen vascular disease, to detect interstitial fibrosis, inflammatory pneumonitis, and alveolitis that may be amenable to immunosuppressive therapy. The CT scan can detect PH in parenchymal lung disease. A main pulmonary artery diameter larger than 29 mm has a sensitivity of 87%, a specificity of 89%, and a positive predictive value of 0.97 for identifying patients with an mPAP >20 mmHg [13].

Cardiac Magnetic Resonance (CMR)

This imaging method is renowned for its accuracy, lower operator dependency and interstudy variability, advantages over echocardiography and, considered by some, the gold standard for right heart imaging in PAH [6, 14–16]. It yields high-quality images of the RV and is playing an emerging role for evaluation of RV size, function, volume, mass, viability, interventricular septal configuration and LV-RV relationships. Further, it allows for non-invasive assessment of blood flow including stroke volume (measuring the volumetric flow in the main pulmonary artery) and distensibility of pulmonary arteries, all prognostic factors in patients with PAH-induced HF.

Increased RV end-diastolic volume may be the most appropriate marker for progressive RV failure [16]. Cardiac magnetic resonance parameters independently associated with poor long-term outcome, treatment failure and death in PAH patients are a large RV end-diastolic volume index ($\geq$84 mL/m^2) and low LV end-diastolic volume index ($\leq$40 mL/m^2) [17]. Lower left volume might be a result of a decrease RV stroke volume or compression of the LV due to increase RV volume. Chronically high pulmonary pressures lead to RV remodeling and hypertrophy. The degree of RV wall thickness is proportional to PVR levels, however is not significantly related to mortality as RV dilation.

Tagged CMR showed a significant interventricular asynchrony caused by a longer RV systolic contraction time compared to the LV, presumably due to a decrease of electrical conductivity over the RV [18]. This ventricular asynchrony allows for septal bowing, decrease RV function and reduce left end-diastolic volume. Another application consists of CMR analysis of main pulmonary artery distensibility, which was highly correlated with vasodilator response. Patients with PAH that have a positive hemodynamic response to vasodilators have significantly better long-term prognosis than those "non-responders".

While CMR-based assessment is not yet ready to replace right heart catheterization (RHC) with respect of confirmation of PAH diagnosis, it could be considered an alternative to RHC for follow-up purposes [18]. Its high degree of reproducibility makes it an ideal tool to monitor RV changes and the impact of therapy. Progressive RV dilation predicts RV failure at an early stage which enables the prediction of treatment failure, and thus offers an opportunity to change treatment or list for transplantation before fatal decompensation and death occurs [17]. CMR allows for the early identification of patients at higher risk of clinical deterioration, allowing intensification and optimization of their therapy [18, 19]. Although CMR has been generally contested as a monitoring

tool because of its complexity and cost, this may not hold true in PAH [16]. The decision to continue or change the mode of therapy in a PAH patient, sometimes evading the need to perform a RHC, usually has long-term consequences, markedly exceeding the costs of a CMR examination.

Serologic and Hepatic Function Studies

Collagen vascular disease is significantly associated with PAH and accounts in some registries for up to 50% of PAH cases [20]. Serologic studies are necessary to screen for collagen vascular diseases: sedimentation rate, C-reactive protein, antinuclear antibody, rheumatoid factor, and SCL-70 antibody. Distinguishing the scleroderma-related disorders and other collagen vascular disease from idiopathic PAH has prognostic implications and often requires specialty consultation.

Portopulmonary hypertension, found in nearly 1% of patients with chronic liver disease and 10% of those referred for liver transplantation, can be excluded in the absence of a history of alcohol abuse, blood transfusions, or hepatitis and in the presence of normal liver function. Because of the clinical implications, HIV screening should be considered in PAH.

Pulmonary Function Studies (PFTs) and Arterial Blood Gas Measurements

Pulmonary function testing is useful in the assessment of dyspnea but is not diagnostic of PH [20]. The main role of PFTs in PH is to evaluate if the elevated pressures are due to severe lung disease and hypoxia. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (DLCO, 40–80%), and mild to moderate reduction in lung volumes. Mild peripheral obstruction can also be seen. Diseases like chronic thromboembolic pulmonary, interstitial lung disease, mixed obstructive/restrictive lung disease and obstructive sleep apnea could produce mild elevation of pulmonary pressures, but usually do not produce severe PH. Chest CT imaging usually complements information provided by PFTs and assist making appropriate diagnosis. In scleroderma-related disorders with PH, pulmonary fibrosis, and hypoxemia, there is often a marked reduction in diffusion capacity and a restrictive ventilation pattern.

Functional Capacity Assessment

Assessment of exercise capacity in patients with PH is recommended for risk stratification, for selection of a treatment strategy, to measure the response to therapy, and to assist in determining eligibility for more aggressive therapies [8, 20]. The two most useful measures are a standardized 6-min walk test with continuous measurement of cutaneous oxygen saturation and a submaximal or symptom-limited bicycle or treadmill exercise test with or without direct measurement of oxygen consumption. Peak oxygen consumption is not easy to obtain in PAH patients as most of them are on supplemental oxygen therapy. The 6-min walk have been the standard of care for PAH patients and a common endpoint for most clinical trials. The walk is easily tolerated, and results correlate highly with PAH class and prognosis. A walking distance ≥440 mts correlates with reduced mortality, while the ability to walk <165 mts is correlated with worse prognosis [8].

Lung Biopsy

Lung biopsy is not necessary for confirming the diagnosis in patients with PAH. There is a significant risk of morbidity and mortality from major bleeding from lung biopsies in severe PH. In centers with a multidisciplinary team that includes an experienced thoracic surgeon and a pathologist interested in lung disease, open-lung biopsy may be conducted in patients with mild to moderate PH to diagnose active vasculitis, pulmonary venoocclusive disease (PVOD), pulmonary capillary hemangiomatosis, and the rare overlap syndromes, and interstitial lung disease. Knowledge of each of these findings would have an impact on therapeutic strategies.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension is a diagnosis of exclusion (after exclusion of left-sided HF and severe pulmonary disease) and is based on hemodynamic criteria (mean pulmonary artery ≥25 mmHg and wedge ≤15 mmHg) [20]. It was first described in Europe in a patient that had used aminorex fumarate, a popular anorexigen, for treatment of obesity in the 1960s [21]. The disease is progressively fatal disease, caractherized by medial hypertrophy, intimal proliferation and fibrotic changes, complex lesions (plexiform) and thrombotic lesions. Pulmonary veins are classically unaffected. The "driver" of disease progression is increase in pulmonary vascular resistance (PVR). Patients usually die of right-sided HF.

Several conditions or triggers have been associated with PAH, the most common one is collagen vascular disease [4]. Associated PAH accounts for approximately half of the PAH patients followed at specialized centers. About 6–10% of cases are sporadic or idiopathic and some are heritable. In 80% of families with multiple cases of PAH, mutations of the bone morphogenic protein receptor type 2 ($BMPR_2$), a member of the tumor growth factor (TGF) β super family, can be

Table 30.6 Drug- and toxin-induced PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex	Interferon α and β
SSRI (newborns)	Amphetamine-like drugs
Likely	Unlikely
Amphetamines	Oral estrogen
L-tryptophan	Estrogen
Methamphetamines	Cigarette smoking
Dasatinib	

identified. The disease is transmitted as an autosomal dominant trait with incomplete penetrance. In addition, 5% of patients have rare mutations in other genes belonging to the TGFβ super family: activin-like receptor kinase-1 (ALK_1), endoglin (ENG), and mothers against decapentaplegic 9 (Smad 9). Approximately 20% of families have no detectable mutations in currently known disease-associated genes. Patients with heritable PAH are caractherized by earlier onset of symptoms (genetic anticipation). Other recognized triggers of plexogenic arteriopathy include toxins toxic rapeseed oil, cocaine, and L-tryptophane, which was available over the counter in the United States as a diet supplement and used for restless sleep in the past (Table 30.6).

Pulmonary arterial hypertension is more prevalent in women [20, 22, 23]. The reason for the female predisposition is incompletely understood. The peripartum presentation, the association with oral contraceptives (possibly coincidental because of age and gender), and the known prothrombotic effects of estrogens, there is speculation that estrogens play a role in the initiation or progression of PAH. However, animal studies suggest that estrogen also has favorable effects in experimental PAH, there is better outcome in female animals, exacerbation of the disease after ovariectomy and a strong protective effect of estrogen: a phenomenon known as the "estrogen paradox" [24, 25]. Studies in multiple organ systems have shown cross-talk between signaling through the $BMPR_2$ and estrogen pathways [26]. Increased exogenous estrogen decreases $BMPR_2$ expression in cell culture. $BMPR_2$ gene expression is reduced in females compared to males in live humans and in mice, likely through direct estrogen receptor α binding to the $BMPR_2$ promoter. This reduced $BMPR_2$ expression may contribute to the increased prevalence of PAH in females. In addition, estrogen has several effects on the pulmonary vasculature: (1) estradiol, increases prostacyclin release and production of nitric oxide and, (2) through estrogen receptor-dependent mechanisms increases endothelial nitric oxide synthase mRNA levels and activity [25]. Low levels of prostacyclin and nitric oxide and increase endothelin-1 leads to PAH.

The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) has been the largest database to date [23]. It is a 55-US center, observational, prospective registry that included approximately 3500 patients with new and previously diagnosed PAH. Patients were enrolled between March 2006–September 2007 and followed for at least 5 years from time of enrollment. The data set included 2318 females and 651 males. More females had PAH associated with connective tissue disease ($p < 0.001$) and congenital heart disease associated PAH ($p = 0.017$); more males had portopulmonary hypertension ($p < 0.001$) and HIV-associated PAH ($p < 0.001$). At diagnosis, males had higher mean pulmonary arterial pressure (53 ± 14 vs 51 ± 14.3 mm Hg; $p = 0.013$) and mean right atrial pressure (10 ± 6 vs 9 ± 6 mm Hg; $p = 0.031$). Females had better survival estimates for 2 years from enrollment and for 5 years from diagnosis. Stratifying by age showed that survival from enrollment was similar between males and females aged <60 years at enrollment, while males aged >60 years have lower survival rates compared with females over age 60. Most women are diagnosed during reproductive age and unfortunately pregnancy poses a vast risk to PAH patients and experts advice to avoid pregnancy [20]. The first month after delivery represents the period of highest risk. Immediately postpartum, PVR increases and RV contractility may decrease. These changes, in the face of a drop in preload, sets the stage for cardiovascular collapse in the PAH patient. Sudden death may also occur from numerous other mechanisms, including pulmonary embolism, arrhythmias, or stroke from intracardiac shunts.

The classic presentation for PAH is a healthy-appearing young to middle-aged woman complaining of dyspnea and fatigue and often atypical chest pains that are ignored or considered anxiety until months later when accompanied by edema, syncope, or both. Pulmonary arterial hypertension remains a rare disease and despite the progress in treatment, there remains an unacceptable long delay from the onset of clinical symptoms to diagnosis. Most patients are diagnosed late in the course of their disease, when the pathologic changes are advanced and irreversible, patients already had developed RV failure and are functional class III or IV [2, 27]. Diagnosis at this stage is associated with worse prognosis [8, 28, 29], emphasizing the importance of early disease diagnosis and aggressive treatment. Data from PAH registries suggest that there has been little improvement in the early recognition of PAH over the last 20 years (Table 30.7), 21.1% of patients in the REVEAL Registry had a > 2 year delay between onset of symptoms and diagnosis of PAH [2]. The patients most likely to experience a delay in diagnosis were: (1) younger than 36 years old; (2) had confounding histories of obstructive airway disease and sleep apnea; (3) had 6-min walk distance

Table 30.7 Delay of diagnosis and symptoms at presentation—clinical registries in PAH

Registry	Period of enrollment	Delay between onset of symptoms and diagnosis	NYHA class at diagnosis
NIH-PPH [27]	1981–1985	2.03 ± 4.9 years	71% were III or IV
France [30]	2002–2003	2.25 years	75% were III or IV
REVEAL [33]	2006–2007	2.84 years	73.6% were III or IV

Table 30.8 Poor prognosticators in Pulmonary Arterial Hypertension (adapted from Benza [8, 29]; Humbert [30]; Thenappan [40])

Factors associated with poor prognosis
Male gender (particularly if >60 years old)
Association with collagen vascular disease or portal hypertension
Functional class III or IV
Low 6-min walk distance
Right ventricular failure (low cardiac output, high right atrial pressure)
Markedly elevated pulmonary vascular resistance
Low systolic BP and tachycardia
High BNP
Pericardial effusion

<250 mts (in other words, those with severe functional limitation or ~ class IV); (4) had a RA pressure < 10 mmHg or PVR < 10 WU (which is present in less advanced disease). The challenge remains on early diagnosis. Dyspnea, which is a nonspecific symptom, should be fully evaluated and a RHC to exclude pulmonary hypertension ought to be considered if other testing is negative.

Further, data from several contemporary PAH registries from different parts of the world suggest that the epidemiology of PAH has changed significantly in the last three decades [30–34]. The mean age of the patients enrolled in the contemporary registries ranged from 48 to 53 years, which is significantly higher when compared to the National Institute of Health (NIH) registry [35], and there was an increase in the female to male ratio. In the mid-1980s, the NIH reported a 1.7:1 female-to-male ratio [35]. Similar US registries reported a 3.3:1 ratio in the period 1982–2006, 4.3:1 ratio for 1998–2001 and 4.1:1 ratio for 2006–2007 [23, 33, 36]. National registries in France, Scotland and China have reported ratios of 1.9:1, 2.3:1, and 2.4:1, respectively [30, 32, 37]. There is no clear explanation for the change in PAH demographics and an intriguing question is whether pulmonary hypertension in the elderly (>50 years) is truly a different phenotype of PAH or is it a classification drift. Are we misclassifying patients with pulmonary hypertension associated with heart failure with preserved ejection fraction as PAH due to overreliance on a single measurement of a resting PCWP? This question raises since the phenotype of the elderly patients diagnosed with PAH based on the current diagnostic criteria (mean pulmonary artery pressure ≥25 mmHg and resting PCWP ≤15 mmHg) shares several similar characteristics with PH secondary to HF with preserved ejection fraction [34, 38]—both groups have increased incidence of comorbidities including hypertension, diabetes, atrial fibrillation, and ischemic heart disease; the severity of PH is only moderate, as opposed to severe, as in younger patients with PAH; and finally survival in both groups is worse as compared to younger patients with PAH, despite the presence of only moderately elevated pulmonary pressures. The differentiation between PAH and PH associated with HF with preserved ejection fraction is important since the treatment and prognosis significantly differs between the two diagnoses. Further studies are needed in the future to better differentiate these two phenotypes, and also to assess the response to PAH-specific therapies in elderly patients with PAH.

The field of PAH has seen remarkable advances in patient outcomes, due to advancements in drug therapy as well as better predictive models for disease prognostication, yet, it remains unsatisfactory. Prognosis of PAH in the modern management era has improved, but it remains a progressive, fatal disease. Patients in the modern registries had a better survival when compared to the patients in the landmark NIH registry. The NIH registry in 1981 was the first registry evaluating survival in PAH patients in an era when modern, standard therapies were not yet available, and therefore does not accurately reflect the current state of the disease [39]. Their 1-, 3-, and 5- year survival were 67%, 45%, and 37% respectively. Modern day registries, the French Registry [30], the Pulmonary Hypertension Connection registry (PHC) [40], and the largest of all, the REVEAL Registry [8, 29], have consistently demonstrated improvement in PAH survival across PAH subgroups, compared with the historical NIH control group. Factors that indicate worse prognosis include: (1) syncope, (2) functional class IV, (3) severe RV dysfunction (high RA pressures, low cardiac output), (4) pericardial effusion (any size), and (5) association with collagen vascular diseases, among the most important ones (Table 30.8). Prognosis is more related to a change in a modifiable risk factor (i.e., 6-min walk distance, BNP, or hemodynamic parameters). Thus, it is not a particular drug that has been associated with better prognosis, but the relative ability of therapy to change the patient's functional capacity [8].

The prognostic equations generated from these registries, which incorporate multiple, incremental clinical and hemodynamic data, are useful in clinical practice for predicting survival in patients with similar cohort population characteristics. If further studies confirm the utility of these equations for serial risk prediction over time, individual disease trajectories could be ascertained and targeted with timely medical interventions to avoid future morbid and fatal events. In this manner, an incremental benefit in survival may be realized by facilitating a personalized management

profile for individual patients. It is important to recognize however, that more contemporary predictors of survival, using modern imaging techniques and biomarkers, may emerge as important and more accurate predictors of survival. In particular, evaluations of RV function, RV-PA coupling, and RV energetics by cardiac magnetic resonance imaging and PET, respectively, will likely provide additive prognostic power if incorporated into future risk models. Given the power of RV function in mortality prediction, identification of novel imaging or biomarker signals of early RV failure, and studies assessing the direct effects of newer therapeutic agents on the RV, should remain a top research priority.

Therapy for Pulmonary Arterial Hypertension

Because PAH is a rare disease whose complexity poses tremendous challenges to the treating physician, it is recommended that patients be referred to a center with experience in the management of this disease [41, 42]. The drugs available to improve effort tolerance, increase cardiac output, and decrease pulmonary artery pressure and resistance in PAH patients are listed in Table 30.5. In patients with evidence of pulmonary artery vasodilator reserve, approximately 6% of idiopathic PAH patients, the oral calcium channel blockers nifedipine, diltiazem, and amlodipine may reduce symptoms and prolong life [43]. Because of an increased risk of hypotension and clinical deterioration, a trial of oral calcium channel blockers should not be performed regardless of the response to iNO or intravenous epoprostenol in patients in functional class IV symptoms, low systemic blood pressure, overt right-sided heart failure or cardiac index of less than 2 L/min/m^2. Even the initial administration of a small dose (10–20 mg) of nifedipine can result in severe systemic hypotension and death.

Endothelin Antagonists (ERA)

Endothelin-1 (ET-1) is an endogenous vasoconstrictor that promotes smooth muscle proliferation and appears to play a role in the pathogenesis and natural history of PAH. Levels of endothelin-1 are elevated in the lungs of patients with PAH [44]. There are two receptors: A (ET_AR) and B (ET_BR) [45]. They are both simultaneously expressed in all cell types, with one notable exception; only the ET_BR is expressed on endothelial cells. This particular and unique distribution of the endothelial ET_BR is associated with distinct preclinical effects and has generated some debate as to the optimal pharmacological approach to blockade of the ET system.

- ET_AR are found in the smooth muscle tissue of blood vessel and upon ET-1 stimulation, leads to vasoconstriction and sodium retention.
- $ET_{B1}R$ mediates vasodilation. When ET-1 binds to this receptor, nitric oxide is released (also called endothelium-derived relaxing factor), natriuresis and diuresis.
- $ET_{B2}R$ mediates vasoconstriction. Under normal conditions, the endothelial ET_BR does not seem to contribute significantly to pulmonary vascular tone

There are three ERAs currently available [42]. Ambrisentan is a selective ER_AB antagonist [46]. Bosentan was the first endothelin-receptor antagonist (ERA) used for PAH therapy, approved by the FDA in 2001 [47, 48]. It is a dual ET_AR and ET_BR antagonist. Macitentan is the newest ERA approved by the FDA and is also a dual receptor antagonist. There have been no head-to-head comparisons of these medications. They are indicated for patients NYHA class II-IV and they all have demonstrated an improvement in 6-min walk distance (6MWD) [42]. Bosentan and Macitentan have also published their effect in cardiovascular hemodynamic improvement and reduction in clinical worsening (hospitalizations).

These medications have significant side effects, including teratogenic effects (a monthly pregnancy test is required for females), peripheral edema and anemia. Nonfatal hepatotoxicity has occurred with bosentan, which is metabolized in the liver and interacts significantly with drugs through the P-450 system. Ambrisentan and Macitentan have not exhibited liver toxicity in clinical trials.

Phosphodiesterase-5 Inhibitors (PDE5)

They work via the vasodilatory nitric oxide (NO) pathway. Nitric oxide is a very fast-reacting endogenous free radical, which is reduced in patients with PAH. NO in high concentration is quickly oxidized into toxic nitrite (NO_2^-) or nitrate(NO_3^-); however, at low concentrations, NO diffuses into the smooth muscle. Once inside the muscle cells, NO combines with and activate guanylate cyclase, which raises the concentration level of intracellular cGMP. Intracellular cGMP induces vasodilation via many mechanisms.

There are two PDE5 inhibitors available for PAH therapy: sildenafil and tadalafil [42]. Sildenafil was studied in treatment-naïve patients with placebo, 20, 40 and 80 mg TID for 12 weeks. An improvement in 6 MWD was seen at each dose and there was no statistical difference among doses. Therefore, the US FDA approved only the 20 mg TID dose. There was no difference in clinical worsening with Sildenafil. Tadalafil was also studied in treatment-naïve patients and only the highest dose (40 mg QD) showed improvement in 6 MWD as well as reduction in clinical worsening.

Soluble Guanylate Cyclase (sGC) Stimulator

The only medication of this class approved by the US FDA is Riociguat [42]. Riociguat is an oral sGC) stimulator with a novel dual mode of action. It can (1) directly stimulate sGC, independent of NO, and (2) increase sensitivity of sGC to NO. Riociguat thereby restores the NO–sGC–cGMP pathway, which is impaired in pulmonary hypertension. Riociguat is approved for treatment of PAH as well as chronic thromboembolic pulmonary hypertension (only medical therapy for this type of pulmonary hypertension and indicated for those that are not surgical candidates) [42]. Riociguat has shown improvement in 6 MWD, PVR and hemodynamics. The most important side effect is hypotension, therefore the medications is started at low doses and titrated slowly up to 2.5 mg TID as tolerated by blood pressure.

Prostacyclins

Prostacyclin levels are reduced in patients with PAH. The prostacyclin analogue epoprostenol markedly improved the quality of life and changed the natural history of PAH [49–52]. It was the first medication approved for the treatment of PAH and to showed improvement in survival in this otherwise fatal disease. Epoprostenol is administered by continuous intravenous infusion through an indwelling Groshong catheter and an infusion pump the size of a portable radio. It is a short-acting (3- to 6-min half-life) analogue of prostaglandin I_2, the naturally occurring vasodilator prostacyclin. It may acutely decrease mPA and PVR and increase CO and oxygen transport, but the absence of an acute initial response is not predictive of the subsequent clinical or hemodynamic outcome. The long-term hemodynamic benefits are associated with pulmonary arteriole remodeling, gradual improvement in RV function, and antiplatelet/antithrombotic effects [53]. The initial infusion therapy (Flolan) required ice packs to maintain the drug stability, however now Room Stable Epoprostenol (Veletri) is approved by the FDA and does not required ice packs [54].

Treprostinil, an analogue of epoprostenol with a longer half-life (4 h), was subsequently approved by the FDA for intravenous and subcutaneous infusion and has similar indications as epoprostenol [55]. In comparison with placebo, treprostinil has similar but less powerful effects on hemodynamic parameters than epoprostenol. It increases the distance on the 6-min walk, reduces dyspnea, and improves quality of life. The longer half-life, as compared to epoprostenol, adds a better safety margin of time to prevent cardiopulmonary collapse, in case of abrupt accidental discontinuation of drug. A major limitation of SQ treprostinil is pain at the infusion site. Recently, better tolerability has been demonstrated with pre-medication and the ability to use the site for longer periods of time [56]. Inhaled treprostinil is also available and the dose if one inhalation every 6 h. It has demonstrated in a clinical trial to showed improvement in 6 MWD, BNP and quality-of-life measurements, when was used with background therapy of Bosentan or Sildenafil [41]. Oral treprostinil has also been evaluated in clinical trials and approved by the FDA for improvement in 6 MWD [57, 58]. It is dose BID or TID and titration is limited by significant gastrointestinal side effects.

Iloprost is another prostacyclin analogue available for intravenous, oral and inhaled administration [41]. The FDA has only approved its inhaled formulation in the US. It requires 6–9 inhalations per day and has been shown to increase exercise capacity, symptoms, PVR and clinical events. Cough and headache are the most common side effects for the inhaled formulation. The dosing and very frequent administration is a limitation for its use.

Side effects are similar in all drugs, parental prostacyclin administration have more intense side effects. Most patients tolerate side effects, which include rash, flushing, jaw claudication, and diarrhea. Thrombocytopenia (platelet count range, 25–75,000 mL [3]) occurs in about 10–20% of patients. The mechanism is obscure but may be exaggerated by hypersplenism in portal hypertension and possibly by hyperperfusion of the spleen from excessive dosages and a higher cardiac output. A local skin infection, bacteremia, and septicemia occur in about 5–10% of patients taking intravenous medication. Despite the potential problems, patients are tolerant because of the improvement in well-being that occurs in more than 75%, which is accompanied by a marked reduction in mortality rate. The dose of medication is increased gradually by experienced physicians according to symptoms and tolerance of side effects. Parental prostacyclins are the drug of choice for patients with PAH who have Class IV symptoms and patients with Class III symptoms with poor prognostic features [41, 42].

Combination Therapy for Pulmonary Artery Hypertension

After initial therapy, the next steps are based on the clinical response, which is usually reassessed at 3–6 months after treatment start. The clinical response is based on the evaluation of different parameters including WHO-FC, exercise capacity, cardiac index, right atrial pressure, BNP levels, echocardiographic parameters, and perceived need for additional/change of therapy. The exact definition of clinical response is debatable but PAH experts recommend that our goals of therapy should be: (1) achieving Class I-II symptoms; (2) normal hemodynamics, right atrial pressure <8 mmHg and cardiac index >2.5–3.0 L/min/m^2; (3) 6 MWD >380–440 mts; (4) peak VO_2 > 15 mL/min/kg; (5) normal

BNP; (6) echocardiograph and/or cardia MRI demonstrating normal or near normal RV size and function [59]. If the clinical response is considered not adequate, combination therapy is considered. It is an attractive option in PAH, because three separate signaling pathways are known to be involved in the disease: prostacyclin, endothelin and nitric oxide pathway, although it is not used systematically [41].

The patterns to apply combination therapy may be sequential or upfront [41]. Sequential combination therapy is a "goal oriented" therapy and most widely utilized strategy in clinical trials as well as clinical practice. A second or third medication is added in cases of inadequate clinical results or deterioration. Upfront combination therapy is utilized in hypertension and heart failure therapy and several studies have shown benefit in PAH. The potential of upfront dual combination therapy started with the small BREATHE-2 [60], which failed to demonstrated any significant difference between upfront epoprostenol and bosentan as compared to epoprostenol alone after 16 weeks. The statistically nonsignificant trend towards an enhanced benefit of the combination regimen over epoprostenol monotherapy provided a rationale for studying upfront combination therapy further, but not enough evidence for this treatment regimen to be adopted in treatment guidelines. Upon the most important combination therapy trials are AMBITION [61] and PACES [62].

The AMBITION trial [61] included patients with PAH functional class II-III that were treatment naïve. Patients were randomized 2:1:1 to received combination upfront therapy (tadalafil+ambrisentan) or ambrisentan+placebo or tadalafil+placebo. The trial included 500 participants and showed a 50% reduction in events in the upfront combination therapy compared to monotherapy groups, which is an impressive improvement clinically. Hospitalizations for worsening PAH was the primary end-point, and the largest observed difference in occurrence between the combination-therapy group and the pooled-monotherapy group (4% vs. 12%).

In the PACES [62] trial, patients receiving IV prostacyclins for at least 3 months, and no change in dose in the last month, were randomized to sildenafil or placebo. Patients in the sildenafil group received sildenafil, 20 mg three times daily, for the first 4 weeks. Per protocol, at week 4, the dosage was titrated to 40 mg three times daily for the next 4 weeks and, at week 8, to 80 mg three times daily for the last 8 weeks. Sildenafil or placebo were continued for at least 16 weeks. The addition of sildenafil to long-term intravenous epoprostenol therapy improves exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life.

Lastly, there also has been a pilot non-randomized study on an initial triple combination therapy in 19 patients, functional class III and IV and severe haemodynamic impairment (cardiac index <2 L/min/m^2 and/or mean right atrial pressure >20 mmHg and/or PVR ≥12.5 WU) [63]. In this study, newly diagnosed PAH patients were initiated in upfront combination of IV epoprostenol, bosentan and sildenafil. IV epoprostenol and bosentan 62.5 mg BID were started at same time. Epoprostenol was titrated to 16 ng/kg/min and bosentan to 125 mg BID per protocol. Sildenafil was started on day 5 at 20 mg TID. Overall survival estimates were 100% at 1, 2 and 3 years, and respective transplant-free survival estimates were 94% at each interval. These findings are particularly relevant given that, despite increasing awareness, the majority of PAH patients are in functional class III/IV at diagnosis [28, 30]. Survival rates for patients with these hemodynamics, even in the modern treatment era, remain poor; in the French Network on Pulmonary Hypertension, for example, estimated survival was 85.7% at 1 year, 69.6% at 2 years and 54.9% at 3 years [28]. The analysis of upfront dual or triple combination therapy provide preliminary evidence that there may be a role for this regimen, particularly in patients with severe PAH. Large, randomized controlled trials are required to provide further long-term data about the survival/prognosis of patients with severe PAH treated with upfront combination therapy.

Treatment of Refractory Pulmonary Artery Hypertension

For patients that showed persistent functional class III or IV symptoms, despite therapy with parental prostacyclin and combination therapy, high-risk options include atrial septostomy and lung or heart-lung transplantation. Atrial balloon septostomy is primarily a bridge to transplantation. It should not be performed in patients with end-of-life indicators or in extremis. This procedure should be avoided in patients with mean right atrial pressure >20 mmHg or oxygen saturation at rest <85% on room air. The experience with blade septostomy was relatively poor, but balloon septostomy is performed safely by experienced teams using intraatrial ultrasound guidance [64, 65]. By creating a right-to-left intra-atrial shunt that results in arterial oxygen saturation percentage in the mid-80s, balloon septostomy increases left ventricular filling and stroke volume and "unloads" the right side of the heart.

The use of veno-arterial extracorporeal membrane oxygenation (ECMO) should be considered for selected patients with PAH and RV failure [66]. A veno-venous approach may improve oxygenation but does not unload the RV, which makes it unsuitable for this patient population. ECMO is performed usually as a bridge to transplantation, especially when used in awake patients.

Current-era specific PAH vasodilators has reduced and delayed the need for lung transplantation, however it continues to be an important option for those patients that failed

therapy and remain in functional class III-IV. Also, the etiology of PAH may guide over an earlier lung transplantation referral, for example, in scleroderma, PVOD or PCH. The overall survival post lung transplantation has is 5.5 years, and conditional on survival of at least 1 year, the half-life is 7.7 years. Both heart-lung and double-lung transplantation have been performed in PAH, although the threshold for unrecoverable RV systolic dysfunction and/or LV diastolic dysfunction is unknown. Currently, the vast majority of patients worldwide received bilateral lungs, as indicated by the ISHLT registry figures.

Practical Points

- The diagnosis of Pulmonary Hypertension requires an extensive evaluation as many cardiopulmonary disease can produce elevated pulmonary pressures.
- The diagnosis of Pulmonary Arterial Hypertension (PAH; WHO group 1) is a diagnosis of exclusion and patients with non-PAH disease should not be treated with specific PAH vasodilators
- Treatment of patients with PAH, encouraged combination therapy of prostacyclins, endothelin receptor antagonists and nitric oxide donors.

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Simple Congenital Cardiac Lesions

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Advances in cardiac surgery and the care of young patients with congenital heart disease have resulted in drastic improvement in survival of children with congenital heart disease. As a result, a greater number of children with congenital heart disease survive to adulthood. It is currently estimated that there for more adults than children with congenital heart disease in the United States. As interventional cardiology procedures and surgical techniques evolve, so will the profile of adult patients with congenital heart disease. Until the early 1980s, hypoplastic left heart syndrome was almost always a lethal diagnosis. Now, with palliative surgeries, many such children can be expected to survive to adulthood, and are beginning to populate adult congenital cardiology clinics. This chapter will discuss relatively simple congenital heart disease, including the common left-to-right shunt lesions atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), and coarctation of the aorta. More complex lesions, including tetralogy of Fallot, transposition of the great arteries, and single ventricle lesions, will be addressed in the following chapter.

Atrial Septal Defect

Isolated ASDs account for approximately 5–10% of congenital heart disease in children. It is not uncommon for atrial septal defects to be diagnosed in adulthood, as ASDs account for 30% of congenital heart disease diagnosed in adults. The most common type of ASD is a secundum defect, which occurs in the region of the fossa ovalis and accounts for 75% of all ASDs (Fig. 31.1). Ostium primum atrial septal defects are typically associated with a cleft mitral valve and occur in 15% of patients with ASD. Primum atrial septal defects occur at the lower aspect of the atrial septum at the crux of the heart (Fig. 31.2). Sinus venosus septal defects (10% of all ASDs) occur either at the entry of the superior vena cava (SVC) to the right atrium (superior sinus venous septal defect) or, less commonly, near the entry of the inferior vena cava (IVC) to the right atrium (inferior sinus venosus septal defect). Superior sinus venosus septal defects are often associated with anomalous return of the right upper pulmonary vein to the SVC, while inferior sinus venosus septal defects may be associated with anomalous return of the right lower pulmonary vein to the IVC. Rarely, a defect can occur between the coronary sinus and the left atrium (coronary sinus ASD). The direction of flow is from the left atrium into the coronary sinus and then the right atrium, with pathophysiology similar to that of other types of atrial septal defect.

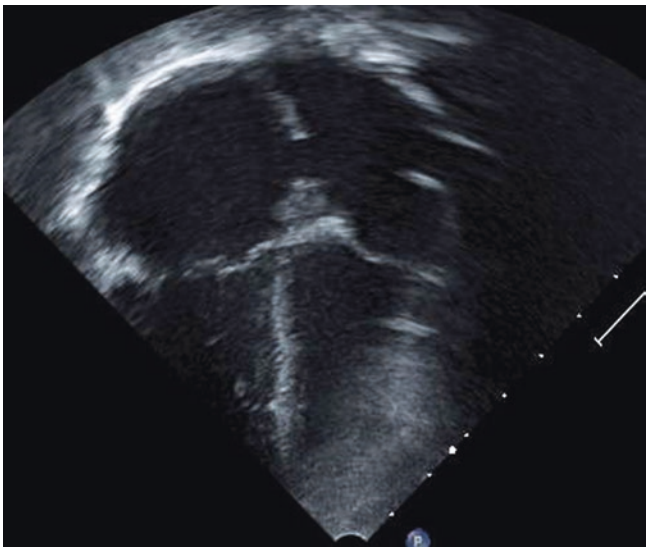

Fig. 31.1 Apical 4-chamber view of a secundum atrial septal defect

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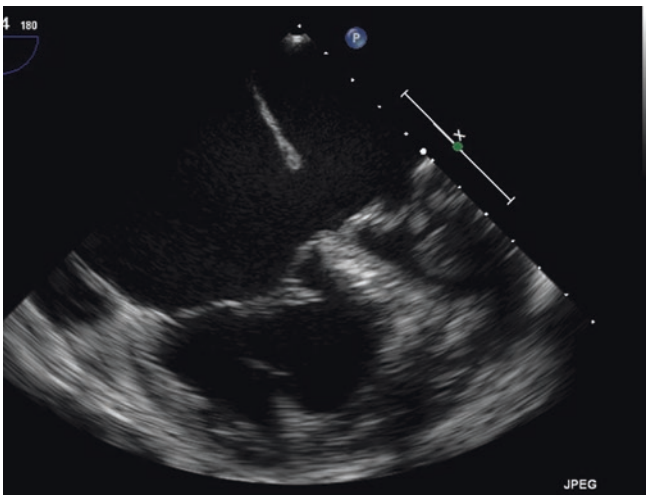

Fig. 31.2 Trans-esophageal echocardiogram view of a moderate primum atrial septal defect

A patent foramen ovale (PFO) is the result of the failure of the flap of the septum primum to seal against the septum secundum after birth. PFO is extremely common, occurring in 25% of adults between the age of 30 and 80 on autopsy studies [1]. There is the possibility of paradoxical embolism across at PFO at times when the right atrial pressure is greater than the left atrial pressure (Valsalva maneuver). PFO has been implicated in multiple disease processes; including transient ischemic attack, migraine headache, and decompression sickness [2].

Presenting Symptoms and Signs

Many adults with atrial septal defect are asymptomatic and are referred for cardiac evaluation because of a heart murmur. The pathophysiology of ASD is related to left to right shunting across the defect with increased flow through the right side of the heart, ultimately resulting in increased right atrial and ventricular chamber dimensions. The amount of shunting across the atrial septal defect is related both to the size of the defect as well as the relative compliances of the left and right ventricles. Advancing age is associated with decreased left ventricular compliance due to hypertension, ischemic heart disease, or other cardiomyopathies. This may result in increased shunting across the defect and onset of symptoms. Dyspnea on exertion is generally the most common presenting symptom for ASD, occurring in 30% of patients by the third decade of life and 75% by the fifth decade of life. Atrial fibrillation may be the presenting sign of ASD. Less common presentations include symptoms of severe right ventricular dysfunction or hypoxemia and cyanosis related to Eisenmenger syndrome (reversal of shunt due to severe pulmonary hypertension). Finally, patients may present with a cerebrovascular event or peripheral emboli as a result of paradoxical embolism through the defect.

Many of the characteristic physical findings of ASD are due to increased flow through the right side of the heart. Patients generally are acyanotic in the absence of advanced pulmonary hypertension. A right ventricular lift may be palpated. A systolic murmur of relative pulmonary stenosis is very common. It is important to note that flow across the defect is not audible given that the pressure difference between the atrial is small and the velocity of flow is low (Table 31.1). The classic auscultatory finding of significant ASD is a wide and fixed second heart sound. A loud P_2 suggests pulmonary hypertension. A diastolic murmur of relative tricuspid stenosis may be heart in large defects. In patients with primum atrial septal defect and cleft mitral valve, a regurgitant murmur of mitral regurgitation may be heard.

Helpful Tests

The electrocardiogram can be quite helpful in the diagnosis of ASD. The classic ECG finding of secundum atrial septal defect is right bundle branch block with or without right axis deviation. First degree AV block suggests the presence of a primum atrial septal defect, but may occur in older patients with a secundum defect (Fig. 31.3). A superior QRS axis (left axis deviation or extreme right axis deviation) is the hallmark ECG finding of a primum atrial septal defect. Patients with significant pulmonary hypertension may develop ECG findings of right ventricular hypertrophy.

The chest X-ray may demonstrate cardiomegaly as a result of right heart dilatation. In patients with primum atrial septal defect and significant mitral regurgitation, left atrial and ventricular dilatation may occur. Dilatation of the central pulmonary arteries and increased pulmonary vascular markings are common.

Transthoracic echocardiography is extremely useful in the diagnosis and assessment of ASD. Echocardiography may demonstrate the size and location of the defect, chamber size, direction of flow across the defect, and identify additional lesions. Right sided chamber enlargement suggests the presence of ASD or other lesion and deserves further study if transthoracic echocardiogram does not confirm a diagnosis. The subcostal views, in both the coronal and sagittal plane, may be quite helpful in the evaluation of the atrial septum. The atrial septum is parallel to the direction of imaging in the apical four chamber view, so it is not uncommon for there to be "dropout" in the area of the atrial septum. In primum atrial septal defect, careful imaging of the mitral valve should be performed to assess for cleft mitral valve. A parasternal short axis view can be quite helpful in this assessment.

Injection of agitated saline may be used to assist in the diagnosis of ASD, but is not necessary if the defect is seen

Table 31.1 Clinical symptoms, signs, and evaluation of the adult with congenital heart disease

	Common presenting symptoms	Characteristic physical examination finding	ECG findings	Chest radiograph findings	Other Helpful Tests
ASD	Dyspnea Fatigue Atrial fibrillation	Fixed Split S2	Secundum ASD: IRBBB with RAD Primum ASD: IRBBB with LAD	Cardiomegaly with shunt vascularity	Echocardiography, MRI, cardiac catheterization
VSD	Asymptomatic murmur Cyanosis if Eisenmenger's syndrome present	Systolic regurgitant murmur	RAD, RVH if Eisenmenger syndrome present	Cardiomegaly with shunt vascularity	Echocardiography, cardiac catheterization
Coarctation of the aorta	Hypertension	Blood pressure differential between upper and lower extremities	LVH	"3" sign Rib notching	MRI or spiral CT
PDA	Asymptomatic murmur	Continuous murmur Differential cyanosis if Eisenmenger syndrome	Normal RVH if Eisenmenger syndrome present	Normal	Echocardiography

ASD atrial septal defect, *CT* computed tomographic scanning, *ECG* electrocardiographic, *IRBBB* incomplete right bundle branch block, *LAD* left axis deviation, *LVH* left ventricular hypertrophy, *MRI* magnetic resonance imaging, *PDA* patent ductus arteriosus, *RAD* right axis deviation, *RBBB* right bundle branch block, *RVH* right ventricular hypertrophy

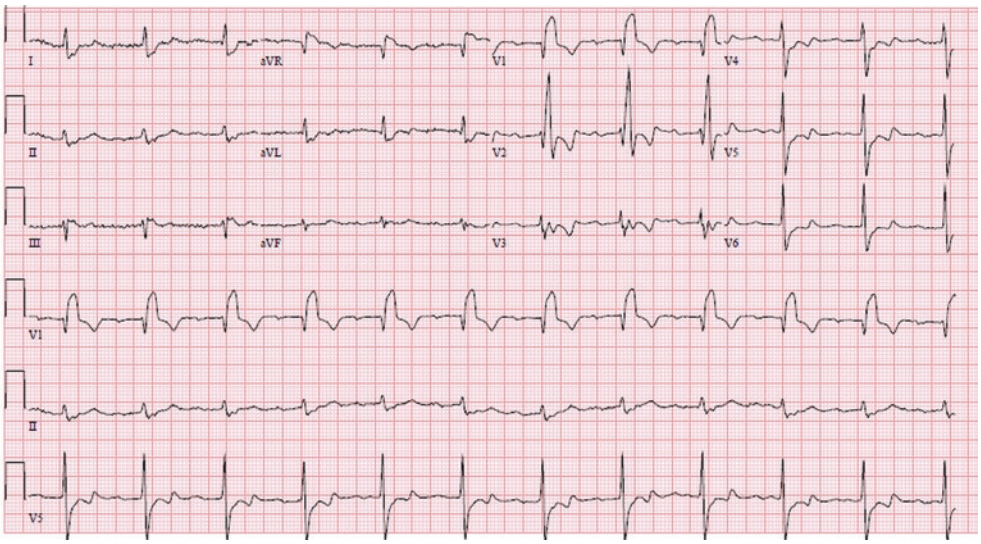

Fig. 31.3 12-lead electrocardiogram of a 71 year-old man with recent diagnosis of large atrial septal defect. There is first-degree AV block and right-bundle branch block

well with two-dimension imaging or Doppler echocardiography. An ASD may be suggested by "negative contrast washout," a clear space in the bubble-filled right atrium as a result of left to right shunting across the defect.

Transesophageal echocardiography (TEE) may be helpful in diagnosing ASD, particularly in patients with suboptimal transthoracic imaging windows. TEE can also be helpful in determining whether or not a defect is amenable to device closure, and can be used during percutaneous closure to identify anatomic structures and ensure proper device position. TEE may also identify additional lesions, such as anomalous pulmonary veins.

Cardiac magnetic resonance imaging (MRI) may also play a role in the diagnosis and evaluation of patients with ASD. In patients with borderline right ventricular size, accurate measurement of the right ventricle size may be performed. Additionally, clarification of pulmonary venous anatomy is possible. Phase-contrast imaging may be performed to estimate pulmonary and systemic blood flow and determine the ratio of pulmonary to systemic blood flow (Qp:Qs) [3].

Cardiac catheterization is not routinely necessary in the diagnosis and management of ASD. Catheterization may be performed if there is concern for significant pulmonary hypertension or if coronary angiography is required prior to surgical intervention in patients greater than 40 years of age.

Differential Diagnosis

ASD should be suspected in adults presenting with exertional dyspnea, exercise in tolerance, or new onset atrial

arrhythmias. A dilated right heart on echocardiogram or chest X-ray should raise suspicion for ASD. The differential diagnosis for a dilated right ventricle includes atrial septal defect (including secundum defects as well as the less common types), anomalous pulmonary venous connection, tricuspid regurgitation, primary pulmonary hypertension, and arrhythmogenic right ventricular cardiomyopathy. The primary differential diagnosis for the classic examination finding of a fixed split second heart sound is the presence of right bundle branch block. Careful imaging should be performed to rule out the presence of additional defects as well as to identify all pulmonary veins.

Complications

Unrepaired ASDs may be associated with significant morbidity and mortality with advancing age. Early natural history studies suggested annual mortality as high as 6% in adults greater than 40 with unrepaired atrial septal defects [4]. Complications of atrial septal defect in adults include atrial arrhythmias, progressive right ventricular dysfunction, paradoxical emboli, and the development of pulmonary hypertension (Table 31.2). As mentioned previously, atrial arrhythmias are a common presenting symptom of ASD. In a single retrospective study, atrial fibrillation was reported in 19–26% of patients (mean age of 56 years) [5]. An early natural history study reported normal PA pressures (PA systolic pressure less than 25 mmHg) in 35% of patients, mildly elevated PA pressures (PA systolic pressures 25–50 mmHg) in 43% of patients, moderately elevated PA pressures (50–75 mmHg) in 9.3% of patients, and severely elevated PA pressures (>75 mmHg) in 13% of patients [6].

Exertional dyspnea has been reported in 75% of patients, NYHA class III or IV symptoms in 23–32%, and recurrent respiratory infections in 11–14%, and paradoxical embolism in 4–8% [7]. Endocarditis is a rare complication of unrepaired atrial septal defect. Pregnancy is usually well tolerated in women with ASD, including those with unrepaired defects. Women are at risk for paradoxical embolism in the peri-partum period and should have careful attention to the prevention of deep vein thrombosis. Women with right ventricular dysfunction may be at increased risk for heart failure during pregnancy.

Therapy

Current American College of Cardiology/American Heart Association guidelines recommend closure of atrial septal defect if right atrial and right ventricular dilatation are present, with or without symptoms [8]. ASD closure may also be considered if there is a history of paradoxical embolism or orthodeoxia platypnea. ASD closure should be avoided in presence of advanced pulmonary hypertension and no evidence of left to right shunting. Patients with significant pulmonary hypertension but a net left-to-right shunt should undergo a thorough multi-disciplinary evaluation at an experienced center prior to closure of ASD. This includes patients with PA pressures less than two-thirds systemic or pulmonary vascular resistance less than two-thirds systemic vascular resistance. Some patients may require cardiac catheterization for assessment of response to pulmonary vasodilators or test occlusion of the defect.

The preferred method of closure of secundum ASD is percutaneous device closure. Device closure is not possible for primum or sinus venosus septa defects. Patients with very

Table 31.2 Inverted apical four chamber image of a patient with a large primum atrial septal defect

Condition	Recommendations for repair	Common complications	Follow-up	Endocarditis prophylaxis
ASD	All primum ASD and sinus venosus if symptomatic and Qp/Qs ≥ 1.5:1 *or*	CHF Atrial fibrillation	Every 2–5 years after repair	Only required for first 6 months after repair. Not required for unrepaired defects
	Secundum ASD if asymptomatic with big RV			
VSD	Qp/Qs ≥ 1.5:1 and symptoms	CHF Endocarditis	Every 2–5 years after repair	Only required for first 6 months after repair. Not required for unrepaired defects
	Qp/Qs ≥ 2.0:1 without symptoms	Eisenmenger's syndrome		
Coarctation of the aorta	Upper extremity hypertension and gradient ≥20 mmHg	Stroke Aortic aneurysm Aortic valve disease Endocarditis and endarteritis	Yearly with MRI or CT of aorta every 2–5 years	No
PDA	Audible murmur	Rare Eisenmenger's syndrome	Periodically	Only required for first 6 months after repair. Not required for unrepaired defects
		Rare endarteritis		

ASD atrial septal defect, *CHF* congestive heart failure, *CT* computed tomography, *MRI* magnetic resonance imaging, *PDA* patent ductus arterious, *Qp/Qs* ratio of pulmonary blood flow to systemic blood flow, *RV* right ventricle, *VSD* ventricular septal defect

large defects (stretched diameter > 34 mm) or those with inadequate atrial septal rims to support deployment of the device are not candidates for percutaneous closure. Device closure is usually done with the assistance of transesophageal echocardiography or intracardiac echocardiography. An experienced echocardiographer can be invaluable in the assessment of ASDs for device closure providing imaging support in the cardiac catheterization laboratory. Device closure has a reported success rate of 95–99% at experience centers [9–11]. If device closure is not feasible, surgical closure may be performed with excellent results. Long-term complications after ASD closure are related to the age at intervention and the intervention performed. Cardiac erosion is a potentially catastrophic complication of device closure, and may present with chest discomfort, syncope, or hemodynamic collapse. To date, approximately 100 cases of erosion after been reported in the literature [12]. The precise incidence of erosion is unknown, but is estimated to be 0.1–0.3% [12]. Although device over-sizing and insufficient retroaortic rims have been hypothesized to be related to device erosion, the cause remains controversial.

Prognosis and Follow-Up

The prognosis for patients undergoing ASD closure before 25 years of age is excellent, with hospital survivors showing normal long-term survival as compared with healthy controls. Patients undergoing ASD closure beyond the age of 25 showed increased mortality as compared with healthy controls. The 30 year survival for patients undergoing ASD closure after 25 years of age was 74%, as compared with 85% in the control group [7]. Stroke related to atrial arrhythmias was a significant contributor to mortality in this patient group.

Atrial arrhythmias remain a significant concern even after surgical or percutaneous closure. Post-operative atrial arrhythmias are more common in patients undergoing defect closure later in life. Patients undergoing surgery at age 40 or greater appear to be at the highest risk [13]. Endocarditis prophylaxis is required for the first 6 months after surgical or device closure, but may be discontinued at that point in the absence of residual shunting. Patients who underwent repair at a young age are at low risk for complications and require minimal follow-up. Periodic follow-up is required for patients repaired later in life, as well as those with atrial arrhythmias, ventricular dysfunction, or residual lesions.

Ventricular Septal Defect

Excluding bicuspid aortic valve, ventricular septal defect (VSD) is the most common form of congenital heart disease, accounting for 15–20% of all congenital heart disease. A basic understanding of the anatomy of the ventricular septum is helpful in understanding the nomenclature of ventricular septal defects. The two major components of the ventricular septum are the membranous and the muscular septum. The membranous septum is a fibrous structure located at the base of the heart immediately below the aortic valve. The muscular septum may be divided in to three components based on the three parts of the right ventricle; inlet, apical trabecular, and outlet. Multiple nomenclature systems exist, which makes terminology for describing VSDs confusing. The Society for Thoracic surgery has proposed a classification system based on the anatomic location and margins of the defect [14]. Many centers have not adopted this system, so it is important to understand where in the septum the defect occurs. Type 1 defects have also been referred to as supracristal, subarterial, subpulmonary, conal, or doubly committed defects and account for 5% of all VSDs in the Western world. Supracristal defects are immediately beneath the pulmonary valve, with the superior margin of the defect formed by the fibrous continuity of the aortic and pulmonary valves. Prolapse of an aortic valve leaflet into the defect may occur, resulting in aortic insufficiency. Supracristal defects are most common in patients of East Asian descent, accounting for 30% of VSDs in this patient population. Type 2 defects are located in the membranous septum and generally extend into the muscular septum. These defects are commonly referred to as perimembranous VSDs and account for 70% of all VSDs (Fig. 31.4). Perimembranous defects may also be associated with progressive aortic insufficiency. Type 3 defects or inlet VSDs, occur posteriorly, at the entry of the atrioventricular valves into the ventricles and account for 5–8% of all VSDs. Inlet VSDs may occur as isolated defects

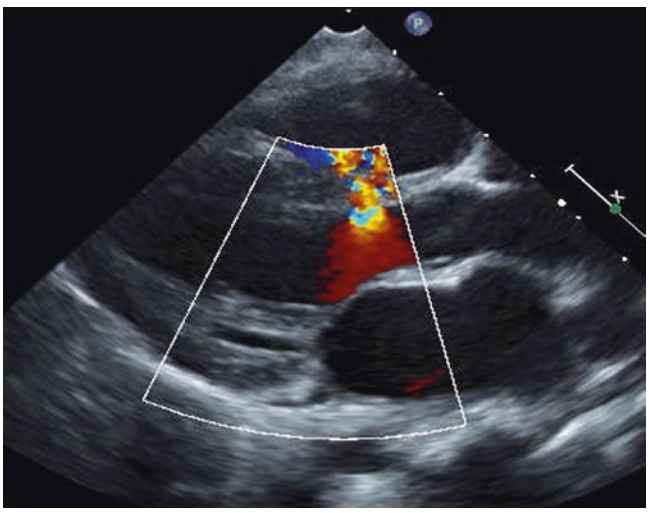

Fig. 31.4 Parasternal long-axis echocardiogram with Doppler color flow mapping view of a small to moderate perimembranous ventricular septal defect. The direction of flow is from the left ventricle to the right ventricle

or as part of a complete atrioventricular septal defect (AVSD). A complete AVSD includes an inlet VSD, primum atrial septal defect, and abnormalities of the atrioventricular valves. Both isolated inlet VSD and AVSD commonly occur in patients with Trisomy 21 (Down syndrome). Type 4 defects are located in the trabecular portion of the muscular septum and account for 5–20% of all VSDs. Muscular VSDs are completely surrounded by muscle, and are described according to their location in the trabecular septum (mid-muscular, apical, posterior, or anterior). VSDs commonly occur as isolated defects, but are a very common component of more complex lesions, including tetralogy of Fallot, transposition of the great arteries, double outlet right ventricle, and tricuspid atresia. Other lesions commonly associated with VSD include coarctation of the aorta or pulmonary valve stenosis.

Presenting Symptoms and Signs

Adult patients with isolated VSD may categorized into three broad groups. The first includes patients with significant defects which were repaired in infancy or childhood. The second is patients with small, hemodynamically insignificant defects which do not require intervention. Some of these patients may have borderline defects which may have some degree of volume overload which may raise the possibility of need for closure in adulthood. Finally, the third group includes patients with large, unrepaired defects who have developed pulmonary vascular disease and right-to-left-shunting (Eisenmenger physiology). A patient with a small defect will generally be asymptomatic but may report a history of a prominent heart murmur. The murmur of a small VSD is classically a high pitched, systolic regurgitant murmur at the left sternal border. Small defects may generate murmurs which are quite prominent. Very small muscular defects may close during systole, which result in an early systolic murmur. The examination should include careful auscultation for a diastolic murmur of aortic insufficiency, particularly in patients with supracristal ventricular septal defect. Rarely, infective endocarditis may be the presenting feature of VSD.

Patients with large, unrepaired defects and Eisenmenger physiology will generally be quite symptomatic, with cyanosis and exercise intolerance. Additional symptoms may include syncope, palpitations, or symptoms of hyperviscosity, including transient ischemic attack, stroke, or new neurologic symptoms due to cerebral abscess. Hemoptysis is a concerning symptom and may be due to pulmonary hemorrhage. Physical examination should include assessment of oxygen saturation. Peripheral clubbing is common. On cardiac examination, a right ventricular heave may be palpitated and a prominent S2 is common. Although a patient may have no murmurs, a murmur of tricuspid regurgitation may be heard. A high pitched diastolic murmur of pulmonary insufficiency (Graham-Steell murmur) may be heard at the left sternal border [15].

Helpful Tests

The ECG is usually normal in patients with small, hemodynamically insignificant defects. The ECG of patients with previously repaired perimembranous VSD commonly shows right bundle branch block as the inferior border of the patch is often secured to the area of the right bundle. In patients with VSD and pulmonary vascular disease, the ECG may demonstrate right atrial enlargement, right axis deviation, and right ventricular hypertrophy. A superior QRS axis may be present in patients with inlet ventricular septal defects and atrioventricular septal defects.

The chest radiograph is usually normal in patients with a small ventricular septal defect. In patients with a large VSD and pulmonary vascular disease, the heart size may be normal, but with dilated proximal pulmonary arteries and oligemia of the peripheral pulmonary vasculature.

Echocardiography is important in determining the location and physiology of VSDs. In patients with history of surgical repair of VSD, careful interrogation of the ventricular septum should be performed to assess for residual ventricular septal defect. Biventricular size and function should be assessed. Aneurysmal tissue of the tricuspid valve may be visualized partially or completely occluding a perimembranous ventricular septal defect. As manipulation of the tricuspid valve leaflets may be required with surgical VSD closure, quantification of tricuspid regurgitation should be performed. In patients with repaired VSD at risk for pulmonary hypertension, estimation of right ventricular pressures should be done using the peak systolic velocity of the tricuspid regurgitation jet. Assessment for aortic insufficiency should be performed in all patients, particularly those with supracristal or perimembranous defects. In patients with unrepaired defects and Eisenmenger physiology, assessment of biventricular function should be performed. A recent study showed decreased tricuspid annular plane systolic excursion (TAPSE) to be an independent predictor for poor outcomes in adults with Eisenmenger physiology [16]. Transesophageal echocardiogram may be helpful in defining ventricular septal defects if transthoracic imaging is not optimal.

Cardiac catheterization is rarely indicated in adults with VSD. Patients with lesions that are felt to be borderline for closure may undergo catheterization to assess Qp:Qs as well as right ventricular pressures. Patients with significant pulmonary hypertension who are under consideration for pulmonary vasodilator therapies may also be considered for catheterization. Patients with Eisenmenger syndrome are at

particularly high risk with cardiac catheterization and should undergo the procedure at an experienced center.

Differential Diagnosis

The differential diagnosis for ventricular septal defect will generally include lesions which present with a regurgitant systolic murmur. These include tricuspid regurgitation and pulmonary regurgitation. However, the murmur of ventricular septal defect is generally a characteristic high-pitched murmur. For adult patients presenting with cyanosis and a concern for Eisenmenger, it is important to rule out the presence of right ventricular outflow tract obstruction. A patient with tetralogy of Fallot or a related lesion would likely have a protected pulmonary vascular bed and be a candidate for definitive repair. Such a patient would likely have an ejection-type murmur as opposed to a regurgitant murmur.

Complications

Most patients with repaired ventricular septal defect do quite well. Patients with significant VSD who underwent late repair may develop progressive pulmonary vascular disease and deserve close follow-up [17]. Additionally, patients with perimembranous VSD should be followed for the development of subpulmonary obstruction (double chamber right ventricle), which may present in adulthood [18]. Although heart block may occur at the time of surgery, with pacemakers required in 1.1% of patients, late heart block extremely is rare in patients with repaired VSD [19]. Infective endocarditis (IE) is an important complication in patients with unrepaired VSD, with an incidence of 1.9 per 1000 patient years [20]. IE is more common in patients with unrepaired VSD and aortic insufficiency (incidence of 3.5 per 1000 patient years) and less common in patients with repaired VSD (incidence of 0.75 per 1000 patient years). A study of patients with repaired VSD and endocarditis demonstrated that 22% were known to have a residual VSD leak. Infective endocarditis should be suspected in patients with fever and or unexplained constitutional symptoms. Progressive aortic insufficiency may occur in patients with perimembranous or supracristal VSDs. Finally, some operative repairs may involve manipulation of the tricuspid valve and tricuspid insufficiency may occur later in life.

Therapy

Ventricular septal defects rarely require closure in adulthood. Surgical closure should be performed if the Qp:Qs is greater than 2:1 and signs of left ventricular volume overload are present [8]. Closure should not be performed in patients with severe irreversible pulmonary hypertension. Recent guidelines recommend closure of VSD if a patient has had one episode of infective endocarditis. This is a class I recommendation in the American College of Cardiology/American Heart Association guidelines and a class IIa recommendation in the European Society of Cardiology Guidelines [8, 21]. Surgical closure is preferred for most defects. Device closure may be performed for muscular defects or defects not easily accessible for the surgeon. Device closure has been reported for perimembranous closure, but is associated with a high risk of heart block and valve insufficiency as compared with surgical closure [22, 23]. For patients with double-chambered right ventricle, surgical intervention should be performed asymptomatic patients with a peak Doppler gradient of 60 mmHg and a mean gradient of 40 mmHg [8]. Symptomatic patients should undergo repair if the peak mid-ventricular gradient is greater than 50 mmHg or the mean gradient is greater than 30 mmHg. It should be noted that it may be difficult to align with the Doppler signal, and that collaboration of findings with the peak regurgitant velocity of the tricuspid valve can be quite helpful.

For patients with large unrepaired VSD and Eisenmenger physiology, a minimally interventional strategy has historically been recommended. Recent studies have demonstrated benefit of pulmonary vasodilators in exercise capacity for patients with Eisenmenger syndrome due to a variety of underlying congenital lesions. The BREATHE-5 trial demonstrated improvement in 6-min hall walk performance as compared with placebo [24]. A more recent retrospective trial suggested survival benefit for patients receiving pulmonary vasodilators [25]. A total of 229 patients were enrolled, of which 68 received pulmonary vasodilators (some received bosentan and some received sildenafil). Mortality occurred in 3% of patients on pulmonary vasodilators and 31% of patients who did not. Patients with Eisenmenger syndrome should undergo surgical procedures only at centers experienced in the care of patients with complex congenital heart disease as they are at significantly increased risk of complications with anesthesia. Patients should have careful monitoring of their hematologic status with monitoring for and treatment of iron deficiency anemia. Prophylactic or scheduled phlebotomy should be avoided, and reserved for patients with symptomatic hyperviscosity or to optimize hemostasis prior to surgical intervention. Bronchoscopy should be avoided if patients present with hemoptysis.

Prognosis and Follow-Up

Most patients with unrepaired VSD do well, although as many as 25% may develop late complications including endocarditis, progressive aortic regurgitation, left ventricular

dysfunction, or atrial arrhythmias [26]. Patients who underwent VSD closure in childhood and have normal pulmonary pressures should have normal life expectancy. Patients with VSD and elevated pulmonary artery pressures have a more guarded prognosis. Adults with unrepaired defects and Eisenmenger syndrome are at particularly high risk. The actuarial survival for adults with Eisenmenger syndrome has been reported to be 94% at age 40, 74% at age 50, and 52% at age 60 [27]. Sudden cardiac death occurred in 30% of patients, with death due to congenital heart failure in 25% of patients, and hemoptysis in 15%.

Patients with small, nonrestrictive VSDs and those who have had VSD closure should be monitored periodically with auscultation, ECG, chest radiography, and echocardiography for potential progression of aortic insufficiency, new development of subpulmonic stenosis, deterioration of left and right ventricular function, and arrhythmias. Patients with Eisenmenger syndrome should be seen at least yearly at a center experience in the care of adults with congenital heart disease [8]. Endocarditis prophylaxis is indicated for patients with unrepaired VSD and Eisenmenger physiology and patients with repaired VSD and evidence of a residual defect [28]. Prophylaxis is also indicated for patients with VSD and a history of previous infective endocarditis.

Coarctation of the Aorta

Approximately 20% of all cases of coarctation of the aorta are diagnosed in adolescence and adulthood. In the adult, coarctation of the aorta is characterized by a narrowing of the descending thoracic aorta distal to the left subclavian artery at the site of the ligamentum arteriosum. The narrowing is composed of a discrete ridge of tissue extending into the aortic lumen (Fig. 31.5). In rare cases, the patient may have hypoplasia of the aorta proximal to the subclavian artery, which may extend distally. Coarctation is two times more common in men than in women, but it is the most common congenital cardiac anomaly in individuals with Turner's syndrome (chromosomal XO). A bicuspid aortic valve is present in 50–85% of individuals with coarctation. Other non-cardiac abnormalities associated with coarctation include berry aneurysms of the circle of Willis in as many as 10% of patients and aneurysm of the ascending aorta with or without dissection (most often in conjunction with bicuspid aortic valve and hypertension) [29].

Presenting Symptoms and Signs

Other than upper extremity hypertension, most adults with coarctation are asymptomatic before the second or third decade of life. Coarctation of the aorta is suspected when

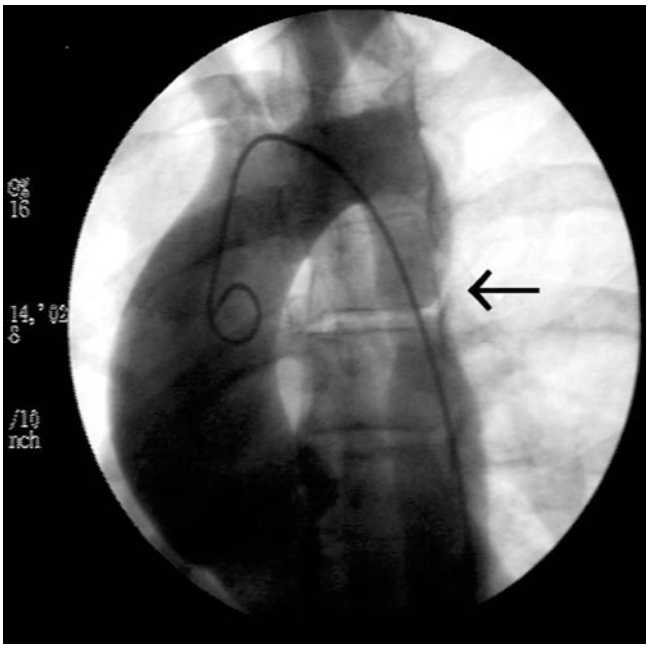

Fig. 31.5 Angiogram of the aorta from the posteroanterior projection. A discrete ridge of tissue is noted distal to the ostium of the left subclavian artery at the *arrow*

hypertension is detected on routine physical examination in the upper extremities (in patients with a discrete ridge distal to the left subclavian artery) or only in the right upper extremity (in patients with hypoplasia of the transverse portion of the arch). If hypertension is severe, the patient may experience headache, dizziness, epistaxis, or symptoms of congestive heart failure. If the coarctation is severe and collateral vessels are few, the patient may experience lower extremity fatigue or claudication. Rarely, the presenting symptom of untreated coarctation in the adult can be catastrophic, with aortic dissection or rupture, subarachnoid hemorrhage, myocardial infarction from premature coronary artery disease, or infective endocarditis. On physical examination, the individual has systolic hypertension in the right or both arms and a widened pulse pressure. The systolic pressure of the legs is diminished, although the diastolic pressures in the upper and lower extremities are usually similar. Femoral arterial pulses are diminished or absent, and there is a delay between the brachial and femoral pulse upstrokes. However, it is important to remember that femoral pulses may be fairly normal and the systolic pressure gradient between the arms and the legs may not be excessive if extensive collateral vessels have developed. If prestenotic dilation of the aorta is marked, a pulsatile aorta may be palpated in the suprasternal notch with a systolic thrill. On cardiac examination, the left ventricular impulse may be hyperdynamic. A systolic ejection click from the bicuspid aortic valve can be heard with an aortic ejection murmur and/or diastolic decrescendo murmur if either aortic stenosis and/or

insufficiency are present. A harsh, late systolic murmur from the coarctation is usually audible loudest in the posterior left interscapular region at the site of the aortic narrowing, but also may be heard at the left sternal border. A crescendo-decrescendo systolic murmur may be heard widely throughout the back and chest from large intercostal collateral arteries.

Helpful Tests

The ECG may be normal or display left ventricular hypertrophy and/or left atrial enlargement. The pathognomonic chest radiographic abnormality is the "3 sign" on the posteroanterior view: the upper limb of the "3" is caused by prestenotic dilation of the aorta or the left subclavian artery, followed by the indentation of the coarctation and poststenotic dilation of the aorta, which forms the lower limb of the "3." Resorption of bone from increased flow through intercostal arteries causes the characteristic notching of the posterior of ribs three through eight bilaterally. If the left subclavian artery arises below the coarctation, rib notching may occur only on the right side. Because the anterior intercostal arteries do not travel in the costal grooves, anterior rib notching does not occur. If the coarctation is anatomically located in the abdominal aorta, rib notching is observed in the lower ribs.

From the suprasternal notch view (a view not always part of the standard adult echocardiographic examination), the sensitivity for visualization of the coarctation site is 87% by transthoracic echocardiography. Turbulence at the site of narrowing will be evident on color-flow Doppler echocardiograms. Persistent flow in the descending or abdominal aorta throughout diastole on spectral Doppler echocardiography is consistent with the diagnosis of coarctation. A gradient across the coarctation may be measured by continuous-wave Doppler imaging. However, if the high proximal aortic velocity is not taken into account, Doppler imaging may overestimate the "true" gradient across the narrowing. In addition, in the presence of large collateral vessels, Doppler also may underestimate the true anatomic severity of the obstruction. Finally, the status of the aortic valve, left ventricular mass and function, and ascending aorta can be ascertained by echocardiography.

Magnetic resonance angiography or spiral computed tomographic scanning are imperative for visualizing the entire aorta, to assess for aneurysm and abnormalities of branch vessels. Aortography with hemodynamic measurements of the gradient, evaluation of branch vessels, and identification of collateral arteries should be performed before intervention. In most adults, coronary angiography should be performed before surgery because premature coronary artery disease is prevalent.

Differential Diagnosis

Although the differential diagnosis of hypertension in the young adult includes essential hypertension and other secondary causes of hypertension, coarctation of the aorta is suspected when differential blood pressures and pulses are detected in the upper and lower extremities. In rare cases, a coarctation of the aorta may be confused with a "pseudocoarctation" caused by tortuosity and "buckling" of the descending thoracic aorta without true narrowing or a gradient. Aortography with pressure measurements across the "coarctation" clarifies the diagnosis in these patients.

Complications

Untreated coarctation of the aorta is associated with very high mortality rate: 75% at age 50 years and 90% by age 60 [30]. Before the age of 30, coarctation-related death usually results from aortic rupture, infective endocarditis of the bicuspid aortic valve or endarteritis at the coarctation site, or cerebral hemorrhage from ruptured berry aneurysm. After 30 years of age, congestive heart failure is common, and two-thirds (2/3) of affected adults older than 40 years have symptoms of heart failure [31]. Hypertension with possible secondary organ system involvement is universal in older adults with untreated coarctation. Aortic dissection at the coarctation site or the noncoarcted proximal ascending aorta is common and can occur in women during pregnancy. Approximately 10% of individuals, whether they undergo coarctation repair or not, will require aortic valve replacement later in life. Premature coronary artery disease may lead to myocardial infarction in affected young men in the second or third decade of life. The risk of hemorrhagic stroke persists even after repair.

Therapy

All patients with coarctation of the aorta who have upper extremity hypertension and an upper-to-lower extremity gradient or directly measured gradient of at least 20 mmHg across the coarctation should have repair. In most adults, the preferred method for treatment of coarctation is either the use of balloon-expandable stents or surgical repair [32, 33]. Because the coarctation is more fibrotic and less distensible than in children, balloon angioplasty alone is much less effective in adults than in children. Surgical repair is associated with low mortality rate (less than 1%) and, rarely, with paraplegia from spinal cord ischemia (0.4%), a more common complication in patients with poorly developed collateral vessels [34].

Percutaneous balloon dilatation of native aortic coarctation may be the initial catheter based intervention performed in adults with coarctation. In one study of 27 adults, the procedure was successful initially in 23 patients [35]. After balloon angioplasty, recoarctation is common, developing in 23% of patients in one study [36]. Late aneurysm formation has also been reported. The use of endovascular stent implantation for coarctation has resulted in excellent immediate and intermediate outcomes with little restenosis and few immediate complications [37, 38]. Complications of catheter based therapy for coarctation have included stent migration, aortic disruption, pseudoaneurysm of the femoral artery access site, and stroke [37–40]. Covered stents are of potential benefit in the lesion to decrease with risk of aneurysm or dissection. Early studies of covered stents in the management of coarctation are promising, although covered stents remain under study and are not yet approved for routine use in the United States [41].

Although surgical repair is effective in treating adults with coarctation of the aorta, in most centers, the use of endovascular stents has become the preferred method for treating the adults with coarctation of the aorta (Fig. 31.6a, b). The types of surgical repair that are used to treat the adult with coarctation include the following: extended end-to-end anastomosis, subclavian flap, Dacron patch aortoplasty, and interposition graft Percutaneous balloon angioplasty alone does not result in good long-term outcomes in most adults. Endocarditis prophylaxis is required for adults within 6 months of repair with patch material or stent placement [28].

Prognosis and Follow-Up

Late survival after repair of aortic coarctation is influenced by age at time of repair and the presence of associated lesions including: aortic valve disease, early coronary artery disease, aneurysm of the ascending aorta or at the repair site, recoarctation, and cerebral aneurysm. Of patients who undergo repair of coarctation in childhood, 83% survive 25 years, in comparison with a 25-year survival rate of 75% among those who undergo repair between the ages of 20 and 40 and a 15-year survival rate of 50% among patients who undergo repair after 40 years of age [22]. Late deaths after coarctation repair are related to: coronary artery disease, sudden from unknown cause, heart failure, ruptured of aortic aneurysm either in the ascending aorta or at the repair site, stroke, at the time of repair of associated cardiovascular lesion, and endocarditis [42–44].

Although hypertension resolves or lessens in severity in many patients after repair, blood pressure response is dependent on age at the time of surgery. Among patients who undergo coarctation repair during childhood, the incidences of normotension are 90% at 5 years, 50% at 20 years, and 25% at 25 years after surgery. Of patients who do not undergo repair until after age 40, 50% have persistent hypertension, and most others have a hypertensive response to exercise, although the need for antihypertensive medication is reduced [42, 45]. Recoarctation after surgical repair of the adult is generally infrequent, averaging 3–5% in most studies [46]. In one study of 891 patients who underwent surgical repair

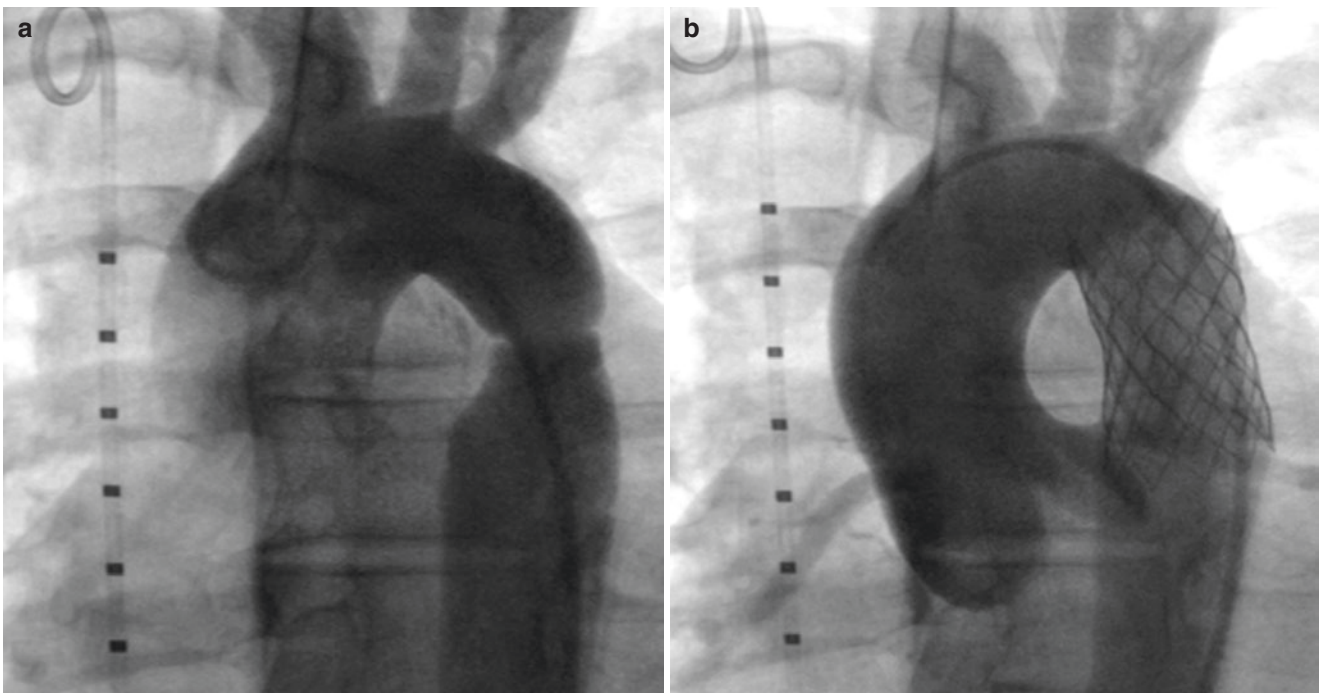

Fig. 31.6 Angiograms of patient with coarctation of the aorta prior to (**a**) following (**b**) percutaneous angioplasty and stenting

with a Dacron patch aortoplasty and were monitored for up to 24 years, aneurysms formed at the site of repair in 48 patients (5.4%) [47]. Of these, 30 patients underwent reoperation, and there were four deaths. All 18 patients who did not undergo aneurysm repair died of aneurysm rupture. Because of the high risk of late aneurysm formation, Dacron patch aortoplasty is rarely used today to repair coarctation. Aneurysms also have been reported after placement of aortic stents [37, 38].

All adults with coarctation of the aorta should be monitored yearly for complications or sequelae of the repair; for the development of other cardiovascular complications, including aortic valve stenosis or insufficiency, cerebral aneurysm rupture, and aneurysm of the ascending aorta; and for aggressive treatment of hypertension and modification of other risk factors for coronary atherosclerosis. Women with coarctation who wish to become pregnant should undergo coarctation repair before conception because of the risk of aortic dissection and rupture. Periodic echocardiography may be required for the assessment of progression of aortic valve disease. The American College of Cardiology/American Heart Association guidelines recommend magnetic resonance angiography or computed tomographic scanning at baseline and every 5 years to study the entire thoracic aorta [8]. All patients with aneurysm formation at the site of prior coarctation surgery or stent placement should be monitored carefully with consideration for reoperation with aneurysm repair or placement of cloth covered stent graft.

Patent Ductus Arteriosus

The ductus arteriosus is a fetal structure that in utero permits right ventricular output to bypass the lungs and be directed down the descending aorta to the placenta. Anatomically the ductus connects the main pulmonary artery to the descending aorta. At birth, as arterial oxygen levels increase, the ductus begins to constrict at its pulmonary end and in most infants is usually closed within 72 h after birth. The ductus has an increased likelihood of remaining patent in the following situations: twin pregnancies, premature and low birth weight infants, infants born at high altitude, infants with chromosomal anomalies such as Downs syndrome, infants with maternal rubella exposure, and other conditions. If the duct does not close spontaneously by 6 months of age, it is very likely to remain patent unless closed by either surgical or catheter based interventions.

Presenting Symptoms and Signs

In many adults, a tiny patent ductus arteriosus (PDA) may be found serendipitously on echocardiography or CT scans of the chest performed for other reasons (Fig. 31.7). These PDA's are referred to as "silent" PDA's and require no follow-up or therapy. Individuals with a soft continuous murmur and a PDA that anatomically is small (1.5 mm or less) are usually asymptomatic and their only long term risk is the potential for developing endocarditis. If the duct is of moderate size and was not closed in childhood, later in life, the individuals may present with symptoms of left ventricular volume overload from the left-to-right shunt, including dyspnea, effort intolerance, fatigue, palpitations, and left-sided heart failure. If the adult has had a large PDA since childhood they will invariably develop irreversible pulmonary hypertension, symptoms of right-sided heart failure and ultimately develop Eisenmenger's syndrome.

In patients with small PDAs, jugular venous pressure is normal. The first and second heart sounds are usually normal. A continuous murmur is heard in the second left intercostal space, with a crescendo beginning immediately after S1, peaking at or shortly after S2, and with a decrescendo throughout diastole. The murmur is usually described as having a machinery-like quality. In the patient with a moderate to large shunt and low pulmonary vascular resistance, peripheral pulses are bounding and the pulse pressure is widened. The left ventricular impulse also is hyperdynamic. With a large left-to-right shunt, an aortic flow murmur and a diastolic rumble of increased mitral flow may be heard. If pulmonary hypertension develops and the pulmonary and systemic pressures equalize, the continuous murmur

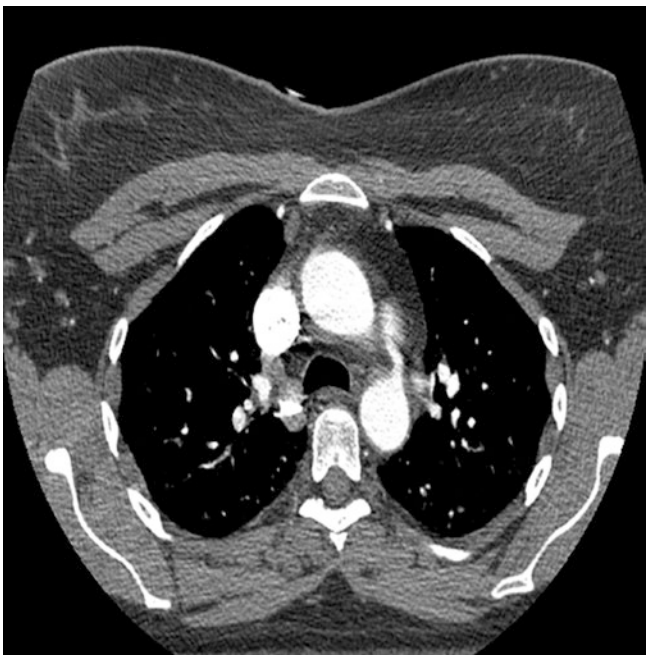

Fig. 31.7 CT Pulmonary Angiogram in an adult with incidental diagnosis of a small patent ductus arteriosus(arrow). The ductus is a communication between the descending aorta and the base of the left pulmonary artery

diminishes and may be either heard only in systole or not at all. When pulmonary resistance increases such that it is greater than systemic vascular resistance, then the shunt direction reverses and becomes predominantly right to left. In this situation, the individual may develop cyanosis and clubbing or the lower extremities but not of the head and upper extremities (differential cyanosis).

Helpful Tests

The ECG is usually normal in the patient with a small PDA. In individuals with a moderate PDA the ECG will develop a pattern consistent with left ventricular volume overload with left atrial enlargement. Right ventricular hypertrophy with a classic "strain" pattern is seen in patients with a large PDA and pulmonary artery hypertension who have Eisenmenger's physiology. The chest radiograph is also usually normal if the shunt is small. With a moderate PDA, there is cardiomegaly, increase pulmonary vascularity and left atrial enlargement. If the individual has Eisenmenger's syndrome, the heart size will be normal to mildly enlarged with prominent central pulmonary arteries and decreased peripheral vascularity. Occasionally, calcification of the ductus may be observed on chest radiographs in older adults. Transthoracic echocardiography is sensitive and specific for the detection of even tiny PDAs. Although the ductus itself is not always visualized, a high-velocity, continuous, jet is usually evident in the main pulmonary artery near the take-off of the left pulmonary artery branch (Fig. 31.8). Pulmonary artery systolic pressure can be estimated with the modified Bernoulli equation by subtracting the product of four times the square of the peak velocity across the duct from the patient's systolic blood pressure measured by sphygmomanometer or by adding estimated right atrial pressure to four time the square of the peak velocity of the tricuspid valve regurgitant jet. In very rare cases, patients with PDAs may develop an aneurysm of the ductus, which can be seen on chest radiographs or by magnetic resonance imaging or computed tomography.

Differential Diagnosis

The differential diagnosis of PDA is the same as that of the continuous cardiac murmur and includes coronary artery-to-pulmonary artery fistula, ruptured sinus of Valsalva, bronchial systemic-to-pulmonary artery collateral vessels, and venous hums. The diagnosis is usually easily made by transthoracic echocardiography.

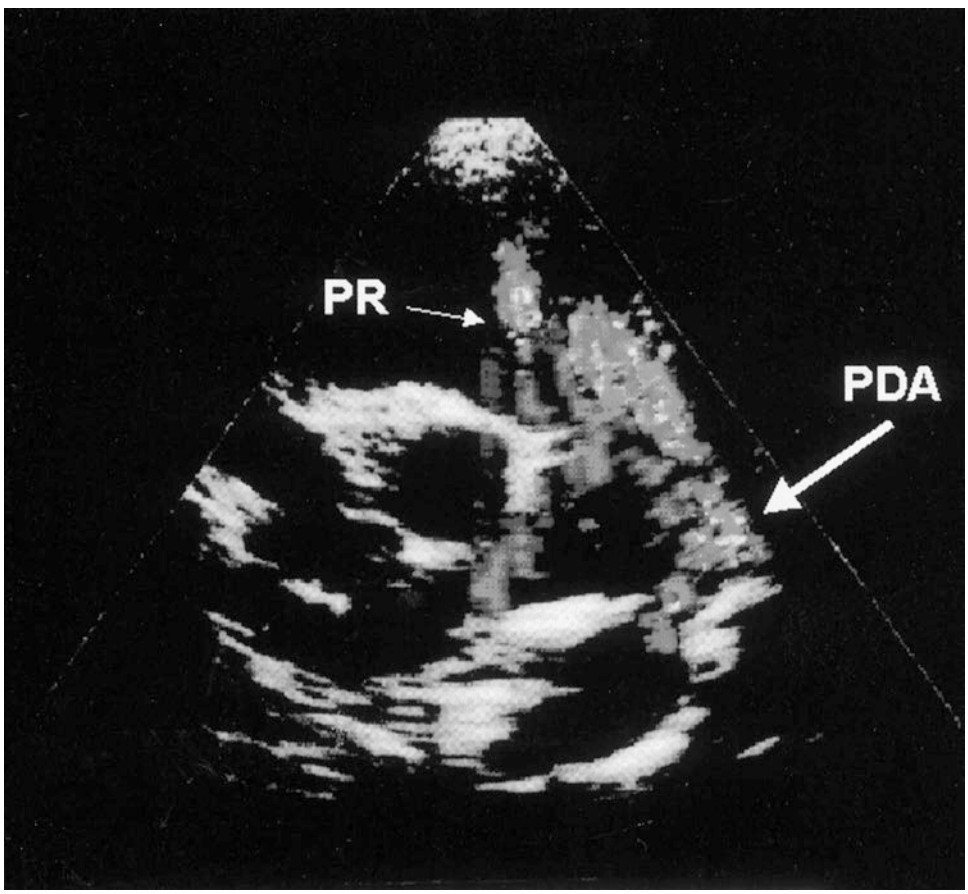

Fig. 31.8 Transthoracic echocardiogram in the parasternal short-axis view at the level of the great arteries of a small patent ductus arteriosus (PDA). A dilated pulmonary artery is noted. Two jets are apparent in diastole on the color-flow Doppler echocardiogram. The first, at the level of the pulmonic valve, is from pulmonic regurgitation (PR). The second high-velocity turbulent jet entering the main pulmonary artery near the left pulmonary artery branch at the bifurcation is from left-to-right flow from the descending thoracic aorta to the pulmonary artery through the PDA

Complications

In individuals with a continuous murmur and echocardiography evidence of a small PDA, infective endarteritis is infrequent, occurring in only 2 of 270 patients followed-up for over 33 years in Sweden [48]. In patients with moderate to large PDAs, the major risk is of developing progressive pulmonary vascular obstructive disease with right-sided heart failure and complications of cyanosis associated with Eisenmenger's syndrome. In rare cases, a large aneurysm of the ductus may form and rupture, causing hemoptysis and death.

Therapy

"Silent" PDA require no specific therapy. All individuals who have a continuous murmur, echocardiographic evidence of a PDA (regardless of size) and who do not have irreversible pulmonary hypertension should have their PDA closed. Closure should also be considered if a patient has a previous history of endarteritis [8]. Surgical closure of PDA is highly effective, but in adults has an operative mortality rate of 1.0–3.5% [49]. The major surgical complications include bleeding and damage to the recurrent laryngeal nerve. Percutaneous transcatheter closure of PDA with a variety of devices (Gianturco coil and Grifka-Gianturco vascular occluder, Cook, Inc., Bloomington, Indiana; and AMPLATZER Ductal Occluder and AMPLATER Vascular Occluder, AGA Medical, Golden Valley, Minnesota) have been shown to be highly effective in the short and long term and is very safe in patients with PDAs smaller than 8 mm [50–52]. Currently percutaneous closure of PDA is considered the procedure of choice in all patients with a PDA diameter of less than 8 mm. The major risk of device closure is device embolization.

Prognosis and Follow-Up

Life expectancy is normal in patients with small PDAs and those that were closed before the development of pulmonary hypertension. In 117 adults with PDA, 39% of those whose PDAs were not closed had died by a mean follow-up time of 36 years [53]. Only 34% of nonsurgically managed survivors were asymptomatic at follow-up. Patients who do not have small PDAs closed should be monitored periodically by auscultation and possibly echocardiography. Individuals who have undergone device closure of a PDA should be followed for 1 year after the procedure to ensure continued closure of the duct, as recanalization may occur. Current guidelines do not recommend antibiotic prophylaxis for patients with isolated patent ductus arteriosus. Prophylaxis should be used for 6 months after surgical or device closure [28].

Practical Points

- Closure of ASD is recommended for adults with secundum ASD and right-sided heart enlargement who do not have fixed pulmonary hypertension. A dilated right ventricle deserves a thorough evaluation for anatomic lesions including all types of atrial septal defects and anomalous pulmonary veins.
- Patients with Eisenmenger syndrome are at high risk and times of non-cardiac surgery, and should be referred to an experience center. Phlebotomy should be avoid except in instances of symptomatic hyperviscosity.
- Patients with coarctation of the aorta should have lifelong follow-up for multiple lesion-specific complications, including hypertension, recoarctation, repair site complications, ascending aortic aneurysm, and early coronary artery disease.
- Percutaneous closure of PDA at experienced centers is the preferred method for closure in most adults.
- For patients with left-to-right shunt lesions, endocarditis prophylaxis is indicated for patients who have residual defects at patch margins. Patients with completely closed defects do not require prophylaxis. Prophylaxis is also required for patients within 6 months of percutaneous or surgical closures of ASD and VSD.

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Complex Congenital Lesions

32

Timothy B. Cotts

Advances in cardiac surgery which began in the 1940s have allowed for the long-term survival of patients with complex, cyanotic congenital heart disease. This chapter reviews three relatively common complex lesions: Tetralogy of Fallot, Transposition of the great arteries, and Single ventricle lesions. An overview of the diagnosis of these lesions is shown in Table 32.1, while an overview of complications and therapeutic options is shown in Table 32.2.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the prototypical lesion of congenital heart disease in adults. TOF is the most common form of cyanotic congenital heart disease, accounting for approximately 5–10% of all congenital heart disease. The introduction of palliative surgeries in the 1940s and definitive repairs in the mid-1950s has resulted in the survival of patients with TOF beyond the 6th and 7th decade of life [1, 2]. The four components of tetralogy of Fallot include a large VSD, right ventricular outflow tract obstruction, aortic override, and right ventricular hypertrophy. From a pathologic standpoint, the sole lesion responsible for the tetralogy is anterior malalignment of the conoventricular septum, which creates the ventricular septal defect, causing right ventricular outflow tract obstruction and aortic override with subsequent right ventricular hypertrophy (Fig. 32.1). When an atrial septal defect is present (10% of cases) the complex has historically been referred to as pentalogy of Fallot. If a right aortic arch is present, which occurs in 25% of patients with TOF, 22q11 deletion (associated with DiGeorge syndrome) should be considered. Coronary artery anomalies are common, occurring in approximately 5–10% of patients, the most common of which is a left anterior descending coronary artery arising from the right coronary artery and passing over the right ventricular outflow tract. This can have important implications for repairs involving surgical manipulation of the right ventricular outflow tract.

Presenting Symptoms and Signs

The vast majority of adults with TOF have previously undergone surgical intervention. Rarely, adults may present for medical care with no previous surgery, or after only having had a palliative procedure such a systemic-pulmonary shunt. Unrepaired or palliated patients will generally present with exercise intolerance and cyanosis. A history of paradoxical emboli as a result of obligatory right-to-left shunt include stroke, brain abscesses, or other thromboemboli may be present. There may also be a history of infective endocarditis. The physical examination will be characteristic of long-standing right to left shunt, and include significant cyanosis, clubbing, and laboratory findings of erythrocytosis. A patient with a history of previous surgical palliation may have a lateral thoracotomy and abnormal pulse and blood pressure in an upper extremity if the subclavian artery has been sacrificed during the course of a palliative subclavian artery-to-pulmonary artery (classic Blalock-Taussig) shunt. Cardiac examination findings may include a pulmonary systolic ejection click and significant murmur of pulmonary stenosis.

Most patients who have undergone complete surgical repair are asymptomatic or have minimal cardiac symptoms. Important symptoms include exercise intolerance, palpitations, and syncope. Syncope may be indicative of a serious ventricular arrhythmia and deserves further

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Table 32.1 Clinical symptoms, signs, and evaluation of the adult with complex congenital heart disease

	Common presenting symptoms	Characteristic physical examination finding	ECG findings	Chest radiograph findings	Other Helpful Tests
TOF	Uncorrected: dyspnea and cyanosis Corrected: dyspnea	Uncorrected: single P2 pulmonic flow murmur Corrected: murmurs of pulmonic insufficiency	Uncorrected: RVH Corrected: RBBB with wide QRS	Uncorrected: RVH with decreased pulmonary vessels Corrected: depends on sequelae of operation	Echocardiography, MRI, cardiac catheterization
D-TGA	Mustard or Senning: Progressive dyspnea Palpitation Arterial Switch: Exercise intolerance Chest discomfort	Mustard or Senning: RV heave Prominent S2 Murmur of AV valve insufficiency Arterial switch: Pulmonary outflow murmur	Mustard or Senning: RAD RVH Arterial Switch: Often Normal Possible ST-T wave changes or Q-waves	Mustard or Senning: Often normal Can have RVH or Cardiomegaly Arterial Switch: Often Normal	Mustard or Senning: Echocardiogram MRI Cardiac catheterization Arterial Switch: Echocardiogram Exercise Testing Cardiac Catheterization
Single Ventricle Fontan Procedure	Unoperated Patients: Cyanosis Fontan: Palpitations Exercise intolerance	Single S2	Depends on underlying anatomy	Depends on underlying anatomy	Echocardiogram Cardiac Catheterization MRI

ECG electrocardiographic, *IRBBB* incomplete right bundle branch block, *LVH* left ventricular hypertrophy, *MRI* magnetic resonance imaging, *RAD* right axis deviation, *RBBB* right bundle branch block, *RVH* right ventricular hypertrophy, *TOF* tetralogy of Fallot, *D-TGA* D-transposition of the great arteries

Table 32.2 Treatment, complications, and follow-up of adults with congenital heart disease

Condition	Recommendations for repair	Common complications	Follow-up	Endocarditis prophylaxis
TOF	All affect adults who have not previously undergone repair As needed for sequelae of operation	Pulmonary insufficiency RV failure Atrial and ventricular dysrhythmias	Yearly	Yes, if patient has undergone pulmonary valve replacement
D-TGA	All adults will have had previous repairs	Atrial Switch Procedures: Arrhythmias RV Dysfunction Tricuspid Regurgitation Baffle leaks or stenosis	At least yearly	No (for most patients)
Single Ventricle Fontan Procedure	Most patients will have previously had procedures	Atrial arrhythmias Ventricular dysfunction Atrial thrombi Protein losing enteropathy Cirrhosis Chronic venous stasis Plastic bronchitis	At least yearly	Yes

MRI magnetic resonance imaging, *RV* right ventricle, *TOF* tetralogy of Fallot, *D-TGA* D-Transposition of the great arteries

evaluation. Additionally, patients may have symptoms of right ventricular failure including abdominal bloating, lower extremity edema, or chronic venous stasis. Physical examination should include a careful assessment of the chest for surgical scars which help the clinician to understand the surgical history of it is not immediately available. Patients with increased right ventricular diastolic pressures may have increased jugular venous pressure. On cardiac examination, a thrill should raise suspicion for significant right ventricular outflow tract obstruction. A right ventricular heave or lift may be present. Fixed splitting of the S2 is very common and is due to right ventricular volume overload or right bundle branch block. A systolic ejection murmur of pulmonary stenosis may be heard. A low pitched diastolic murmur is common and is indicative of pulmonary insufficiency. A high pitched diastolic murmur suggests aortic insufficiency. A regurgitant murmur could be consistent either tricuspid regurgitation or residual VSD (usually a characteristic, high pitched murmur) (Table 32.1). As above, upper extremity blood pressures and pulses may be decreased if the patient has previously had a classic Blalock-Taussig shunt

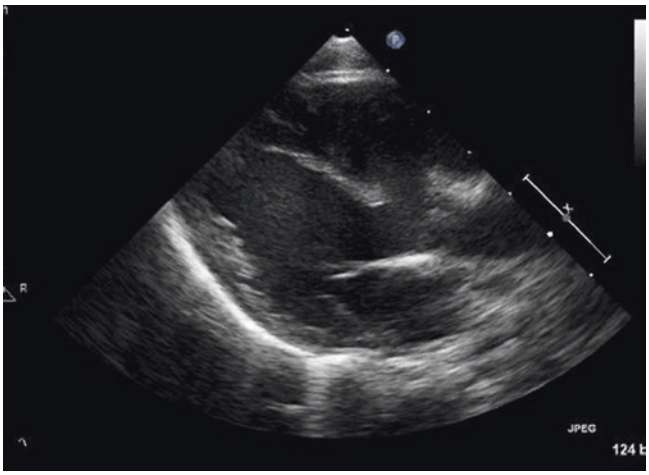

Fig. 32.1 Parasternal long-axis echocardiogram view of a patient with unrepaired tetralogy of Fallot. Note the large ventricular septal defect and overriding aorta. *Ao* Aorta, *LV* Left ventricle, *VSD* Ventricular Septal Defect

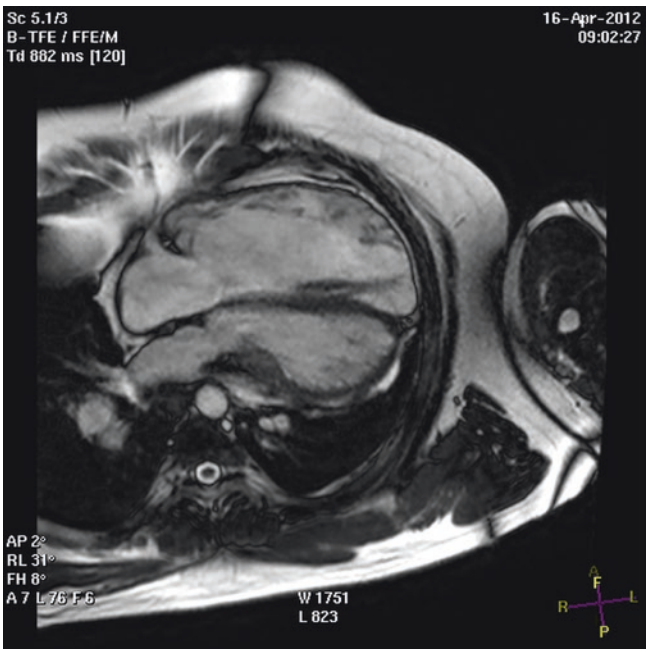

Fig. 32.2 Four chamber end diastolic MR image of a patient with repaired tetralogy of Fallot. The right ventricle is severely dilated, measuring 236 mL/m^2. (Image courtesy of Dr. Jimmy Lu)

Helpful Tests

The ECG typically shows right axis deviation and right ventricular hypertrophy in the patient with unrepaired TOF. The ECG in patients with repaired TOF characteristically shows right bundle branch block, often with a very wide QRS complex, which correlates with the degree of right ventricular dilation. Ambulatory ECG monitoring may be helpful if there is concern for atrial or ventricular arrhythmias.

In children, the classic chest X-ray finding of TOF is a "boot-shaped" heart. This is due to a small MPA segment which narrows the superior mediastinum, as well as upturning of the cardiac apex. The chest radiograph of the patient with corrected TOF may show cardiomegaly from right ventricular dilation or left ventricular dilation and a dilated ascending aorta. A right aortic arch may be sign on chest X-ray in approximately 25% of patients with TOF.

Transthoracic echocardiography is instrumental in the evaluation of an adult with TOF. Careful measurement of biventricular function should be performed. The pulmonary valve should be carefully interrogated for the presence of pulmonary regurgitation. It should be noted that in cases of severe pulmonary insufficiency, a laminar jet of pulmonary insufficiency may be subtle and go undetected. Pulse-wave Doppler should be performed in both systole and diastole. Rapid return of the diastolic signal to baseline is characteristic of severe pulmonary insufficiency. Quantification of the velocity of the tricuspid regurgitation jet should be performed to estimate right ventricular pressures. This should be correlated with any degree of stenosis seen across the pulmonary valve. Additional components of the echocardiogram include evaluation for residual ventricular septal defect, investigation for presence of an intra-atrial shunt, and measurement of the aortic root. Transesophageal echocardiography (TEE) has a limited role in the assessment of the majority of adults with TOF. Structures of interest such as the pulmonary valve or a right ventricle-to-pulmonary artery conduit are quite anterior and often not seen well on TEE.

Cardiac magnetic resonance imaging (MRI) has gained widespread acceptance for the assessment of the post-operative tetralogy patient (Fig. 32.2). It provides accurate measures of right ventricular size and function, as well as quantification of pulmonary insufficiency. Magnetic resonance angiography can provide excellent non-invasive imaging of the right ventricular outflow tract and branch pulmonary arteries. MRI also allows for accurate measurement of aortic dimensions in patients with aortic dilatation. When patients are under consideration for reoperation, cardiac catheterization with hemodynamic pressure measurement, estimation of pulmonary artery size and vascular resistance, ventriculography or aortography, and determination of coronary anatomy may be necessary. Patients greater than age 40 undergoing repeat cardiac surgery should undergo assessment with coronary angiography prior to surgery. Laboratory testing for 22q11 deletion should be considered in all patients with TOF, particularly women contemplating pregnancy and patients with right aortic arch.

Differential Diagnosis

Many congenital cardiac anomalies other than TOF can cause cyanosis and systolic murmur in adults and should be considered in the differential diagnosis of the adult who presents with these findings. These anomalies include severe pulmonic stenosis, pulmonic atresia, Ebstein's anomaly, uncorrected atrioventricular canal, single-ventricle states, congenitally corrected transposition of the great arteries, double-chamber right ventricle, and other congenital cardiac conditions associated with Eisenmenger's syndrome such as VSD and PDA. Physical examination in conjunction with ECG, chest radiography, and echocardiography establish the diagnosis in the majority of cases.

Complications

The clinical course of the patient with repaired TOF is variable and related to the underlying cardiac anatomy as well as surgical residua. Patients who underwent transannular patch repairs of TOF will uniformly have severe pulmonary insufficiency. Patient who had surgical pulmonary valvuloplasty at the time of their repair can also develop pulmonary insufficiency. In the early era of cardiac surgery, pulmonary insufficiency was felt to be benign. More recently pulmonary insufficiency has been found to be associated with progressive right ventricular dilatation and dysfunction with increased risk for arrhythmias. Pulmonary insufficiency must be ruled out in all adults with TOF, particularly those with evidence of right ventricular compromise or symptoms of exercise intolerance. Left ventricular dysfunction is also a concern. In a recent multicenter study of 511 patients with repaired TOF (mean age 37.2 years), left ventricular systolic function was mildly depressed in 14.4% of patients, moderately depressed in 5.2% of patients, and severely depressed in 1.1% of patients [3]. Left ventricular dysfunction was associated with duration with systemic-to-pulmonary artery shunt, coexistent right ventricular dysfunction, and arrhythmias.

Arrhythmias are a common complication in adults with TOF. A multi-center study of 556 adult patients with TOF (mean age 36.8 years) showed an overall prevalence of sustained arrhythmia or arrhythmia requiring intervention of 43.3% [4]. Risk factors for atrial arrhythmias, which occurred in 20.1% of patients, included right atrial enlargement, systemic hypertension, and number of cardiac surgeries. Risk factors for ventricular arrhythmias, which occurred in 14.6% of patients, included the number of cardiac surgeries, QRS duration, and left ventricular diastolic dysfunction. Prevalence of atrial fibrillation and ventricular arrhythmias increased significantly beyond 45 years of age. Sudden death has been reported in 3% of adults late after repair and usually occurs in patients with prior arrhythmias [5]. Inducible sustained ventricular tachycardia and sudden death correlate with prolonged QRS duration [6]. A retrospective study demonstrated QRS duration of greater than 180 ms to be a risk factor for sudden death and sustained ventricular tachycardia [7]. Progressive pulmonary regurgitation with subsequent right ventricular dilation and dysfunction occurs and may require reoperation [5, 8]. The presence of progressive pulmonary insufficiency is the most common hemodynamic lesion in patients with ventricular tachycardia, whereas tricuspid regurgitation occurs most frequently in patients with atrial arrhythmias [6].

Aortic dilatation is common in adults with repaired tetralogy of Fallot, occurring in approximately 15% of patients [9]. Risk factors for aortic dilatation include the presence of right aortic arch, DiGeorge syndrome, and duration of systemic-to-pulmonary artery shunt. Aortic dissection is rare, with only two cases reported in this patient population [10].

Therapy

Surgical repair is recommended for all adults who have previously unrepaired TOF or who have undergone palliative shunting without repair of TOF, even in older adults. The operative mortality rate is similar to that of pediatric patients (2.5% vs. 3%), although bleeding complications are common because of erythrocytosis and coagulation defects, necessitating re-exploration in 15% of patients in one series [11, 12]. Indications for reoperation after repair of TOF include severe pulmonary regurgitation with compromise of right ventricular function (38% of reoperations), pulmonary conduit revision (22%), ventricular septal patch leak (10%), and tricuspid regurgitation (5%) [13].

Controversy remains over the indications for pulmonary valve replacement in adults with repaired tetralogy of Fallot. The American College of Cardiology/American Heart Association 2008 Guidelines are summarized in Table 32.3 [14]. There is near universal agreement that symptomatic patients with severe pulmonary insufficiency should undergo pulmonary valve replacement. Patients who are asymptomatic but with signs of right ventricular enlargement should undergo careful evaluation including objective measure of exercise capacity with cardiopulmonary valve replacement. A study of 17 adult patients with tetralogy of Fallot and free pulmonary insufficiency showed that only patients with right ventricular end systolic volume of less than 85 mL/m^2 and end diastolic volume of less than 170 mL/m^2 showed normalization of right ventricular dimensions [15]. An additional study demonstrated that there is no threshold above which

Table 32.3 Indications for pulmonary valve replacement based on the ACC/AHA 2008 guidelines for the management of adults with congenital heart disease [14]

Recommendation for pulmonary valve replacement in patients with repaired TOF and severe pulmonary insufficiency
Class I
Severe Pulmonary insufficiency and symptoms or decreased exercise tolerance
Surgeons with training and experience in congenital heart disease should perform operations with previous repair of tetralogy of Fallot.
Coronary artery anatomy, specifically the possibility of an anomalous anterior descending coronary artery across the right ventricular outflow tract, should be ascertained before operative intervention.
Class IIa
Pulmonary valve replacement is reasonable in adults with any of the following:
Moderate to severe RV dysfunction
Moderate to severe RV dilatation
Development of symptomatic or sustained atrial and/or ventricular arrhythmias
Moderate to severe tricuspid regurgitation

Data from Warnes et al. [14]

the right ventricle will not decrease in size, but confirmed that larger ventricles (right ventricular end diastolic volume > 160 mL/m^2) will not normalize in size [16]. Studies suggest that right ventricular function deteriorates if pulmonary valve replacement for pulmonary regurgitation is not performed before right ventricular ejection fraction decreases to 40% [17]. As surgical indications continue to evolve, patients should be referred for evaluation at a center experienced in the care of adults with congenital heart disease. Although pulmonary valve replacement has historically been done surgically, percutaneous valve replacement may be an option for some patients. Percutaneous pulmonary valve replacement is current available for patients with appropriately sized right ventricle-to-pulmonary artery conduits or bioprostheses. Technology is under development to permit percutaneous deployment of pulmonary valves into native right ventricular outflow tracts.

Pulmonary valve replacement in conjunction with intraoperative cryoablation reduced the incidence of preexisting atrial and ventricular arrhythmias in 70 patients who underwent valve replacement late after repair [18]. Studies of pulmonary valve replacement alone have failed to demonstrate decreased risk of ventricular arrhythmias after surgery. A recent retrospective study nearly favored controls in the risk for ventricular tachycardia, death or combined ventricular tachycardia/death [19]. This study was limited in its retrospective design and differences in right ventricular size and function at baseline between patients undergoing pulmonary valve replacement and controls. Pulmonary valve replacement generally results in decrease in right ventricular dimensions and symptoms of exercise intolerance, but not in oxygen consumption at peak exercise [20].

Implantable cardioverter defibrillators (ICD's) are indicated for secondary prevention of sudden cardiac death, alongside repair of all potential hemodynamic abnormalities. A multi-center trial of 121 patients with a mean age included 68 patients with ICD's for primary prevention and 53 patients with ICD's for secondary prevention [21]. The annual actuarial rates of appropriate shocks were 7.7% in primary prevention and 8.8% secondary prevention. Elevated left ventricular end diastolic pressure and non-sustained ventricular tachycardia were independent predictors of appropriate shocks in patients undergoing ICD placement for primary prevention. Inappropriate shocks occurring at an annual rate of 5.8%. Generator and lead related complications were common, occurring in 29.8% of patients. In summary, ICD's can be life-saving in adults with tetralogy of Fallot, but complications are common. Patients should be carefully selected for device placement at experienced centers.

Prognosis and Follow-Up

The long-term outlook for the patient with unrepaired TOF is poor, with survival rates of 3% by age 40 [22]. Surgical repair has had a drastic effect on long-term outcomes for patients with TOF. Although patients are at increased risk for cardiac complications and require lifelong follow-up, patients generally do quite well. Survival 32 years after surgery was 86% vs. 96% in age-matched controls without congenital heart disease [23]. Among 162 patients who underwent operation before 1967, the cumulative 25-year postoperative survival rate was 94.4% [24]. Among 658 patients who underwent correction of TOF, actuarial survival rates were 97%, 94%, 89%, and 85% at 10, 20, 30, and 36 years, respectively [5]. Multivariate correlates of impaired long-term survival were earlier operation, preoperative polycythemia, and use of a right ventricular outflow tract patch. Patients without polycythemia and a right ventricular outflow tract patch had a life expectancy of 36 additional years after surgery.

Based on 2007 American Heart Association guidelines, endocarditis prophylaxis is indicated for patients who are unrepaired or palliated, those with previous endocarditis, those with bioprosthetic or prosthetic valves, and those with residual hemodynamic lesions adjacent to patch material [25]. Patients should be evaluated at least yearly by a cardiologist experienced in the care of adults with congenital heart disease and monitored for progressive pulmonary insufficiency, atrial and ventricular arrhythmias, and other sequelae of the repair [14].

Transposition of the Great Arteries

Transposition of the great arteries is a relatively common lesion, accounting for 5–7% of congenital heart disease [26]. It is also the most common cyanotic congenital heart disease presenting in the first year of life, with a prevalence of 2.64 per 10,000 live births [27]. In general terms, transposition of the great arteries describes anatomy in which a morphologically right ventricle gives rise to the aorta, and a morphologically left ventricle gives rise to the pulmonary artery. Terminology related to transposition can become quite confusing. The term D-Transposition implies dextroposition of the embryologic bulboventricular loop which places the right ventricle to the right of the left ventricle [28]. This is associated with an aorta which is rightward and anterior to the pulmonary artery, as well as parallel orientation of the great arteries. Oxygenated blood returning from the lungs is re-circulated to the lungs via the pulmonary artery, and deoxygenated blood returning from the body is re-circulated to the systemic circulation. The defect most commonly associated with D-transposition of the great arteries is ventricular septal defect, occurring in 40–45% of cases [29]. Additional lesions include left ventricular outflow tract obstruction (10% incidence) and coarctation of the aorta (5% incidence). L-TGA, or congenitally corrected transposition describes ventricular inversion, in which a right sided morphologically left ventricle gives rise to the pulmonary artery, and a left sided morphologically right ventricle gives rise to the aorta. As a result, oxygenated blood returning to the left atrium enters the right ventricle, and proceeds through the aorta to the systemic circulation. The right ventricle thus serves as the systemic ventricle. A detailed discussion of congenitally corrected transposition is beyond the scope of this text.

A patient's clinical status is highly dependent upon both their underlying anatomy and surgical history. Most adolescents and young adults currently transitioning to adult care have undergone the arterial switch, while older adults will have undergone Senning or Mustard procedures. Knowledge of a patient's surgical history is of great importance, as it impacts both a patient's natural history, as well as the physician's approach to their management.

The Senning and Mustard repairs involve redirecting the pulmonary venous return to the right ventricle, and the systemic venous return to the left ventricle. The Senning procedure, first reported in 1959, makes use of the patient's endogenous tissue (atrial wall and atrial septum), whereas the Mustard procedure, first reported in 1964, makes use of synthetic material [30, 31]. These procedures have a common physiologic consequence—a systemic right ventricle.

The arterial switch procedure involves transection of the great vessels above the semi-lunar valves, translocation of the coronary artery origins, and re-anastomosis of the great vessels to the appropriate ventricle. The arterial switch procedure was first reported by Jatene in 1976 and popularized by Castaneda in the early 1980s [32, 33]. Although the arterial switch is a more technically challenging procedure, it has important advantages. The left ventricle becomes the systemic ventricle, and extensive atrial surgery is not required, minimizing the long term complications of sinus node dysfunction and atrial arrhythmias.

Presenting Symptoms and Signs

D-TGA most commonly presents with cyanosis in the neonatal period. Given the parallel circulations resulting from transposition anatomy, the degree of cyanosis is directly related to the amount of mixing between the two circulations. Mixing can occur at an atrial septal defect, ventricular septal defect, or a patent ductus arteriosus. Initial palliative measures have the aim of increasing this mixing. Historically, a surgical Blalock-Hanlon atrial septectomy was performed. This procedure has since been replaced by percutaneous balloon septostomy. Additional palliative measures include maintaining patency of the patent ductus arteriosus with prostaglandins.

Because of the extremely poor survival rates of unoperated patients in the first year of life, adults presenting with D-Transposition have almost uniformly undergone previous surgical intervention [34]. Symptoms occurring in adults following repair are dependent upon the surgical history.

Senning and Mustard Procedures

Adults following atrial switch repairs can be asymptomatic, although progressive dyspnea on exertion and palpitations are common. The physical examination following Senning and Mustard procedures can be quite non-specific. The heart rate and rhythm should be assessed for the possibility of sick sinus syndrome or atrial tachyarrhythmias. The examination should focus on careful auscultation of the atrioventricular valves for a systolic regurgitant murmur of tricuspid insufficiency. Additionally, a general examination searching for signs of congestive heart failure should be performed.

Arterial Switch Procedures

Patients who have undergone arterial switch procedures are generally asymptomatic. Chest discomfort could represent coronary ischemia and should be investigated. Progressive exercise intolerance due to right ventricular outflow tract obstruction is also possible. On examination, a right ventricular

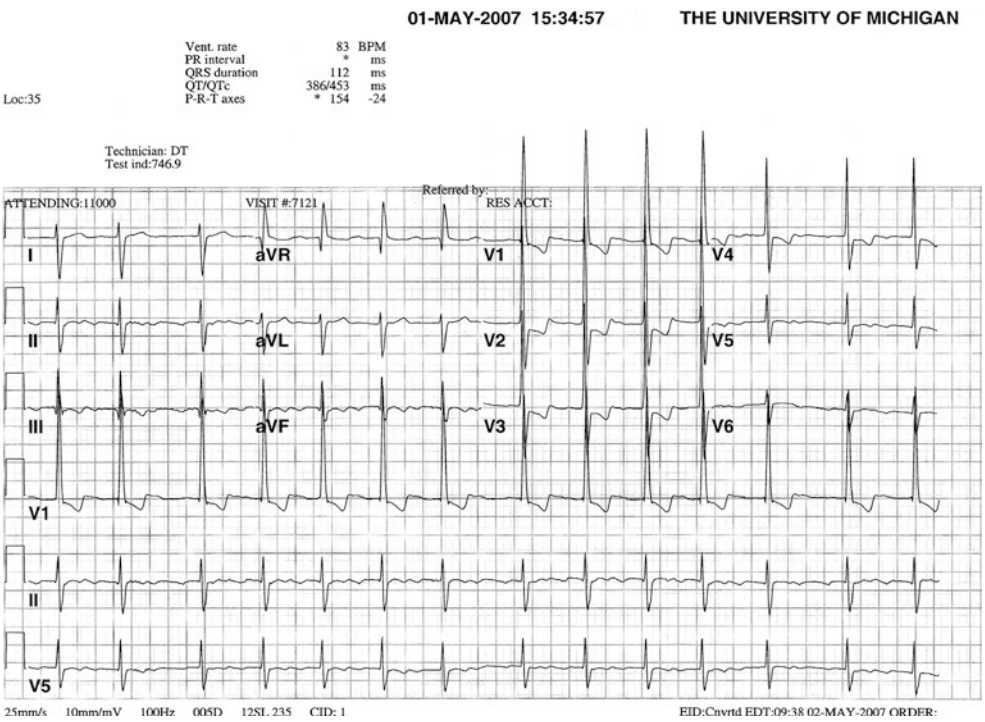

Fig. 32.3 Characteristic 12-lead EKG of a patient following mustard procedure, demonstrating atrial fibrillation/flutter, right axis deviation, and right ventricular hypertrophy

outflow murmur is relatively common. Additionally, careful auscultation should be performed to evaluate for aortic insufficiency or supravalvar aortic stenosis.

Helpful Tests

Senning and Mustard Procedures

In patients following Senning and Mustard operations, the EKG should be examined to document presence or absence of sinus rhythm. Underlying atrial flutter or atrial flutter can be seen, as well as the presence of junctional rhythm. Right ventricular hypertrophy and right axis deviation are common (Fig. 32.3). Right bundle branch block can be seen as well, particularly in those patients who have undergone ventricular septal defect closure. The echocardiogram is quite helpful in the assessment of patients following atrial switch procedure. Estimation of right ventricular function can be performed, as well as evaluation for systemic atrioventricular valve insufficiency. The systemic and pulmonary venous pathways should be assessed for obstruction and baffle leaks. These details can often be seen by transthoracic echocardiogram, although a transesophageal echocardiogram may be required in some patients. As adults following atrial switch procedures have been shown to have decreased exercise capacity, exercise testing with oxygen consumption can be helpful both for baseline measurement, as well as to follow changes over time [35]. Both blood pressure and heart rate response to exercise should be assessed as well.

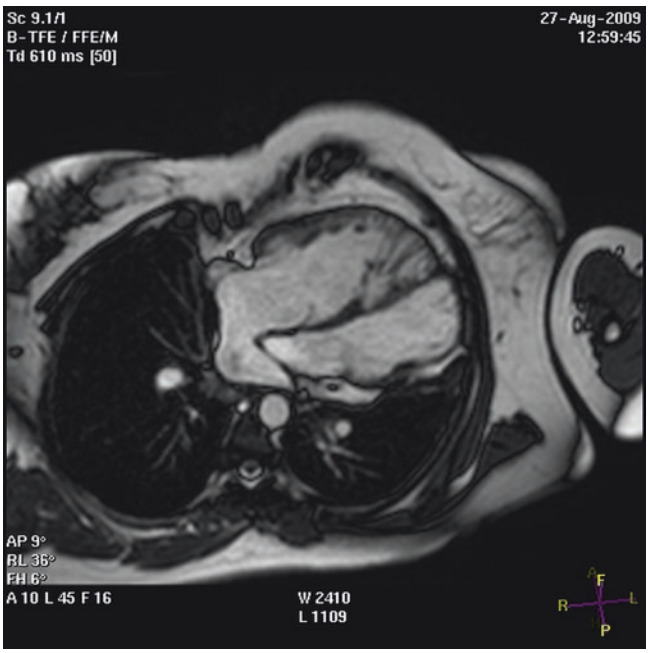

Fig. 32.4 Cardiac MR of a patient following a Mustard Procedure. The right ventricle (systemic ventricle) is dilated. The pulmonary venous pathway can be seen between the left atrium and the tricuspid valve. (Image courtesy of Dr. Jimmy Lu)

Cardiac MRI is becoming an important imaging modality for adults following atrial switch procedures. It provides accurate assessment of systemic right ventricular function, as well as assessment of the intra-atrial baffles (Fig. 32.4). The role for MRI is somewhat limited by the common

requirement for pacemakers in this patient population. Cardiac catheterization can provide helpful hemodynamic data, as well as angiographic assessment of the systemic and pulmonary venous pathways. Holter monitors can be helpful in assessing for sinus node dysfunction, heart block, and atrial or ventricular dysrhythmias.

Arterial Switch Procedures

In patients following arterial switch procedures, the EKG should be examined for changes suggestive of coronary ischemia and right ventricular hypertrophy or right axis deviation suggestive of right ventricular outflow tract obstruction. Transthoracic echocardiography can be used to assess both outflow tracts for valvar and supravalvar stenosis. The neoaortic valve and root should be evaluated for aortic insufficiency as well as root dilatation. Finally, the ventricles should be assessed for wall motion abnormalities. Exercise testing is also indicated for periodic assessment of individuals following arterial switch procedures, to evaluate for exercise induced coronary ischemia. Cardiac catheterization can be used in select patients to measure gradients across the right ventricular outflow tract, image the branch pulmonary arteries with angiography, and to perform coronary angiography to assess for coronary arterial abnormalities.

Differential Diagnosis

As mentioned above, adults with transposition of the great vessels will have been previously diagnosed. There are several related congenital anomalies which can have similarities late in their course. L-transposition, or congenitally corrected transposition shares similar pathophysiology with D-Transposition which has been palliated with an atrial switch procedure. In both situations, the right ventricle serves as the systemic ventricle. Associated lesions are common in corrected transposition, including ventricular septal defect, pulmonary stenosis, systemic AV valve abnormalities, heart block, and supraventricular tachycardia. D-transposition of the great arteries with subaortic ventricular septal defect and pulmonary stenosis is a variant of D-Transposition which requires a different surgical approach. The Rastelli procedure involves closing the ventricular septal defect such that the blood from the left ventricle is directed across the ventricular septal defect to the aorta. A conduit in then placed from the right ventricle to the pulmonary artery. A final associated lesion is double outlet right ventricle with sub-pulmonary ventricular septal defect, which is commonly known as the Taussig-Bing anomaly. This lesion is currently treated with the arterial switch procedure and ventricular septal defect closure.

Complications

Late complications after the Senning and Mustard procedures are common and progressive. Sinus node dysfunction is common, with a progressive decline in the presence of sinus rhythm over time. In one series, 40% of patients were in sinus rhythm 20 years following surgery [36]. The etiology of sinus node dysfunction is felt to be due to damage to the sinus node itself, as electrophysiology studies performed in children 1–8 years following Mustard procedures demonstrated that sinus nodal automaticity was abnormal in over 50% of children [37]. Tachyarrhythmias, generally atrial in origin, are also quite common. In a retrospective study of 86 patients greater than 18 years of age, 48% had experienced supraventricular tachycardia, of which 73% were atrial flutter [38].

The second major late complication for patients following the Senning or Mustard procedures is progressive systemic ventricular dysfunction. A single center study demonstrated uniformly good right ventricular function in patients following Mustard procedure 14 years following surgery with 65% demonstrating moderate to severe dysfunction by echocardiography at 25 years [39]. Progressive tricuspid valve insufficiency is also commonly seen, and is linked to the degree of ventricular dysfunction. Additional late complications include obstruction of the systemic or pulmonary venous pathways or baffle leaks. In a recent meta-analysis, systemic venous pathway obstruction was more common in those with a Mustard procedure, while there was a trend towards increased pulmonary venous obstruction in those following a Senning procedure (7.6% vs. 3.8%). In terms of baffle leaks, the prevalence was 7% for those with a Mustard Procedure, and 14% for those with a Senning Procedure [40].

Late complications after the arterial switch procedure are still under investigation. A recent single center study identified at least one significant residual cardiac lesion in 17% of patients follow the arterial switch procedure. These included ventricular dysfunction, valvular disease, or arrhythmias [41]. Aortic insufficiency was common, with aortic insufficiency of any degree present in 52% of adults. Aortic root dilatation was also common, occurring in 31% of the adult population. No patients in this study required intervention for aortic insufficiency or aortic dilatation. The potential for coronary insufficiency is also a significant concern. Possible mechanisms for coronary ischemia include anatomic

distortion related to the initial repair, extrinsic compression, and intimal proliferation [42]. In a retrospective study of hospital survivors after arterial switches performed between 1982 and 2001, coronary events occurred in 7% of patients [43]. An additional concern is for supravalvar or branch pulmonary artery stenosis, which may require reoperation. The incidence of this complication may be decreasing as surgical techniques have improved.

Therapy

Almost all patients have had significant surgical intervention by the time of presentation. Treatment is aimed a treating minimizing the effects of late complications. In Senning and Mustard patients, ablation of atrial flutter can be performed with reported success rates of approximately 70% [44]. Many patients require pacemakers because of sinus node dysfunction resulting in symptomatic bradycardia. The role for biventricular pacing is evolving, with anecdotal reports of benefit. A multi-center study of 103 pediatric and adult patients with congenital heart disease included 17 patients with systemic right ventricles receiving resynchronization therapy [45]. Patients showed an increase in right ventricular ejection fraction and a decrease in QRS duration. Of these at patients, 13 showed clinical improvement. Patients should be evaluated on an individual basis, and carefully assessed for ventricular dysynchrony if this modality is considered. Indications for placement of implantable cardioverter-defibrillators (ICDs) are also evolving. A multicenter study 37 patients who had undergone ICD placement showed a reasonably high annual rate (6%) of appropriate shocks for patients receiving ICDs for secondary prevention and a low annual rate (0.5%) of appropriate shocks in patients receiving ICDs for primary prevention [46]. Electrophysiology studies and pacemaker placement should be performed in centers with experience in the complex anatomy of these patients [14]. A thorough assessment of the anatomy should also be performed to exclude pathway obstruction or baffle leaks.

In terms of medical management, the extrapolation of studies of medical therapy from the general adult congestive heart failure population is controversial. It is not known as to whether a systemic right ventricle responds similarly to medical therapy as does a systemic left ventricle. A small non-randomized trial of beta-blockers in eight patients following atrial switch procedure suggested improvement in functional capacity and tricuspid insufficiency [47]. Beta-blockers should be used with caution because of concerns for worsening bradycardia and heart block. A retrospective study of the use of angiotensin-converting enzyme inhibitors in patients following Mustard procedures demonstrated no significant differences cardiopulmonary exercise test results or right ventricular volume and ejection fraction by MRI. As some individual patients did show improvement in peak VO_2, and MRI parameters, the authors concluded that there is a role for further study of this matter [48]. Symptomatic treatment with diuretics and digoxin can also be considered. Late surgical intervention may be required in certain circumstances. Baffle obstruction can be addressed surgically, or at times, percutaneously. Hemodynamically significant baffle leaks can also be approached either surgically or percutaneously. Ultimately, heart transplantation may be required for many patients in this population.

Prognosis and Follow-Up

A single center study examining long term outcome after the Mustard procedure estimated 89% survival at 5 years and 76% at 20 years of age [36]. An additional single center study involving both Mustard and Senning patients demonstrated 25 year survival to be 75.9% for Mustard patients and 90.9% for Senning patients [49]. Data for survival in patients following Mustard vs. Senning procedure are conflicting, with the above study showing survival benefit for Senning patients, and a recent meta-analysis suggesting survival benefit for Mustard patients [40]. Presence of a ventricular septal defect or atrial flutter has been consistent risk factors for mortality. Patients following atrial switch procedure should be followed in a center with experience with congenital heart disease [14]. Periodic assessment of systemic ventricular function with echocardiogram or MRI should be performed, as well as Holter monitoring to assess for sinus node dysfunction or atrial arrhythmias.

Although mid-term survival data is available for patients undergoing arterial switch repairs, long-term data is not yet available. Mid-term data for survival is promising, with one report with maximal follow-up of 25 years showing late mortality in only 2 of 151 survivors [50]. A more recent study showed a 97% survival at 20 years of follow-up [41]. Exercise tolerance was reduced in 82% of adults after the arterial switch. Life-long follow-up in a center with experience in congenital heart disease is necessary, generally at 1–2 year intervals [14]. Based on the most recent American Heart Association guidelines, endocarditis prophylaxis is not required for the vast majority of patients following repair or palliation of transposition of the great arteries. Prophylaxis would be required for patients with a previous history of endocarditis, previous valve replacement, those with residual lesions preventing endothelialization of prosthetic material, or those within six months of surgery or device placement [25].

Single Ventricle Lesions and the Fontan Procedure

The Fontan procedure was developed over 40 years ago for palliation of tricuspid atresia [51]. Since that time, it has undergone numerous modifications, and is often the ultimate step in a series of palliative surgeries whose goal is to establish separate pulmonary and systemic circulation in a variety of congenital cardiac lesions involving a single ventricle and/or single atrioventricular valve. It can also be applied to some two-ventricular lesions not otherwise amenable to two ventricle repair. Multiple palliative surgeries preceded the development of the Fontan procedure. The first such surgery was the Blalock-Taussig shunt, an end-to-side anastomosis of the subclavian artery to the pulmonary artery. The Potts and Waterston shunts, direct anastomoses between the aorta and the pulmonary arteries, were subsequently developed and later abandoned due to concerns over pulmonary artery distortion and pulmonary hypertension. The unidirectional Glenn shunt, an end-to-side anastomosis of the superior vena cava to the right pulmonary artery was the first attempt at bypassing the intracardiac circulation completely. Fontan and Baudet subsequently developed the Fontan procedure, which resulted in all systemic venous return being routed to the pulmonary arteries [51].

Physicians caring for this patient population should have an understanding of the surgical repairs, as this knowledge can have a significant impact on management options. Figure 32.5 shows variations of commonly seen postoperative Fontan anatomy. An important distinction is between an atriopulmonary Fontan (Fig. 32.5a) and a total cavopulmonary connection (Fig. 32.5b–d). Patients following atriopulmonary Fontan procedure often develop severe atrial dilation and are therefore at increased risk for arrhythmias and clot formation. Such patients may be candidates for conversion to a lateral tunnel or extracardiac Fontan. The lateral tunnel Fontan (Fig. 32.5c) involves the creation of a surgical baffle along the lateral wall of the right atrium, directing IVC flow to a previously created anastomosis between the pulmonary arteries and the right atrium. The extracardiac Fontan (Fig. 32.5d) involves the placement of a synthetic or tissue conduit between the inferior vena cava and the pulmonary artery. Many institutions also create a fenestration in the baffle of the lateral tunnel to serve as a "pop-off" from the pulmonary circulation to the arterial circulation (Fig. 32.5b, c). While this can support cardiac output, it can also result in mild systemic arterial desaturation.

Presenting Symptoms and Signs

Patients with single ventricle congenital heart lesions generally present in infancy, with presenting symptoms dependent on their underlying anatomy. Even an individual lesion such as tricuspid atresia can have a wide spectrum of presenting symptomatology, ranging from an extremely cyanotic infant with minimal pulmonary blood flow to a pink infant with congestive heart failure and excessive pulmonary blood flow. Single ventricle lesions with systemic blood flow dependent upon a patent ductus arteriosus can present with circulatory collapse at several days of age after closure of the patent ductus. Rarely, patients can present with single ventricle congenital heart disease late in childhood or in adulthood. For this to occur there must not be ductal dependent systemic or pulmonary blood flow. Additionally, there must be a "balanced" circulation, such that there is enough restriction to pulmonary blood flow to prevent the development of congestive heart failure, but sufficient pulmonary blood flow such that there is not severe cyanosis.

Surgically palliated patients are generally asymptomatic. Potential symptoms include palpitations and progressive exercise intolerance. The onset of peripheral edema, ascites, or pleural effusions, could be signs of the serious complication of protein losing enteropathy and should prompt further investigation. Patients following Fontan palliation should have near normal oxygen saturations. Decreases in oxygen saturation should prompt further evaluation, particularly to search for baffle leaks causing right to left shunt, or systemic venous collateralization to the pulmonary venous atrium or pulmonary vein. Physical examination can demonstrate increased venous pulsations due to elevated central venous pressures. The S2 will often be single and prominent. Auscultation should focus on signs of semilunar or atrioventricular valve insufficiency. It is not uncommon to hear systolic ejection murmurs, although murmurs 3/6 or louder can suggest significant AV valve insufficiency or outflow tract obstruction and should be investigated further. Abdominal examination should assess for hepatosplenomegaly and ascites. Clubbing may be present in chronically cyanotic patients.

Helpful Tests

Electrocardiograms are useful to confirm the underlying rhythm. The EKG will vary based on the diagnosis. In tricuspid atresia, there is often a superior QRS axis, left ventricular hypertrophy, and right atrial or combined atrial enlargement. In patients with hypoplastic left heart syndrome, there is often right atrial enlargement, right ventricular hypertrophy, and right axis deviation. Chest X-ray findings are variable, depending on the underlying anatomy, but can be useful for following heart size in those with valvar insufficiency. The echocardiogram is important in the follow-up of this patient population and can be used to assess systemic ventricular function and evaluate for any atrioventricular or semi-lunar valve insufficiency. Attempts at visualizing the Fontan pathway and proximal pulmonary arteries should also be made. Color Doppler should be used to evaluate for baffle leaks and

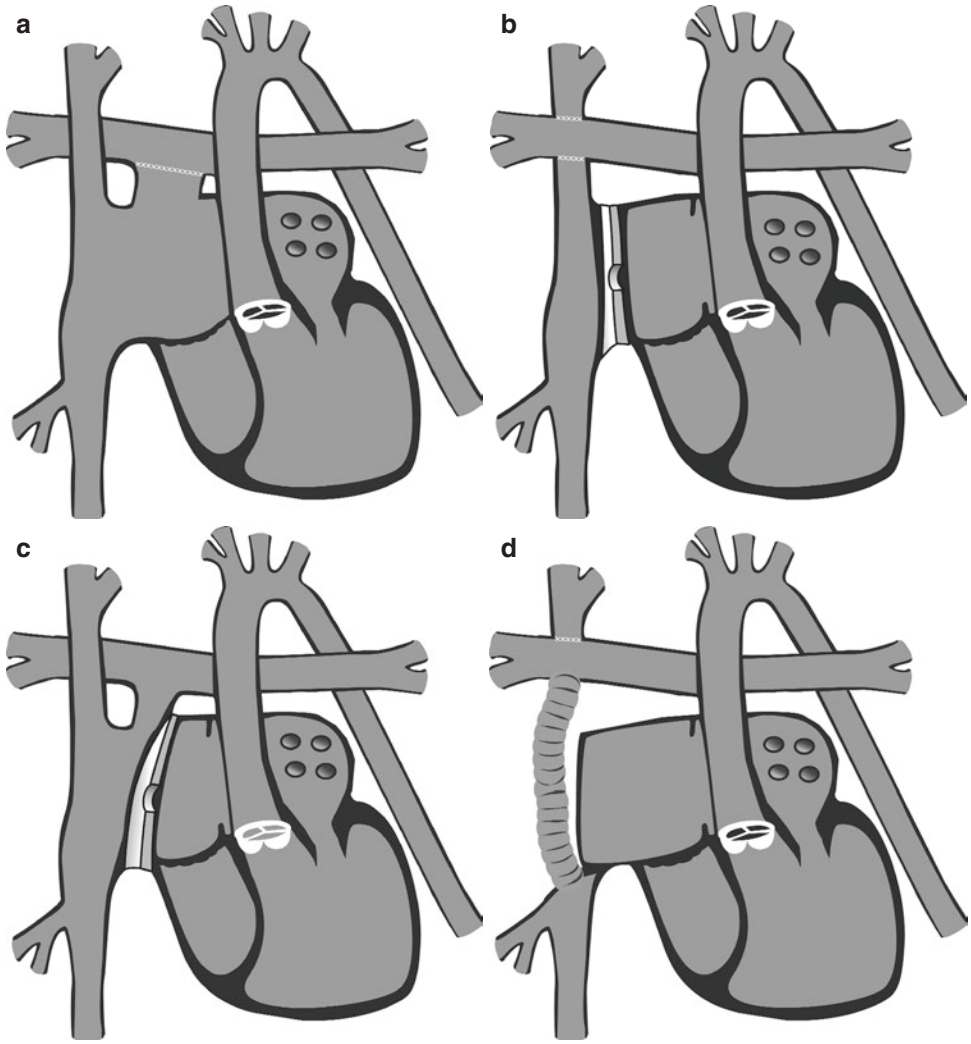

Fig. 32.5 (**a**–**d**) Four common modifications of the Fontan procedure shown with tricuspid atresia as the underlying anatomy. (**a**) Atriopulmonary Fontan. (**b**) Bidirectional Glenn SVC connection with fenestrated lateral tunnel Fontan. (**c**) Hemi-Fontan SVC connection with fenestrated lateral tunnel Fontan. (**d**) Bidirectional Glenn with extracardiac Fontan

surgically created fenestrations. A trans-esophageal echocardiogram can be performed if trans-thoracic images are suboptimal. The trans-esophageal echocardiogram is particularly helpful for assessment of potential thrombi and baffle leaks, often in the setting of neurologic events or cardioversion of atrial arrhythmias.

There is an increasing role for cardiac MRI in the care of adults following Fontan procedure (Fig. 32.6). It can be used to assess ventricular function, particularly in patients with systemic right ventricles. It can also provide important anatomic detail regarding the patency of the Fontan pathway and the pulmonary arteries. Periodic Holter monitoring can be useful in assessing for both sinus node dysfunction and atrial arrhythmias. Cardiac catheterization continues to have a role in the assessment of the post-operative Fontan patient. Catheterization should be considered in the evaluation of patients with worsening symptoms or with cyanosis. Careful hemodynamic assessment should be performed, including oxygen saturations and pressure measurements in the vena cavae, Fontan pathway, and pulmonary arteries and ventricle. Angiography can be performed to document collateral vessels and baffle leaks. Useful laboratory studies include complete blood count and liver function studies to evaluate for hepatic dysfunction, and albumin as screening for protein losing enteropathy.

Differential Diagnosis

A broad variety of anatomic diagnoses can lead to single ventricle pathophysiology. A detailed discussion of nomenclature of these lesions is beyond the scope of this text. When strictly defined, the term single ventricle refers anatomy consisting of two atrioventricular (AV) valves with one ventricular chamber, or the presence of a dominant chamber alongside a diminutive second chamber [52]. A variety of lesions can result in single ventricle physiology or be palliated to the Fontan procedure. The broad categories include atresia of an AV valve, hypoplasia of a ventricle (often associated with atresia or hypoplasia of the associated AV valve), and two-ventricle lesions which are not septatable because of characteristics of the ventricular septal defect or straddling of the

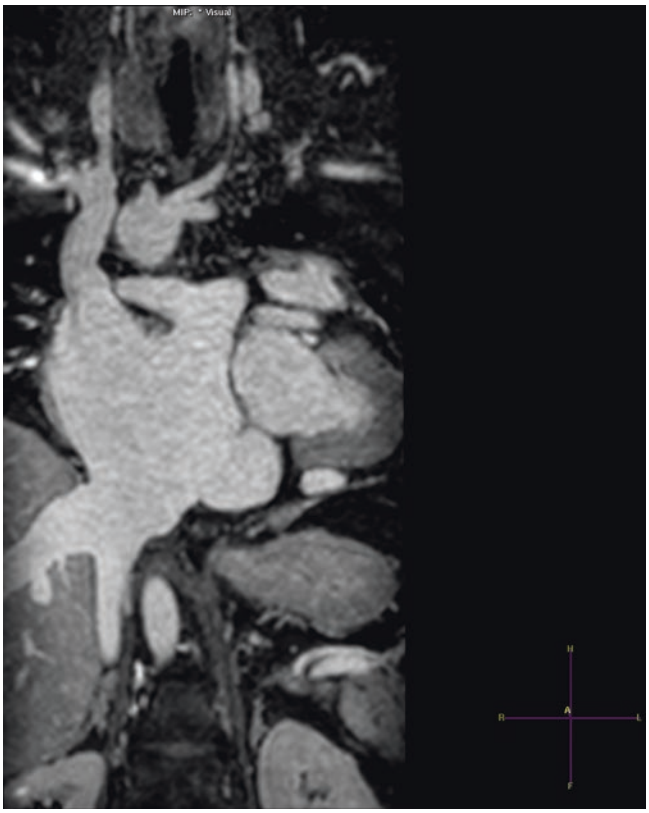

Fig. 32.6 Cardiac MR of a patient following atriopulmonary Fontan procedure. The pulmonary arteries arise from the right atrial appendage. The Fontan pathway is severely dilated. *HV* Hepatic vein, *IVC* Inferior vena cava, *LPA* Left pulmonary artery, *RPA* Right pulmonary artery, *SVC* Superior vena cava. (Image courtesy of Dr. Jimmy Lu)

AV valves. Tricuspid atresia describes absence of a patent tricuspid valve. The right ventricle is hypoplastic, and can this diagnosis can be further classified by the orientation of the great arteries, presence of ventricular septal defect, and the degree of pulmonary stenosis. Hypoplastic left heart syndrome describes the spectrum of lesions involving hypoplastic left ventricle mitral atresia or hypoplasia, aortic hypoplasia or atresia, and coarctation. Double inlet left ventricle (DILV) is the classically described form of single or common ventricle. Both atrioventricular valves enter a common ventricular chamber. DILV can be sub-classified based on the great artery relationships. AV valve abnormalities, pulmonary outflow tract obstruction, and subaortic obstruction are common associated anomalies.

Complications

Complications following the Fontan procedure are common and can be difficult to treat. Atrial arrhythmias have become one of the hallmark complications following the Fontan procedure. In a retrospective review at a single center of 121 patients, freedom from tachyarrhythmia was 23% at 20 years [53]. Arrhythmias have been found to be more common in those with an atriopulmonary anastomosis as compared with those with total a cavopulmonary connection. Additional risk factors have been found to be heterotaxy syndromes and AV valve abnormalities. Intra-atrial reentrant tachycardia is the most common mechanism for atrial arrhythmias. Sinus node dysfunction is also a common problem. In a study of 220 patients surviving Fontan procedure, in 85 patients greater than 4 years following surgery, 44% had sinus node dysfunction [54].

Worsening cyanosis may also occur following Fontan procedure. Mild arterial desaturation with oxygen saturations of 90**.**04% is relatively common, although saturations of less than 90% merit further evaluation. The differential diagnosis for worsening cyanosis is extensive, and includes right to left shunting at a surgically created fenestration or baffle leak, systemic venous collateralization to the left atrium or pulmonary veins, and pulmonary arteriovenous malformations. The development of pulmonary arteriovenous malformations occurs more frequently when the hepatic veins are not incorporated into the Fontan circuit. Primary pulmonary pathology and diaphragmatic paresis should also be ruled out.

A recent study demonstrated chronic venous insufficiency to be highly prevalent in adults with Fontan physiology. The prevalence was 60% in the Fontan population as compared with 32% in healthy controls, which is likely multifactorial but likely due in part to elevation in central venous pressures [55].

Protein losing enteropathy and plastic bronchitis are felt to be related complications both of which portend a poor prognosis. Presenting symptoms for protein losing enteropathy include chronic diarrhea, ascites, pleural effusions, and extremity edema. Elevated α_1-antitrypsin levels in the stool and low serum albumin levels are present. The etiology of protein losing enteropathy is not completely known, although it is felt to be due to chronically elevated systemic venous pressures. In a multicenter study of 3029 Fontan operations, the incidence of protein losing enteropathy of surviving patients was found to be 3.75%. There was high mortality associated with this diagnoses, ranging from 46% in who received medical treatment, to 62% in those who received surgical treatment for this complication [56]. Multiple therapies have been applied, with no obviously superior approach. Treatments have included heparin, dietary modification to a low fat diet, surgical or percutaneous fenestration creation or augmentation, steroids, surgical takedown to a hemi-Fontan or equivalent anastomosis, or cardiac transplantation. Recent studies of oral budesonide have demonstrated improvement in symptoms and serum albumin levels [57, 58]. Plastic bronchitis is a rare complication, characterized by the production of casts within the airways. It is associated with significant morbidity and mortality. Treatment options are

limited, with some reports of success with aerosolized thrombolytic agents such as urokinase or tissue plasminogen activator (tPA) [59].

Thromboembolism can also be also result in significant morbidity following Fontan procedure. The pathophysiology is multifactorial, including a low flow state in the Fontan pathway, atrial rhythm disturbances, and the potential for right to left shunting at a fenestration or baffle leak. There is also the potential for a hypercoaguable state, due to hepatic impairment with decreased levels of protein C, protein S, and antithrombin III [60].

Therapy

A thorough knowledge of a patient's surgical history and pathophysiology is necessary to determine an optimal treatment plan. Many of the above complications are refractory to conventional treatment measures, particularly atrial arrhythmias. For this reason, there has been interest both in optimizing hemodynamics, and minimizing the risk for future atrial arrhythmias. As a result, some centers currently advocate revision of the atriopulmonary Fontan to a total cavopulmonary anastomosis (lateral tunnel or extracardiac conduit). This is performed in conjunction with arrhythmia surgery. Initial reports have been quite favorable, with low early mortality and significant improvement in New York Heart Associate Class. Of 39 patients who underwent Fontan conversion and a right-sided Maze procedure for atrial arrhythmias, three had recurrent of the arrhythmia. Of 39 patients with atrial fibrillation who underwent Fontan conversion and a modified Cox procedure and were available for study, none developed recurrent atrial fibrillation. Six of 30 developed readily treatable atrial reentry tachycardia [61]. As Fontan conversion is a complex procedure requiring multidisciplinary care, it should be performed only in experienced centers.

Patients presenting with atrial arrhythmias should be restored to sinus rhythm. Cardioversion is associated with a high risk of recurrence, so medical therapy is often required. Choice of anti-arrhythmic therapy should be made on a case-by-case basis, and is dependent upon the type of arrhythmia, ventricular function, sinus and AV nodal function, and comorbidities. Trans-esophageal echocardiography can be useful at the time of cardioversion to rule out atrial thrombus. Percutaneous ablation of atrial arrhythmias can be performed, with high procedural success rate, although significant recurrence risk over time [62, 63].

Percutaneous interventional approaches can be used to address to hemodynamic issues following the Fontan procedure. In patients with baffle leaks or persistent fenestrations, these can be closed using devices in the cardiac catheterization laboratory. Stenting of stenotic pulmonary arteries can also be performed. In patients with protein losing enteropathy, some centers advocate percutaneous creation of a fenestration.

The role for medical therapy in patients following the Fontan procedure continues to evolve. There are few studies specific to this population to support the use of individual medications; current standard therapy includes diuretics as needed, digoxin, and ACE-inhibitors. There has been recent interest in pulmonary vasodilators in patients with Fontan physiology. A small randomized, placebo-controlled trial of sildenafil in young patients (mean age 14.9 years) demonstrated improvement in some measures of exercise capacity [64]. Anticoagulation should also be considered, although there is no convincing data to support the use of one mode of anticoagulation as opposed to another. Aspirin and warfarin are both commonly used. A randomized study in children demonstrated no benefit of warfarin over aspirin during a 2-year follow-up period [65]. The mode of anticoagulation should take into account a patient's post-operative anatomy, arrhythmia history, and history of previous thromboembolism. Cardiac transplantation is often considered for patients with failing Fontan physiology. The procedure takes on increased complexity, as most patients have had multiple previous surgeries, and can have multi-system organ involvement at the time of transplantation. Additionally, there may be concomitant abnormalities of systemic or pulmonary venous return and pulmonary artery anatomy. A multi-center review of transplant outcomes in 35 patients with previous Fontan or Glenn procedures demonstrated 71.5% 1-year survival and 67.5% 5 year survival [66].

Prognosis and Follow-Up

Most long-term data regarding outcomes of patients following the Fontan procedure were obtained from the tricuspid atresia or double inlet left ventricle population. Only now are patients with systemic right ventricles reaching adulthood, so long term data is not yet available. Although there is a general feeling that long-term outcomes will likely be better for those with systemic left ventricles, there is not sufficient data to support this statement at this time. In a single-center study, actuarial freedom from death or transplantation was 87%, 83%, and 70% at 15, 20, and 25 years following surgery, respectively [67]. As this study reflects Fontan procedures performed in the early era, these numbers are expected to improve with increased use of fenestrations perioperatively as well as the transition from the atriopulmonary Fontan. Patients with Fontan physiology require lifelong follow-up at a center experienced in congenital heart disease [14]. Based on most recent guidelines, bacterial endocarditis prophylaxis is indicated for those patients with unrepaired or palliated single ventricle physiology, including those who have undergone a Fontan procedure [25].

Practical Points

- Patients with tetralogy of Fallot should be carefully evaluated for the presence of pulmonary insufficiency. Pulmonary valve replacement should be considered for symptomatic patients and in certain patients with significant right ventricular dilatation, dysfunction, tricuspid regurgitation, or arrhythmias.
- Patients who have undergone atrial switch repairs for transposition of the great arteries are at risk for multiple late complications, including right ventricular dysfunction, arrhythmias, baffle leaks or obstruction, and sinus node dysfunction.
- Patients with single ventricle lesions following a Fontan procedure should be followed at an experienced center. Complications include arrhythmias, atrial thrombi, chronic venous stasis, protein losing enteropathy, liver disease, and plastic bronchitis.

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33 Perioperative Evaluation and Management of Patients Undergoing Noncardiac Surgery

Ajay Vallakati, Ragavendra R. Baliga, and Kim Allen Eagle

Over 36 million patients undergo surgical procedures in the United States annually [1]. Around one-third of the patients undergoing surgeries have risk factors for or known cardiovascular disease [2]. The risk of perioperative cardiac complications is related to underlying cardiovascular disease burden [3]. Given the prevalence of cardiovascular disease, it is imperative for a practicing physician to perform an individualized evaluation of the surgical patient to provide an accurate preoperative risk assessment, risk stratification, and allow for modification of management strategies. This chapter outlines a systematic algorithm approach for cardiovascular risk assessment to guide perioperative strategies that may improve outcomes.

Definitions of Urgency and Risk

Determining the urgency of the surgery should be included in the initial evaluation. The urgency of surgery is dictated by patient- or surgery-specific factors, and in some instances, there may not be adequate time for comprehensive cardiac assessment. Depending on the urgency, the American College of Cardiology/American Heart Association (ACC/AHA) Perioperative Clinical Practice Guideline classified procedures into emergent, urgent, time-sensitive, and elective categories [4]. A procedure is considered an emergency when life or limb is endangered if the patient is not taken to the operating room within 6 h. A procedure is treated as urgent when the life or limb is endangered if the patient is not operated within 6–24 h. A procedure is considered time-sensitive when a delay of more than 1–6 weeks may lead to adverse outcomes. A procedure is defined as an elective procedure if it can be delayed for up to 12 months [4]. Based on the risk of major adverse cardiac events (MACE), the procedures can be classified into low-risk and elevated risk. A procedure like cataract surgery with MACE of less than 1% is considered low-risk. Conversely, a procedure is treated as elevated risk when the risk of MACE is >1% [4].

Risk Prediction

Risk prediction models take into account, the patient- and surgery-specific risk factors, to estimate the perioperative risk. Commonly used risk indices include Revised Cardiac Risk Index (RCRI), American College of Surgeons National Surgical Quality Improvement Program (NSQIP) Myocardial Infarction and Cardiac Risk (MICA), and American College of Surgeons NSQIP Surgical Risk Calculator [5–7].

The RCRI relies on the presence or absence of six identifiable predictive factors which include high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, and renal failure (Table 33.1). Each of the RCRI predictors is assigned one point, when present. The risk of cardiac events (including myocardial infarction (MI), pulmonary edema, ventricular fibrillation or primary cardiac arrest, and complete heart block) can then be predicted. Based on the presence of 0, 1, 2, 3, or more of these clinical predictors, the rate of major cardiac complications is estimated to be 0.4–0.5%, 0.9–1.3%, 4–6.6%, and 9–11% respectively. The risk of MACE particularly increases with two or more predictors, and is highest with three or more predictors [5].

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Table 33.1 Revised cardiac risk index markers

1. High risk surgical procedures
2. Ischemic heart disease
(a) History of myocardial infarction
(b) Current angina considered to be ischemic
(c) Requiring sublingual nitroglycerin
(d) Positive exercise test
(e) Pathological Q-waves on ECG
(f) History of PTCA and/or CABG with current angina considered to be ischemic
3. Congestive heart failure
(a) Left ventricular failure by physical examination
(b) History of paroxysmal nocturnal dyspnea
(c) History of pulmonary edema
(d) S3 gallop on cardiac auscultation
(e) Bilateral rales on pulmonary auscultation
(f) Pulmonary edema on chest X-ray
4. Cerebrovascular disease
(a) History of transient ischemic attack
(b) History of cerebrovascular accident
5. Diabetes mellitus
(a) Treatment with insulin
6. Chronic renal insufficiency
(a) Serum creatinine >2 mg/dL

Data from Lee TH, et al. [5] "Revise Cardiac Risk Index"

The NSQIP MICA risk prediction model estimates the risk of perioperative MI and cardiac arrest [6]. This model incorporates five variables for risk prediction; namely type of surgery, functional status, elevated creatinine, advanced age, and the American Society of Anesthesiology's physical status class [6]. The predictive accuracy of this model is superior to RCRI, especially in patients undergoing vascular surgery [6].

The NSQIP Surgical Risk Calculator is a more comprehensive model which incorporates 20 patient-specific factors and the type of surgery [7]. This tool estimates the risk of death, MACE and eight additional complications [7]. NSQIP-based models have not been externally validated [4]. These models use American Society of Anesthesiologist's physical status classification for risk prediction. However, there is a wide inter-rater variation in classification and physicians other than anesthesiologists may not be familiar with this classification [4].

Assessing Perioperative Cardiac Risk for Patients Undergoing Noncardiac Surgery [4, 8]

The purpose of preoperative evaluation is to present the clinicians and the patient with the information regarding the risk and benefits of the surgical procedure to aid in the process of informed consent. It allows the patient to consider the alternative options if the perioperative risk of complications is deemed high. Finally, the evaluation can lead to detection of previously undiagnosed problems which may change the perioperative management decisions. In this chapter, we provide an algorithm approach to perioperative cardiac risk evaluation.

A stepwise approach for assessing risk for patients undergoing noncardiac surgery should address the following questions (Fig. 33.1):

1. Is noncardiac surgery emergently required?
2. Does the patient have acute coronary syndrome?
3. What is the perioperative risk of MACE?
4. Is further testing required if the risk of MACE is elevated (>1%)?
5. Is a non-invasive cardiac test necessary?
6. Is there a benefit for perioperative coronary revascularization?
7. What additional preoperative, intraoperative, and postoperative risk modification strategies need to be initiated?

Is Noncardiac Surgery Emergently Required?

Determining the urgency of the surgery is essential. NSQIP-based risk estimate varies significantly in emergency and elective surgeries [8, 9]. Surgery in an emergency situation is associated with a higher risk of perioperative events [4]. If surgery is deemed to be an emergency, there may not be adequate time for rigorous cardiac evaluation. In such circumstances, recommendations for perioperative medical management and monitoring are equally important.

Does the Patient Have Acute Coronary Syndrome?

If the surgery is not an emergency, the next step is to determine whether the patient has unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) or STEMI. Cardiology team should be contacted if the patient has acute coronary syndrome [4]. Management should be according to the recommendations in UA/NSTEMI and STEMI guidelines [10, 11].

What Is the Perioperative Risk of MACE?

A baseline comprehensive history and physical examination with 12-lead resting electrocardiogram (ECG) provides important data to estimate the cardiac risk. Specific type of surgery also affects the risk of cardiac complications, as depicted in Table 33.2 [12]. Aortic, peripheral

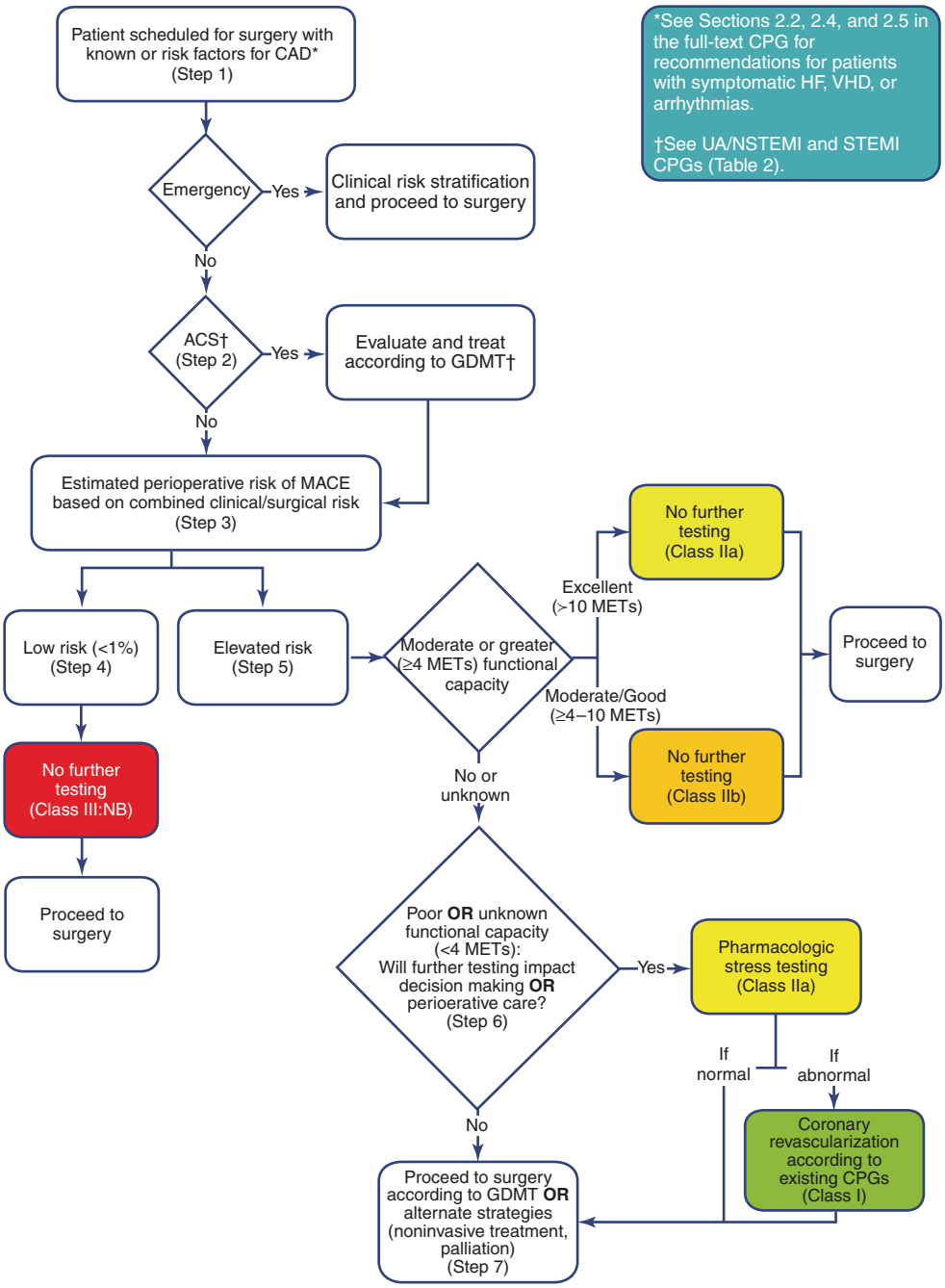

Fig. 33.1 Stepwise approach to perioperative cardiac assessment for CAD. *ACS* indicates acute coronary syndrome, *CABG* coronary artery bypass graft, *CAD* coronary artery disease, *CPG* clinical practice guideline, *DASI* Duke Activity Status Index, *GDMT* guideline-directed medical therapy, *HF* heart failure, *MACE* major adverse cardiac event, *MET* metabolic equivalent, *NB* no benefit, *NSQIP* National Surgical Quality Improvement Program, *PCI* percutaneous coronary intervention, *RCRI* Revised Cardiac Risk Index, *STEMI* ST-elevation myocardial infarction, *UA/NSTEMI* unstable angina/non–ST-elevation myocardial infarction, and *VHD* valvular heart disease. (From Fleisher et al. [4]; with permission)

arterial, and other major vascular surgery or operations associated with large fluid shifts or blood loss are associated with increased risk of cardiac complications [13]. The perioperative risk with these procedures is elevated irrespective of the risk factors. Conversely, very low risk surgeries which do not involve significant fluid shifts would not be associated with elevated risk even if the patients have >1 risk factors [14]. ACC/AHA perioperative guideline recommends using a validated risk prediction model to estimate the risk of MACE [15]. If the perioperative risk is <1%, no further cardiovascular testing is indicated before surgery [16].

Is Further Testing Required If the Risk of MACE Is Elevated (>1%)?

If the perioperative risk of MACE is >1%, then further risk stratification is based on the functional capacity [17]. Activity scales such as the Duke Activity Status Index [18] and the Specific Activity Scale [19] objectively estimate the functional capacity. Studies confirm that functional capacity is predictive of future cardiac events [20, 21]. Perioperative risk is elevated in patients with poor functional capacity. Conversely, the perioperative risk is low in patients with good or excellent functional capacity [22].

Table 33.2 Surgery-specific cardiac risk (combined risk of cardiac death and nonfatal myocardial infarction)

High (reported cardiac risk, often >5%)
Emergency major operation, particularly in elderly
Aortic and other major vascular
Peripheral vascular
Anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss
Intermediate (reported cardiac risk, generally <5%)
Intrathoracic
Intraperitoneal
Carotid endarterectomy
Head and neck
Orthopedic
Prostate
Low (reported cardiac risk, generally <1%)
Endoscopic procedures
Superficial procedures
Cataract
Breast

From "ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery"; Eagle et al. [174]; with permission

Table 33.3 Functional capacity assessment from clinical history

Excellent or good (activities requiring >7 METs)
Carry 24 lb up eight steps
Carry objects that weight 80 lb
Outdoor work (shovel snow, spade soil)
Recreation (ski, basketball, squash, handball, jog/walk 5 mph)
Moderate (activities requiring >4 but <7 METs)
Have sexual intercourse without stopping
Walk at 4 mph on level ground
Outdoor work (gardening, raking leaves, weeding)
Recreation (golfing, bowling, dancing)
Poor (Activities requiring <4 METs)
Shower/dress without stopping, strip and make bed, dust, wash dishes
Walk at 2.5 mph on level ground
Outdoor work (clean windows)

MET metabolic equivalent
Data from Paul and Eagle [175], Mehta et al. [176]; Hiatky et al. [18]

Functional Capacity

Functional capacity (expressed as MET levels) is classified as excellent (>10 METs), good (7–10 METs), moderate (4–7 METs), poor (<4 METs) or unknown. Table 33.3 represents a sample of activities that characterizes each functional class [18, 22, 23]. Exercise capacity estimated from the history alone can be used to predict the risk of perioperative complications. Patients who could not climb two flights of stairs or walk four blocks experienced higher rates of cardiac and neurologic adverse events [24]. Analysis of the NSQIP data revealed that poor preoperative functional class was associated with high risk of perioperative mortality [25]. The ACC/AHA perioperative guidelines recommend to proceed with surgery without further testing in patients who have excellent, good or moderate functional capacity [21].

When the functional capacity is poor or cannot be assessed, further testing should be considered if the patient is willing to pursue revascularization strategies and if it influences (a) perioperative care or (b) patient's decision to proceed to surgery [26]. If the stress test is normal, the patient can proceed to surgery. In case of abnormal stress test, revascularization should be considered depending on the degree of myocardial ischemia. The next step would be one of the following: (a) surgery with optimal medical therapy, (b) other therapeutic options such as radiation, or (c) palliative care [12].

Is Non-invasive Cardiac Testing Necessary?

Evidence discourages widespread application of preoperative non-invasive cardiac testing. The ACC/AHA perioperative guidelines summarize the recommendations for supplemental preoperative evaluation in patients undergoing non-cardiac surgery [16].

Evidence Based Indications for Non-invasive Cardiac Testing in Perioperative Assessment

Electrocardiogram

The preoperative 12-lead electrocardiogram (ECG) provides valuable prognostic data in patients with known coronary artery disease [27]. In patients undergoing major non-cardiac surgery, preoperative ECG can predict perioperative adverse events [28]. The resting ECG serves a baseline standard to compare the postoperative ECG. Routine baseline ECG is not indicated for asymptomatic patients undergoing low risk surgeries [16].

Echocardiogram

Baseline left ventricular (LV) systolic function predicts perioperative complications [29]. Even in asymptomatic patients, LV dysfunction is associated with increased perioperative adverse events [30]. The risk increases with the degree of systolic dysfunction, with highest risk noted in patients with LVEF<30% [31]. However, routine evaluation of LV systolic function is not recommended [32]. Echocardiogram can be considered in asymptomatic patients with known LV dysfunction with no evaluation in the last 1 year. Echocardiogram is recommended in patients with dyspnea of unknown origin or heart failure patients with recent change in clinical status [33].

Exercise Testing

Historically, the role of exercise stress testing in preoperative assessment has been evaluated in various studies [34–38]. McPhail et al. [37] performed preoperative exercise testing in 100 patients undergoing vascular surgery and showed that

the highest rate of cardiac complications (33%) was observed in patients with stress-induced ischemia and poor exercise capacity. Cutler et al. [36] demonstrated that the ability to attain 75–85% of maximum age-predicted heart rate was associated with a low rate of perioperative cardiac events. Poor functional capacity associated with ischemia predicted a high rate for perioperative cardiac events [39]. The risk of postoperative complications is elevated in patients who are not able to achieve >4 METs. Conversely, the risk is low in those who can achieve >7 METs [40].

The ACC/AHA Perioperative Guidelines recommend stress testing in patients with elevated risk and poor or unknown functional capacity if the results of the test will affect the management. It is reasonable to perform exercise stress testing in patients who may be able to achieve requisite workload [39].

Pharmacologic Stress Test

In patients with baseline ECG abnormalities and inability to exercise secondary to other co-morbidities, pharmacologic stress testing is preferred. Dobutamine stress echocardiography (DSE) and pharmacologic stress myocardial perfusion imaging (MPI) have excellent negative predictive values (>90%) but poor positive predictive values (<20%) for detection of patients at risk for perioperative myocardial infarction or death [41–48]. Thus, a negative study is reassuring but a positive study is still a relatively weak predictor of perioperative cardiac events.

The sensitivity and specificity of available exercise and pharmacological stress testing (including exercise electrocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy, and dobutamine stress echocardiography) has been analyzed in several meta-analyses and these studies confirmed the utility of different non-invasive testing modalities for preoperative evaluation [49–52]. Routine preoperative pharmacologic stress testing is not recommended in patients undergoing low risk surgeries. Pharmacologic stress testing with either DSE or pharmacologic stress MPI can be considered with patients with poor functional capacity if the results of the test will alter management [48]. A meta-analysis evaluating the utility of stress echocardiography and thallium MPI in patients undergoing non-cardiac surgery demonstrated that both modalities were comparable for detection of moderate to large perfusion defects but stress echocardiogram was marginally superior due to its better negative predictive value [53]. The choices among non-invasive tests should be based on which test is most reliable and available locally.

Myocardial Perfusion Imaging

The role of preoperative radionuclide MPI for risk stratification was first reported by Boucher et al. [54] in 1985 and has since been validated in a number of studies [48, 55–57]. The positive predictive value has been consistently low, but negative predictive value is high [47, 58]. Moderate to large reversible defect suggestive of myocardial ischemia identifies patients at high risk of perioperative cardiac complications [48, 55], whereas fixed defect identifies patients at risk for long term cardiac events [44].

Dobutamine Stress Echocardiography

A number of studies support the utility and safety of dobutamine stress echocardiography (DSE) for preoperative evaluation of patients undergoing aortic and vascular surgeries [41–46]. In these studies, the perioperative event rates ranged from 0 to 15%. The positive predictive value ranged from 0 to 37% whereas the negative predictive value was over 90%. In majority of the studies, the DSE was used as a screening test to identify potential high risk patients which led to changes in perioperative care including preoperative cardiac catheterization and further titration of medical therapy [41–46]. Echocardiogram is preferred imaging modality for stress testing if valvular function and pulmonary hypertension need to be assessed [59]. A study of 46 patients with severe chronic obstructive lung disease demonstrated the utility of DSE for the preoperative evaluation in these patients [60]. If image quality is suboptimal for evaluation of wall motion, intravenous contrast can be used for better delineation of the endocardial border [61].

Preoperative Coronary Angiography for Risk Stratification

Recommendations for preoperative coronary angiography are similar to those for patients with suspected or known coronary artery disease. Routine use of invasive coronary angiography for preoperative evaluation is discouraged [62]. Computed tomography coronary angiography is useful for the estimation of coronary artery calcium score and the detection of significant coronary artery stenosis. This tool provides additional risk stratification information over RCRI [63, 64]. However, there is limited data to recommend its routine use for preoperative evaluation.

Is There a Benefit for Preoperative Coronary Revascularization

The role of preoperative coronary revascularization was evaluated in Coronary artery Revascularization Prophylaxis (CARP) trial which showed that prophylactic coronary revascularization with either coronary bypass grafting (CABG) or percutaneous coronary intervention (PCI) does not provide short or long-term benefit [32]. It is important to note that patients with left main coronary stenosis, severe aortic stenosis, LV ejection fraction <20% were excluded from the trial [32]. The ACC/AHA guidelines discourage

preoperative routine coronary revascularization solely to decrease perioperative complications [32]. If coronary artery bypass surgery is indicated based on preoperative testing, without factoring in the noncardiac surgery, coronary revascularization should be considered. Preoperative percutaneous coronary intervention (PCI) may be appropriate in patients with (a) significant left main disease in whom other co-morbidities preclude bypass surgery, (b) acute coronary syndrome, or (c) ventricular arrhythmias in setting of myocardial ischemia [65]. In summary, preoperative revascularization should be considered for the same indications listed in current clinical practice guidelines for bypass surgery and PCI [65, 66].

Timing of Elective Noncardiac Surgery in Patients with PCI

If revascularization is indicated, the type of intervention depends on the urgency of the surgery, risk of bleeding and ischemic events [67]. If the surgery is time-sensitive and should be performed in 2–6 weeks, then balloon angioplasty may be considered [68]. If the surgery can be delayed for >6 months and bleeding risk is low, then drug eluting stent implantation is appropriate as dual antiplatelet therapy (DAPT) can be safely discontinued after 6 months [69]. If the surgery is likely in 1–3 months or the bleeding risk is high, then bare metal stent implantation should be considered. Ideally, DAPT should be continued for 6 months and 30 days after drug eluting stent and bare metal stent implantation respectively [69]. If surgery is likely in 3–6 months after stent implantation and the risk due to delay in surgery is greater than the risk of stent thrombosis, then discontinuation of DAPT can be considered in patients who have received drug eluting stent. In all patients who have undergone stent implantation, perioperative continuation of aspirin is appropriate. The ACC guideline recommends DAPT for 12 months in patients with recent ACS [69].

What Additional Preoperative, Intraoperative, and Postoperative Risk Modification Strategies?

Role of Medical Therapy

Beta Adrenergic Antagonists

Small studies demonstrated the benefit of perioperative beta blockers in reducing cardiac risk [67, 68, 70, 71]. Subsequent RCT confirmed the efficacy of beta blockers in intermediate and risk patients [72]. This led to incorporation of perioperative beta blockade in the guidelines at that time [73]. But these studies were limited by small sample size. Additionally, meta-analysis and subsequent observational study revealed potential harm with perioperative beta blockers [74, 75]. This gave way to POISE trial, a large randomized controlled multicenter study, in which metoprolol tartarate was started 2–4 h before surgery and continued for 30 days after surgery [76]. The POISE trial showed that perioperative beta blockers were associated with reduced perioperative cardiac events but this came with an increased risk of stroke and overall higher all-cause mortality [76]. One of the criticisms of this study was the initiation of a high dose of long-acting blocker just before non-cardiac surgery. Subsequent meta-analysis revealed that the initiation of beta blockers ≤1 day before surgery decreased nonfatal myocardial infarction but increased the rates of hypotension, bradycardia, and stroke [77]. On the other hand, studies have shown that abrupt discontinuation of beta-blockers in the perioperative period is associated increased mortality and adverse cardiac events [78, 79].

Studies have demonstrated that titration of beta blockers to target rate is important to achieve anti-ischemic benefit [80]. But it is still unclear whether perioperative dose titration is more beneficial compared to fixed dose strategy because most patients, in studies which incorporated dose titration in the protocols, remained on the initiating dose of beta blocker on the day of the surgery [72].

The ACC/AHA guidelines on the recommendations for perioperative beta blocker therapy can be summarized as follows [81]: (1) Beta blockers should be continued in patients on long-term therapy but adjustment of medications should be based on the clinical situation in the perioperative period; (2) Beta blockers may be initiated in the perioperative period in patients identified to have moderate to large ischemia on preoperative assessment; (3) Beta blockers may be initiated in elevated risk patients identified by multiple clinical predictors; (4) Beta blockers should not be initiated on the day of the surgery. Starting beta blockers 2–7 days before surgery is favored [82].

Alpha-2 Adrenergic Agonists

Evidence from two meta-analyses supported the prophylactic use of alpha-2-agonist in the reduction of myocardial ischemia and perioperative cardiovascular complications [81, 83]. A placebo-controlled prospective randomized trial in 2004 demonstrated the benefit of oral and transdermal clonidine for the reduction of preoperative ischemia and mortality [84]. However, this study was underpowered to support the routine and widespread use of perioperative alpha-2 agonists. The POISE-2 trial was a large multicenter, RCT involving 10,010 patients evaluating the benefit of clonidine, when compared to acetyl-salicylic acid and placebo, in patients, with risk factors for or known atherosclerotic disease, undergoing non-cardiac surgery [85]. This study showed that preoperative clonidine was associated with an increased risk of nonfatal cardiac arrest and clinically

significant hypotension. Additionally, there was no effect on death or nonfatal myocardial infarction [85]. The ACC/AHA perioperative guidelines discourage the use of alpha-2 adrenergic agonists for reduction of perioperative cardiac events in patients undergoing surgery [86].

HMG-CoA Reductase Inhibitors (Statins)

The current evidence supports the use of statins for reduction of perioperative cardiac events and mortality [87–94]. A retrospective propensity matched case control study of 780,591 patients demonstrated that statins were associated with a 38% reduction in mortality (adjusted OR 0.62; 95% CI 0.58–0.67) [88]. Data from two RCTs and a meta-analysis revealed that statins decrease perioperative cardiac events [92–94]. The ACC/AHA perioperative guidelines recommend continuation of statins in patients undergoing cardiac surgery. Statins can be started in perioperative period in patients undergoing vascular surgery. Statins can be considered, if indicated according to the current guidelines, in patients scheduled for elevated risk procedures [95].

Calcium Channel Blockers

Evidence to date suggests a beneficial effect with the use of calcium channel blockers in the perioperative period but the data is still inconclusive. A large RCT is required to evaluate the role of these medications. A pooled analysis of 11 studies showed that calcium channel blockers were associated with lower rates of myocardial ischemia, supraventricular tachycardia, and composite of mortality/myocardial infarction. Subgroup analysis revealed that the majority of the benefits were due to diltiazem [96]. The ACC/AHA perioperative guidelines do not support or discourage the calcium channel blockers in a perioperative setting [97].

Angiotensin-Converting Enzyme (ACE) Inhibitors

Current evidence suggests that the use of angiotensin-converting enzyme (ACE) inhibitors in perioperative period is not associated with worse outcomes. A large retrospective study of 79,228 patients showed that perioperative ACE inhibitors did not increase mortality [98]. In a separate meta-analysis, use of renin-angiotensin-aldosterone antagonists in perioperative setting resulted in increased rates of hypotension, but the effect on long term outcomes could not be estimated [99]. Studies reveal that perioperative renin-angiotensin antagonists results in significant hypotension after induction of anesthesia which may require the use of vasopressor agents [86, 100–102]. There are few studies evaluating the impact of discontinuation of renin-angiotensin antagonists before non-cardiac surgery [103]. Current guidelines recommend perioperative continuation of renin-angiotensin antagonists and suggest re-starting these medications at an appropriate time after surgery if stopped preoperatively [104].

Antiplatelet Agents

Evidence to date does not support the preoperative initiation or continuation of aspirin in nonstented patients [105, 106]. The PEP (Pulmonary Embolism Prevention) trial involving 13,356 patients undergoing orthopedic surgery revealed that aspirin did not reduce the rates of myocardial infarction, stroke or death but was associated with increased bleeding [105]. The POISE-2 trial showed that perioperative use of aspirin, in patients undergoing noncardiac surgery and at increased risk of vascular events, does not decrease death or non-fatal myocardial infarction but increases the rates of major bleeding [106].

In patients with prior percutaneous coronary intervention, who are undergoing noncardiac surgery, recommendations depend on the history of myocardial infarction and the type of stent. DAPT should be continued for at least 1 year after myocardial infarction [107]. The risk of stent thrombosis is highest in the first few weeks after stent implantation [108]. Interruption of DAPT in this period, especially in patients undergoing surgery is associated with extremely high risk of stent thrombosis [109]. The recommended minimum duration of DAPT is 1 month for patients who underwent bare metal stent implantation for stable coronary artery disease [107]. For patients who were treated with drug eluting stent, DAPT should be continued for 6 months. However, cessation of DAPT can be considered after 3 months if the patients deemed to be at high risk for bleeding [107]. If interruption of DAPT is necessary for the surgery, aspirin should be continued and $P2Y_{12}$ inhibitor should be restarted as soon as it is feasible [110].

Oral Anticoagulant Agents

Oral anticoagulant therapies include vitamin K antagonists (warfarin) and direct-acting oral anticoagulants (DOACs). Oral anticoagulant agents are recommended for prevention of stroke in atrial fibrillation and for prevention and treatment of deep vein thrombosis [111]. Anticoagulation is also indicated for patients with mechanical heart valves. But in patients with prosthetic valves, dabigatran is associated with increased risk of thrombosis [112]. Therefore, warfarin is the only oral anticoagulant therapy recommended for patients with prosthetic valves. The decision to continue or interrupt oral anticoagulation depends on the surgical bleeding risk and consequences of bleeding [113]. For example, relatively small amount of bleeding with neuraxial anesthesia may lead to significant morbidity [114]; on the other hand, minimal bleeding with dermatology procedure is inconsequential. The ACC/AHA valve guidelines recommend continuation of perioperative anticoagulation in patients with mechanical valves undergoing minor surgeries where hemostatic control can easily achieved [115]. Expert consensus recommendations outline the decision pathway for periprocedural anticoagulation in nonvalvular atrial fibrillation [113]. In patients

with prosthetic valves, bridging with subcutaneous or intravenous anticoagulant is based on the type and location of the prosthetic valve as well as thromboembolic risk factors [115]. Bridging anticoagulation is recommended in patients with (a) mechanical aortic valves and thromboembolic risk factors, (b) mechanical mitral valve, or (c) older generation aortic valves. Temporary interruption is reasonable in patients with newer generation mechanical aortic valves with no risk factors [115, 116].

Reversal of anticoagulation may be needed for urgent or emergent surgeries. In patients receiving vitamin K antagonists, fresh frozen plasma and prothrombin complex concentrates can be administered for urgent reversal of anticoagulation [117]. Idarucizumab was recently approved by FDA for reversal of anticoagulant effects of dabigatran. Reversible agents for factor Xa inhibitors are under investigation [114].

Other Strategies for Reducing Perioperative Risk

Anesthetic Strategies and IntraoperativeManagement

A number of meta-analyses examined the effect of general and neuroaxial (epidural or spinal) anesthesia on cardiovascular outcomes [97, 118, 119]. Rogers et al. performed a pooled analysis of 141 trials involving 9559 patients and demonstrated that overall mortality was reduced by about one third (OR 0.70, 95%; CI 0.54–0.90) in patients randomized to receive neuroaxial anesthesia compared to patients who received general anesthesia [119]. Lower rates of venous thrombosis, pulmonary embolism, pneumonia, and respiratory depression were observed in patients who received neuroaxial anesthesia [119]. Conversely, other studies did not show any significant differences in cardiovascular events between the two techniques [120, 121]. A recent Cochrane review of 15 RCTs revealed that, in patients undergoing abdominal aortic surgery, epidural anesthesia provided more pain relief and was associated with lower rates of myocardial infarction when compared to opiod-based pain management [122]. Other studies have also shown that pain management in the perioperative period is crucial for reducing cardiac risk [97, 123]. There is limited data evaluating the benefit of preoperative analgesia on cardiac outcomes. In a randomized trial of 64 patients, preoperative epidural analgesia, for pain relief in the setting of hip fracture, reduced the rates of preoperative cardiovascular complications such as heart failure, atrial fibrillation and myocardial infarction [124].

Current evidence on the utility of pulmonary artery catheters (PAC) in high risk patients undergoing major noncardiac surgery is controversial. Current guidelines do not support the routine use of PAC in patients with elevated risk [125]. A large multicenter randomized trial showed found no benefit to therapy directed by a PAC over standard care in elderly, high risk surgical patients [126]. PAC may be considered in patients with tenuous hemodynamic state due to underling disease such as significant valvular disease, severe cardiomyopathy which cannot be changed before the procedure.

Since ischemia induced myocardial wall motion abnormalities appear earlier than ischemia-induced electric abnormalities, intraoperative transesophageal echocardiography (TEE) was considered a more sensitive tool for detection of ischemia [104, 127]. However, routine monitoring with TEE or 12-lead EKG, during noncardiac surgery, did not provide any incremental value for detection of perioperative ischemia when compared with intraoperative monitoring using two-lead EKG [128]. Therefore, the routine use of intraoperative TEE is not recommended for monitoring and guiding therapy during noncardiac surgery [4]. However, emergency use of TEE can be considered in hemodynamically unstable patients undergoing noncardiac surgery for understanding the etiology causing hemodynamic derangement [4].

Theoretically, maintaining intraoperative normothermia is a good risk reduction strategy. Core body temperatures commonly fall in the first hour of anesthesia [129]. Hypothermia triggers sympathetic autonomic hypertension due to increase in the levels of circulating norepinephrine and may result in systemic vasoconstriction [130]. Decrease in core temperature about 1 °C results in shivering and increased total body oxygen consumption, which further increase the demand for cardiovascular work [131]. The increase in adrenergic and metabolic demand can lead to a mismatch in myocardial oxygen supply and demand resulting in myocardial ischemia or infarction [132, 133]. However, evidence supporting the maintenance of perioperative normothermia is equivocal. A randomized trial of 300 patients, which compared ambient temperature to normothermia with air warmers, demonstrated that perioperative normothermia was associated with lower incidence of cardiac events [132]. On the other hand, a multicenter study which randomized 1000 patients with subarachnoid hemorrhage to either perioperative normothermia or hypothermia showed no difference in cardiovascular outcomes between the two groups [134].

Perioperative Anemia Management

Perioperative anemia can lead to myocardial ischemia, especially in patients with coronary artery disease. Studies conducted so far have attempted to identify the optimal hemoglobin level for transfusion in patients experiencing symptoms of ischemia and in asymptomatic patients. In a large multicenter study published in 2011, close to 2000 patients with known coronary artery disease or risk factors for coronary artery disease were randomized postoperatively to either a liberal transfusion approach (hemoglobin <10 g/dL) or a restrictive transfusion approach (hemoglobin <8 g/dL or symptoms of anemia) [135]. This study demonstrated

no differences in mortality, myocardial infarction and unstable angina between the two groups [135]. The American Association of Blood Banks clinical practice guidelines recommend a conservative transfusion strategy (hemoglobin <7–8 g/dL) in stable patients without coronary artery disease [136]. Transfusion can be considered in patients with known coronary artery disease if hemoglobin is <8 g/dL or if they develop symptoms suggestive of myocardial ischemia. The goal is to maintain postoperative hemoglobin >8 g/dL [136].

Monitoring for Perioperative Myocardial Infarction

Postoperative elevation in cardiac biomarkers, specifically troponin is associated with higher risk for future cardiac events [110, 137]. Higher levels of creatine kinase and myocardial band fraction elevation are also associated with increased mortality [138]. In a study of 21,842 patients undergoing noncardiac surgery, 3904 patients had an elevation of troponin and 3633 patients did not report ischemic symptoms [139]. Postoperative troponin elevation even in the absence of symptoms was associated with higher 30-day mortality [139]. However, the cause of death was not specifically studied in these trials. Therefore, the management of the patients with troponin elevation especially in the absence of symptoms of myocardial ischemia is not clearly defined. The MANAGE (Management of Myocardial Injury After Noncardiac Surgery Trial) study will shed more light on the role of postoperative troponin monitoring [140]. This study evaluates the role of dabigatran and omeprazole in patients who suffered myocardial injury after noncardiac surgery [140]. Routine monitoring of patients with troponin testing in the absence of myocardial ischemia is not recommended [4].

The role of ECG in postoperative patients with cardiovascular risk factors but no evidence of myocardial ischemia is not clear [4]. Previous studies have shown that ischemic ECG changes predicted future cardiovascular events [141]. But recent studies have demonstrated that the troponin testing is more sensitive for detection of myocardial injury [142]. So troponin testing may be a better screening tool compared to ECG [4].

Noncardiac Surgery in Patients with Specific Cardiovascular Conditions

Valvular Heart Disease

Special consideration has to be given in preoperative risk assessment of patients with valvular lesions. Significant valvular heart disease is associated with increased risk of perioperative cardiac events [16]. Echocardiogram is indicated in patients with suspected valvular disease as it provides valuable information regarding the severity of valve disease, left ventricular systolic function and right ventricular systolic pressures. The main goal is to optimize the perioperative risk by defining the type and severity of valve disease preoperatively, selecting the anesthetic option suitable for the underlying valve pathology, and ensuring close hemodynamic monitoring in the perioperative period [4].

Current guidelines recommend intraoperative and postoperative hemodynamic monitoring in patients with asymptomatic aortic stenosis undergoing noncardiac surgery. The main goal in patients with aortic stenosis is to prevent tachycardia and hypotension which can lead to myocardial injury, arrhythmia and death [4]. A recent study demonstrated that patients with aortic stenosis have a twofold increased risk of perioperative mortality and approximately threefold increased risk of nonfatal myocardial infarction compared to patients without aortic stenosis [143]. Concomitant significant mitral regurgitation, high-risk noncardiac surgery and prior cardiovascular disease increase the risk of perioperative mortality and myocardial infarction in patients with aortic stenosis undergoing noncardiac surgery [143]. Patients with severe symptomatic aortic stenosis should undergo aortic valve replacement before noncardiac surgery. Prior studies have demonstrated the role of percutaneous aortic balloon dilation in patients with severe aortic stenosis before noncardiac surgery [144]. The PARTNER (Placement of Aortic Transcatheter Valves) trial showed that TAVR improves outcomes in patients deemed ineligible or high risk for surgical AVR [145, 146]. More recently, SURTAVI trial showed TAVR was comparable to SAVR even in intermediate risk patients with severe aortic stenosis [147]. To date, there are no studies evaluating the efficacy of transcatheter aortic valve replacement (TAVR) in patients with aortic stenosis undergoing elective noncardiac surgery. If aortic valve intervention is not an option, it is reasonable to proceed with noncardiac surgery using careful hemodynamic monitoring to maintain optimal preload and afterload in the perioperative period [4].

The management of patients with severe mitral stenosis is similar to patients with aortic stenosis in that the goal is to prevent tachycardia and hypotension while monitoring the filling pressures [4]. Valvular intervention, before noncardiac surgery, is recommended if indicated in patients with mitral stenosis [148]. If valve anatomy is not favorable for intervention, hemodynamic monitoring to maintain optimal preload and afterload should be considered [4].

Patients with aortic or mitral regurgitation benefit with careful hemodynamic monitoring in intraoperative and postoperative period. The main goal in patients with left sided regurgitant lesions is to maintain preload and reduce afterload to ensure adequate forward cardiac output. Patients undergoing elevated risk surgery should be monitored postoperatively in an intensive care unit [4].

Arrhythmias and Conduction Defect

Ventricular and atrial arrhythmias were considered as predictors of perioperative cardiac complications [149]. Mahla et al. showed that asymptomatic perioperative arrhythmia such as premature ventricular complex and nonsustained ventricular tachycardia detected by continuous ECG monitoring did not predict adverse cardiac events [150]. However, identification of preoperative arrhythmia warrants careful evaluation for underlying ischemic heart disease, cardiomyopathy, metabolic abnormalities or other condition that may contribute to adverse perioperative outcomes.

Asymptomatic arrhythmias in the perioperative period warrant observation alone. Third-degree atrioventricular block can increase operative risk and require pacing [12]. However, probability of third-degree atrioventricular block in asymptomatic patients with just intraventricular conduction abnormality such as left or right bundle branch block and no prior history of advanced high-grade atrioventricular block is low [151].

Cardiac Implantable Electronic Devices

Cardiac implantable electronic devices (CIEDs) include pacemakers and implantable cardioverter-defibrillators (ICDs). In patients with CIEDs, interaction between electrocautery and device during surgery is sometimes observed [152]. Electromagnetic interference from the electrocautery causes temporary disruption of pacing in pacemaker-dependent patients [153]. With the recent upgrades in device systems, the risk of electromagnetic interference leading to permanent damage to the device is extremely low [154, 155]. Nonetheless, the perioperative team and clinician following the patient with CIED should discuss and formulate a perioperative management plan well in advance before the elective surgery. The management plan is determined by the patient's underlying rhythm, the type of device, the site of surgery and the possibility of electromagnetic interference from electrocautery. The options include changing the device settings to an asynchronous pacing mode, inactivating tachytherapy on ICD, applying a magnet over the device, or no reprogramming [156, 157]. The reader is referred to consensus document jointly published by the Heart Rhythm Society and the American Society of Anesthesiologists for recommendations regarding the perioperative management of patients with CIEDs [158].

Congestive Heart Failure and Left Ventricular Dysfunction

Congestive heart failure (CHF) has been identified as significant marker of cardiac risk for noncardiac surgery [159]. The two signs, which reflect heart failure (preoperative jugular venous distension and third heart sound), were included in the initial Cardiac Risk Index and predicted worse perioperative outcomes [16]. In a pooled study of 38,047 patients, heart failure (9.3% nonischemic; 9.2% ischemic) was associated with higher perioperative mortality compared to coronary artery disease (2.4%) [160]. Six month survival after vascular surgery was significantly lower in patients with EF <29% compared to those with EF >29% [29]. The perioperative risk probably depends on whether the heart failure is stable. Close monitoring of the volume status is essential to avoid perioperative decompensation. In a retrospective study of 557 consecutive patients, short-term mortality after elective procedures was similar in patients with stable heart failure compared to the control group without heart failure. However, patients with stable heart failure were more likely to be readmitted and have worse long-term survival [161].

Pulmonary Hypertension

Pulmonary hypertension increases the risk of adverse outcomes in patients undergoing noncardiac surgery [162–164]. Decreased functional capacity, the severity of pulmonary hypertension, the urgency of the surgery, and right ventricle (RV) systolic dysfunction predict the postoperative complications [163, 165]. A comprehensive preoperative evaluation, including estimation of functional capacity and assessment of RV function by echocardiography, should be performed in all patients with pulmonary hypertension. Preoperative right heart catheterization is useful for confirmation and further evaluation of pulmonary hypertension [4]. The goal is to optimize RV loading conditions and pulmonary hypertension prior to surgery. In the perioperative period, careful monitoring, prevention of systemic hypotension and hypoxia, and use of systemic vasoactive agents and pulmonary vasodilators when indicated are critical to minimize the complications [166].

Hypertrophic Cardiomyopathy

Patients with hypertrophic cardiomyopathy (HCM) are at risk for exacerbation of dynamic left ventricular outflow tract (LVOT) obstruction. General anesthesia or neuroaxial block can lead to peripheral vasodilation and sympathetic autonomic blockade that may decrease venous return and further exacerbate LVOT obstruction. Observational studies of patients with HCM undergoing non-cardiac surgery suggest that for most operations, patients with compensated HCM tolerate the perioperative period well. Perioperative cardiac risk reduction strategies should include avoidance of hypovolemia, vasodilators, phosphodiesterase inhibitors, beta adrenergic agonists, and diligent attention to volume repletion and selected use of alpha adrenergic agonists [167,

168]. Patients with hypertrophic cardiomyopathy are at significant risk for developing perioperative hypotension, CHF, and arrhythmias and should be monitored closely [167].

Congenital Heart Disease

Studies have demonstrated that patients with left-to-right cardiac shunts with residual hemodynamic abnormalities after surgical repair, experience decreased cardiac output in response to stress [169, 170]. Patients with prior repair of coarctation of the aorta have a significant risk of sudden death during follow-up [171, 172] caused by residual cardiac defects with CHF, rupture of a major vessel, dissecting aneurysm, or complications arising from severe atherosclerosis. Patients with congential heart disease especially those deemed as high risk should undergo comprehensive preoperative evaluation at local center with expertise in congenital cardiology [4]. The reader is referred to ACC/AHA 2008 ACHD clinical practice guidelines for specific recommendations regarding perioperative management [173].

Practical Points

- Around one-third of the patients undergoing surgeries have risk factors for or known cardiovascular disease. The risk of perioperative cardiac complications is related to underlying cardiovascular disease burden.
- Risk prediction models take into account, the patient- and surgery-specific risk factors, to estimate the perioperative risk. Commonly used risk indices include RCRI, NSQIP MICA and NSQIP Surgical Risk Calculator.
- All information obtained from a systematic stepwise approach for preoperative cardiac risk assessment for noncardiac surgery should then be used to decide whether the risk of perioperative cardiac events is low.
- Patients with excellent, good or moderate functional capacity can proceed with surgery with no further testing.
- When the functional capacity is poor or cannot be assessed, further testing should be considered if the patient is willing to pursue revascularization strategies and if it influences (a) perioperative care or (b) patient's decision to proceed to surgery and
- Optimal postoperative patient care involves assessment and treatment of modifiable cardiac risk factors, including hypertension, hyperlipidemia, smoking, obesity, hyperglycemia, and physical inactivity.

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Complementary and Alternative Medicine

34

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Complementary and alternative medical (CAM) therapies can be defined as medical interventions that are currently not an integral part of conventional medicine and that, as such, are not taught widely in United States medical schools and are generally unavailable at U.S. hospitals [1]. Since 1990, documentation by several surveys of the widespread and increasing use by consumers of CAM therapies has brought the attention of the health care community, employers and insurers to the importance of this form of therapies. In 1998 Eisenberg et al. reported that 43% of Americans used at least one form of CAM therapy in 1997 [2] and that there had been a 25% increase in the number of users and a 43% increase in visits to CAM practitioners since 1990 [1]. Eighteen percent of patients taking prescription drugs were also using herbal remedies, and the estimated market for CAM therapy was $21 billion annually. More recently, a survey from the Josiah Macy, Jr., Foundation showed that in the year 2001, more than 50% of Americans were using CAM therapies [3]. An estimated 600 million visits per year were made to CAM practitioners, with an estimated market of $30 billion annually. In that survey, the estimated market for herbal remedies was $10 billion, with a growing market share estimated at 20–30% per year. In addition, as shown by another survey of 376 consecutive patients undergoing preoperative or postoperative cardiac surgery evaluation at Columbia Presbyterian Medical Center in New York, many patients use some form of alternative medicine but do not or do not want to discuss its use with their physicians [4]. Among patients surveyed, 75% admitted the use of alternative medical therapy (44% without prayers and vitamins), but only 17% had discussed this use with their physicians, and 48% did not want to discuss it with their physicians.

The most recent statistics from the 2007 National Health Interview Survey found that nearly 34% of adults over the age of 18 and nearly 12% of children had used CAM in some form within the 12 months prior to the survey [5]. The survey also revealed that Americans spent nearly $43 billion out-of-pocket on CAM practices and products [6]. Moreover, in 2006 the National Center for Complementary and Alternative Medicine (NCCAM) and the American Association of Retired Persons (AARP) conducted a survey of individuals aged 50 or older and the survey revealed that more than two-thirds of respondents used some form of CAM. However, less than one-third of the CAM users had talked to their physicians about CAM. The main reasons given for not talking about CAM were that the respondents did not know they should discuss CAM with their physicians and their physicians never asked them about it [7]. Thus, it is increasingly important for practitioners to gain familiarity with various forms of CAM and to specifically elicit and document a history of use of CAM from patients.

Classification of Complementary And Alternative Medical Therapies

CAM therapies can be categorized in five major groups (National Institutes of Health classification [8]): (a) alternative medical systems, (b) mind-body interventions, (c) manipulative and body-based methods, (d) energy therapies, and (e) biologically based treatments.

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Alternative Medical Systems

Alternative medical systems can be defined as complete systems of theory and practice of medicine that have evolved independently and often before the conventional medical system [8]. Examples of alternative medical systems include Asian medical practices, homeopathic and naturopathic medicine, Ayurveda medicine, and other traditional medical systems developed by Native American, Aboriginal, African, Middle-Eastern, Tibetan, and Central and South American cultures. The characteristics and principles of several systems are summarized in Table 34.1.

In contraposition to conventional allopathic medicine, alternative medical systems are generally characterized by the recognition that mind, body, and spirit are integrated and interconnected and that treatment of illnesses should be aimed toward reestablishment of lost balances and promotion of self-healing processes. As outlined in Table 34.2, many alternative medical systems include the use of herbal therapies. Herbal therapies commonly used in cardiovascular care are discussed later in this chapter, in the section on herbal remedies.

Mind-Body Interventions

Mind-body interventions can be defined as interventions aimed toward promoting the ability of the mind to affect body functions and symptoms [8]. Examples of mind-body interventions include art therapy, biofeedback, dance and movements, hypnotherapy, interactive guided therapy, meditation, music therapy, neurolinguistic therapy, poetry therapy, relaxation therapies, spiritual healing and prayer, yoga, and cognitive-behavioral approaches.

There is now extensive evidence supporting the importance of mind-body interactions on the development of cardiovascular disease. In particular, type A behavior, hostility, stress, and low physical activity have been identified as important correlates of the development of cardiovascular

Table 34.1 Alternative medical systems

Medical system	Region developed	Principle
Asian medical systems		
Traditional Chinese medicine	China	Integrated system based on the central concept of Qi, the vital force that connects body, mind, and spirit. It includes acupuncture, Chinese herbs, massage, breathing and moving exercises, food therapy, and lifestyle modification
Acupressure	China	System based on the principle that illness is the results of stressors that challenge the homeostatic mechanism of the body. Pressing on key points on the skin aligned on meridians or pathways along which the energy flows stimulates the body's self-healing abilities
Acupuncture	China	Similar to acupressure. The anatomic points are stimulated by needles rather than by touch. Over several centuries, numerous subsystems have evolved in different cultures
Tai chi (Taiji and Taijiquan)	China	System based on the principle of Y in (receptive, dark, negative, closed, empty) and Yang (creative, bright, positive, open, full). The smooth alteration of the two during movements results in harmony and balance. It includes movements with coordinated and timed breathing, round motion, and alignment of joints
Qi Gong	China	System based on integration of mind, body, and breathing through meditation, movements, self-massage, and special healing techniques. It is one of the major branches of traditional Chinese medicine, and it relies on the principles of Qi, yin/yang, meridians, and pathogenesis of disease
Ayurveda	India	Traditional medical system of India based on the principle that diseases are caused by lack of harmony of the individual with the environment. It includes herbs, meditation, exercise, massage, exposure to sunlight, and breathing exercises
Western medical systems		
Homeopathy	Germany	Empirical system of medicine based on the principle "Similia similibus curantur"—i.e., drugs that produce symptoms in a healthy person will treat the same symptoms in a disease state—and each individual has a self-healing capacity. The system is based on the laws of similars, of single dose (one dose will stimulate the body), of minimal or lowest possible dose, and of dilution (the more the medication is diluted, the stronger the effect)
Naturopathic medicine	Western world	Natural approach to health and healing based on the principle of treating diseases by stimulating the inherent healing capacity of the individual. Its fundamentals includes the healing power of nature, the treatment of the whole person, the identification and treatment of the cause, the "do no harm" principle, prevention as the best cure, and the role of physician as an educator for patients. Standard diagnostic procedures are integrated with herbal medicine, homeopathy, physical medicine, hydrotherapy, clinical nutrition, minor surgery, and mind-body connections

Table 34.2 Herbal products and orthomolecular therapies commonly used in cardiovascular care

Herbal product	Active compound	Mechanism of action	Indication	Clinical evidence
Garlic	Allicin	Inhibition of platelet aggregation, antilipemic effect, antihypertensive effect	Hypertension Hypercholesterolemia	Limited
Soy protein	Soy protein	Phytoestrogenic effect, decreased cholesterol absorption	Hypercholesterolemia	Limited
Cholestin ("red rice yeast")	Statin compounds	Inhibition of HMG CoA reductase	Hypercholesterolemia	Supportive
Guggul gum	Gugulipid	Cholesterol lowering	Hypercholesterolemia	Supportive
Ginkgo biloba	Ginkgo flavone glycosides and terpenoids	Antiplatelet effect, antioxidant effect, vasodilatation (NO mediated)	Dementia Cognitive dysfunction	Supportive
Hawthorn	Poliphenolic compounds (flavonoids and glycosides) and triterpene acids	Positive inotropic effect, vasodilatation, antioxidant and antiinflammatory effects	Congestive heart failure	Study currently ongoing
Coenzyme Q-10	Coenzyme Q-10	Antioxidant effect (obligatory component of mitochondrial electron transport chain)	Congestive heart failure CAD	None
Vitamin E	–	Antioxidant effect on lipoprotein metabolism, antiplatelet effect	Prevention of CAD	None
Vitamin C	–	Antioxidant effect	Prevention of CAD	None
Vitamin A	–	Antioxidant effect	Prevention of CAD	None
Lutein	–	Antioxidant effect	Prevention of CAD	Animal data
Folic acid	–	Pivotal role in DNA synthesis	Prevention of CAD Prevention of restenosis after percutaneous coronary intervention	Supportive

CAD coronary artery disease, *HMG CoA* 3-hydroxy-3-methylglutaryl coenzyme A, *NO* nitric oxide

disease [9, 10]. On the basis of these premises, it is conceivable that mind-body interventions could have an important impact on the natural history of cardiovascular disease. This hypothesis has been confirmed by the results of a meta-analysis of 23 randomized clinical trials evaluating the addition to conventional therapy of interventions addressing emotional and psychosocial issues [11]. In that analysis, the addition of mind-body interventions was found to significantly reduce morbidity and mortality rates. More recently, an extensive review of various mind-body interventions, including social supports, yoga, religious attendance, imagery, and meditation in the treatment of cardiovascular diseases, revealed that many interventions used as complementary or stand-alone therapy might have beneficial effects on disease progression and on long-term outcomes [12]. A 2008 double-blind randomized study found that both relaxation techniques and lifestyle modifications resulted in a reduction of systolic blood pressure. However more people in the response group that used relaxation techniques were able to discontinue antihypertensive medication and still maintain normal blood pressure [13], than those in the group who simply made lifestyle modifications. Moreover, a 2009 study found that the combination of cardiac rehabilitation and relaxation response training significantly reduced blood pressure and blood lipid levels [14]. Scientific evidence of efficacy based on randomized clinical trials is still limited. However, the lack of significant adverse effects and the anecdotal and, in some instances, scientific evidence of effectiveness supports a potential role of mind-body interventions as complementary therapy for cardiovascular disease.

Manipulative and Body-Based Methods

These therapies are based on manipulation of the body and movements and include chiropractic, massage therapy, and osteopathic medicine.

Chiropractic is based on the relationship between body and function and on the foundation of facilitating the body's own healing power. The aims of this therapy are to alter local tissue stresses, to reduce mechanical stimulation, and to allow the organism to recover. The most common and best-known chiropractic treatment is spinal manipulation. However, chiropractic also includes lifestyle counseling, nutrition management, rehabilitation, and other physiotherapeutic modalities. The beneficial effects of chiropractic have been documented in several clinical trials, and it is now considered an effective treatment modality for spine and related disorders [15]. It is important to note that spinal manipulation is not completely risk free and that there have been several reports of stroke and of vertebral and carotid artery dissection during manipulation of the cervical spine. Thus, extreme caution is advisable particularly for patients with cerebrovascular disease. Hypertension is the only

cardiovascular disease listed among conditions treated relatively often by chiropractors [16].

Massage therapy is one of the oldest health care practices; its origin can be traced back to China in 2000 B.C. It can be divided in five major categories: traditional European; contemporary Western; Asian (acupressure, shiatsu, tuina, AMMA therapy, jin shin do); energetic; and structural, functional, and movement integration. Each of these categories is based on different principles, but the common denominator is promotion of the body's ability to heal itself.

Energy Therapies

Energy therapies are based on the concept of healing through manipulation of energy fields originating within the body (biofields) or through application of energy fields from other sources (electromagnetic fields) [8].

Examples of biofields therapies include polarity therapy, Qi gong, reiki, and therapeutic touch. Polarity therapy was developed by Randolph Stone, and it incorporates in its philosophy healing based on the flow or disruption of electromagnetic fields in the human body. Qi gong is based on the integration of mind, body, and breathing through meditation, movements, self-massage, and special healing techniques. It is one of the major branches of traditional Chinese medicine, and it relies on the same principles of *Qi*, the vital force that connects body, mind and spirit, and on the principle of yin/yang and meridians in the pathogenesis of disease. Reiki can be traced back to Tibet (3000 B.C.). It was later developed and practiced in Japan in the mid-1800s. Reiki is a touch healing system ("laying on of hands") that promotes healing on the physical, mental, emotional and spiritual levels. The practitioner, by laying his or her hands on the patient's body, channels the healing energy of the "universal life-force energy." The skills of the practitioner are acquired through training from a reiki master or teacher who has the ability to connect the student to the reiki energy. A 2010 randomized controlled study of inpatients with immediate post acute coronary syndrome found that the application of reiki resulted in an increase in vagal activity as well as a decrease in negative emotional states and an increase in positive emotional states [17]. While more research is needed to determine whether biofields therapies can provide cardiovascular benefits, evidence suggests that they are effective in reducing pain, stress and anxiety.

Other forms of energy therapy include Emotional Freedom Therapy (EFT) and Brainwave Entrainment. Emotional Freedom Therapy (EFT) also draws on traditional Chinese medicine and the concept that there are meridians in the body that carry energy or *Qi* to the vital organs. EFT practitioners tap on these meridians to stimulate the flow of *Qi* while also repeating a positive affirmation or phrase. Studies show that manual stimulation of acupuncture points can reduce activity in the amygdala and other parts of the brain that produce fear, anxiety, pain and stress Proponents of EFT believe that it reprograms the brain through neuroplasticity, thus rewiring the neural connections to reduce trauma, pain, anxiety and stress. A 2010 randomized controlled trial of veterans with Post Traumatic Stress Disorder (PTSD) revealed that EFT was effective in significantly reducing PTSD scores after six 1-h sessions [18]. Brainwave entrainment involves using regular and consistent rhythmic stimulus to evoke electroencephalogram (EEG) frequency–following response in the brain. This causes the brain to synchronize electrical waves to match the rhythm. By slowing down the frequency of the electrical waves, the brain reaches a natural meditative state that slows down the heart rate. Preliminary evidence suggests that brainwave entrainment may be effective in treating stress, anxiety and pain, but further research is required.

Biologically Based Treatments

Biologically based treatments are practices, interventions, and products aimed toward modification of biologic functions and processes [8]. They include herbal, dietary, enzyme, and orthomolecular therapies. Chelation therapy and special diet therapies such as those proposed by Drs. Robert C. Atkins, Dean Ornish, Nathan Pritikin, and Andrew Weil are also part of this group.

Acupuncture

Acupuncture has been extensively used in Western countries for the treatment of numerous conditions, including chronic pain, postoperative pain, asthma, drug addiction, headache, nausea, osteoarthritis, fibromyalgia, allergies, and gastrointestinal motility disorders. An extensive review of available evidence by a National Institutes of Health (NIH) panel of the effectiveness of acupuncture brought consensus that acupuncture is effective for pain control and for the treatment of nausea. It might also be promising in other conditions, including asthma, myocardial infarction, bronchitis, and rehabilitation from stroke [19].

However, data on the use of acupuncture for the treatment of cardiovascular disease are currently limited. In Russia and in China, acupuncture has been used for the treatment of hypertension, congestive heart failure, and myocardial ischemia. However, these uses have not yet been tested in randomized clinical trials. In spontaneously hypertensive rats, acupuncture like electrical stimulation activates central

opioid pathways, which leads to a decrease in sympathetic activity and in blood pressure. Thus, there appears to be a pharmacologic basis for the use of acupuncture in essential hypertension and in other conditions such as congestive heart failure, in which sympathetic activation plays an important role. An NIH-sponsored randomized clinical trial is currently recruiting patients with hypertension to determine the effectiveness of acupuncture in essential hypertension [20].

Herbal Remedies

An herb is a plant or part of a plant that produces and contains chemical substances that can exert a biologic or pharmacologic effect. According to the Dietary Supplement Health and Education Act of 1994, herbal remedies or botanicals are currently not regulated by the U.S. Food and Drug Administration if sold as dietary supplements. Therefore, they are not regulated for purity, potency, standardization, and formulation. The lack of regulation for potency and composition implies that there might be significant batch-to-batch variability and that there are often many active ingredients in the same preparation. The current regulations allow marketing with statements explaining their reported effect on the structure or function of the human body or the role in promoting general well-being, but not for diagnosis, treatment, cure, or prevention of diseases. Table 34.2 lists the most common herbal remedies used for cardiovascular care.

Garlic

The medicinal use of garlic (*Allium sativum*) dates back to early Egyptian times, and it has been advocated for the treatment and prevention of several diseases. The active ingredient is allicin, an odorous sulfurous compound that has been shown to exert several pharmacologic effects, including inhibitions of platelet aggregation (possibly irreversible), lowering of cholesterol and triglyceride levels, and lowering of blood pressure. In animal models, garlic has an antiatherosclerotic effect, as evidenced by a reduction of the development of new atheromatous lesions and a slowing in the progression of existing lesions. Garlic is currently available as fresh cloves, extracts, powders, and tablets. Several studies have suggested that at least ½ garlic clove per day [21, 22] is required for a pharmacologic effect. Dried powders and tablets appear to be more practical formulations, but doses of the active ingredient are often inadequate. Several studies have assessed the effect of garlic on serum lipids and blood pressure control. Two recent metaanalyses showed that garlic administration resulted in a 9–12% reduction in total cholesterol, a modest reduction in triglyceride levels, and no significant changes in high-density lipoprotein levels [21, 22]. A meta-analysis of eight antihypertensive trials showed on average an 11–mm Hg HG reduction in systolic blood pressure and a 6.5–mm Hg HG reduction in diastolic blood pressure [22]. Another well-designed randomized clinical trial evaluating the effect of garlic on claudication secondary to peripheral vascular disease showed no significant effect on pain-free walking distance or on ankle/brachial index. In yet another double-blind, randomized, placebo-controlled clinical trial evaluating the effect of garlic oil on serum lipoprotein levels and potential mechanisms of action, no significant effects on serum lipoproteins, cholesterol absorption, or cholesterol synthesis were identified [23]. Variation in the concentration of the active compound in formulations may explain some of the differences between the results of clinical trials. The most common adverse effects of garlic are on the gastrointestinal system and include flatulence, esophageal pain, and abdominal pain. A significant interaction between garlic and an antiretroviral agent has been reported. This interaction results in marked reduction of blood levels of the anti–human immunodeficiency virus drug saquinavir in patients taking garlic supplements [24].

Soy Protein

Soy protein has been shown to be effective in lowering cholesterol through a decrease of cholesterol absorption, a decrease in bile reabsorption in the gut, and a phytoestrogenic effect. A meta-analysis of 22 trials showed a 9% decrease in total cholesterol levels, a 13% decrease in low-density lipoprotein (LDL) levels, and a 10% decrease in triglyceride levels [25]. A more recent study has shown that the lipid-lowering effect is present both in normocholesterolemic and in hypercholesterolemic men. The health claim for soy protein at a dose of 25 g/day has been approved by the Food and Drug Administration.

Cholestin (Red Rice Yeast)

Cholestin is a fermented product of rice on which red yeast is grown, and it has been used for centuries in China. It contains starch, proteins, fiber, and at least eight statin compounds which function as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Chinese studies have shown that total cholesterol reduction after cholestin administration varies from 11 to 32%. A more recent randomized clinical trial showed a 15% reduction in total cholesterol and a 22% reduction in LDL cholesterol [26]. Because cholestin contains several statin-like compounds, its use requires the same precautions as with prescription statins.

Guggulipid (Guggul Gum)

Gugulipid is an extract from the natural resin (gum guggula) of the mukul myrrh tree. It has been used in India to lower cholesterol, and it has been evaluated in well-designed clinical trials performed in India [27–29]. These studies have shown that gugulipid administration results in a reduction of total cholesterol levels ranging from 11 to 22% and a reduction of triglyceride levels ranging from 12 to 25%. One study showed a 12% reduction of LDL. More recently, oral three times daily doses of guggulipid (1000 mg) were compared with high dose guggulipid (2000 mg) and with matching placebo in a randomized clinical trial including 103 adults with hypercholesterolemia. Contrary to the expectation, administration of standard dose and high dose guggulipid was associated with a 4–5% increase in LDL-Cholesterol. In that study, six patients treated with guggulipid developed a hypersensitivity rash [30].

Ginkgo Biloba

Ginkgo biloba has been used for memory loss and to improve circulation. The EGB 761 extract of ginkgo biloba is highly standardized, and it is currently widely used in Europe. There are at least three active compounds in ginkgo biloba: ginkgo flavone, glycosides, and terpenoids. Ginkgo biloba has an antiplatelet and antioxidant effect, it reduces platelet-activating factors, and it reduces production of thromboxane A_2 [31]. It has also been shown to enhance endothelial cell derived nitric oxide through either an increase in nitric oxide synthase activity or a decrease breakdown of nitric oxide mediated by its antioxidant effect. Ginkgo biloba has been approved in Europe for treatment of dementia. In a study involving 202 patients, ginkgo biloba was found to decrease the Alzheimer's Disease Assessment Scale–Cognitive subscale score better than did placebo [32]. There were no significant differences in the incidence of adverse reactions.

Overall, ginkgo biloba is considered a safe supplement; the most common adverse effects are headache and gastrointestinal. However, cases of subdural hematomas and bleeding have been described [33–35]. It is currently believed that the increase in bleeding risk is due to ginkgolide B, an important inhibitor of platelet-activating factor. Thus, the use of ginkgo biloba is currently not recommended for patients receiving anticoagulants, aspirin, or nonsteroidal antiinflammatory agents or for patients undergoing surgical procedures.

Hawthorn (*Crataegus*)

The use of hawthorn as a cardiac medication can be traced back to Roman physicians in the first century A.D. Since then, it has been used for the treatment of congestive heart failure. Hawthorn is derived from a small, fruit-bearing tree that grows throughout the world in woodlands. It has been used in Japanese, Chinese, European, and Native American traditional medicine and by American herbalists. The active components include two groups of polyphenolic derivatives that are present in the leaf and the flower, and, at a lower concentration, in the berries. The polyphenolic compounds include flavonoids and their glycoside and oligomeric proanthocyanidins. Triterpene acids are additional active components [36]. The pharmacologic effects of hawthorn include a positive inotropic effect, coronary and peripheral vasodilation and antioxidant and antiinflammatory effects, resulting in an overall cardioprotective activity. Hawthorn has been evaluated in several clinical trials enrolling a total of 1500 patients. In these studies, administration of hawthorn was found to improve exercise efficiency, to increase duration of exercise to anaerobic threshold, to increase left ventricular function, and to result in beneficial hemodynamic changes, which include a decrease of systemic blood pressure, a decrease in heart rate, an increase in cardiac output, a decrease in pulmonary artery pressure and pulmonary wedge pressure, and an overall decrease in systemic vascular resistance. These study are limited in that some were unblinded and uncontrolled, they were largely limited to New York Heart Association Class II patients, and background therapy usually included only diuretics and possibly digoxin. The place of hawthorn in the contemporary management of chronic congestive heart failure has been investigated in two randomized, placebo-controlled clinical trials, both using *Crataegus* special extract WS1442 (Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany). The Hawthorn Extract Randomized Blinded Chronic Heart Failure (HERB CHF) study enrolled 120 patients to evaluate changes in exercise capacity, left ventricular function, quality of life, neurohormonal profile, and oxidative stress [37]. The results showed that the use of hawthorn extract in patients with mild-to-moderate chronic heart failure (HF) is not associated with any additional beneficial effect in patients already receiving standard concomitant medical therapy [37]. The Study of Prognosis in Congestive Heart Failure (SPICE) randomized 2681 patients with NYHA class 2–3 heart failure and an LVEF $\leq$35% to receive either WS-1442 (900 mg daily) or placebo for 2 years. All participants received standard drug therapy, which included diuretics in 85%, ACE inhibitors in 83%, beta blockers in 64%, glycosides in 57%, and aldosterone blockers in 39% of patients.

The primary end point was a 24-month composite of sudden cardiac death, death due to progressive heart failure, fatal or nonfatal myocardial infarction, or hospitalization due to progression of heart failure, measured at 24 months. Also in this study, there was no significant difference in the incidence of the primary endpoint between the group of patients treated with WS-1442 and the group of patients treated with placebo (28% vs. 29%) [38].

Ginger

Ginger, the root or rhizome of the plant *Zingiber officinale,* has a long history of being used in Asian, Indian and Arabic healing traditions to treat everything from digestion to arthritis, nausea, pain and heart conditions. The oleoresin from the rhizomes contains many bioactive components that have pharmacological properties and may produce powerful therapeutic and preventative effects. Studies show that ginger is effective in decreasing age-related oxidative stress markers and inflammation and inhibit nitric oxide production. Much research has been done on the potential of ginger to treat various aspects of cardiovascular disease. A 2008 double-blind controlled clinical study showed that volunteers who took 3 g of ginger powder a day in 1 g capsules three times daily had significantly lower triglyceride and LDL cholesterol levels than the placebo group [39]. Another study revealed that rats that were fed ginger had significantly better glucose tolerance and higher serum insulin levels than untreated rats, which may suggest that ginger has anti-diabetic properties [39]. While a great deal of animal data supports the fact that ginger appears to reduce cholesterol and improve lipid metabolism, thereby helping to decrease the risk of cardiovascular disease and diabetes, further research is needed in human trials.

Curcumin (Turmeric)

Turmeric has been used in traditional medicine for thousands of years to treat a variety of diseases. Research shows that curcumin, the natural phenol found in turmeric, contains antioxidant, anti-inflammatory, and anti-thrombotic properties that provide cardiovascular benefits. Research shows that long-term administration of curcumin is effective in preventing and treating atherosclerosis by lowering plasma and hepatic cholesterol and suppressing atherosclerotic lesions [40]. Another recent study showed that curcumin administration significantly reduced the risk of myocardial infarction after coronary bypass [41]. Moreover, studies show that curcumin may be effective in preventing and reversing cardiac hypertrophy, suppressing and modulating glucose levels, and lowering LDL cholesterol and triglycerides. The recommended dosage for standardized curcumin powder supplements is 400–600 mg three times a day. The Food and Drug Administration has declared that curcumin is generally regarded as safe, and there are few reports of adverse side effects.

Arjuna

Ayurvedic practitioners in India have been using the bark from the Arjuna (*Terminalia Arjuna*) plant for thousands of years to combat anginal pain, hypertension, congestive heart failure, and dyslipidemia. Arjuna extracts contain bioactives like polyphenols and flavonoids that may have anti-inflammatory and antioxidant cardiovascular effects. Various studies on animals show that arjuna bark extract has been effective in increasing circulation, strengthening the cardiac muscle, lowering blood pressure, cholesterol and triglyceride levels, and preventing oxidative stress associated with ischemic–reperfusion injury of the heart [42]. In one human study on patients with myocardial infarction with angina and/or ischaemic cardiomyopathy, bark stem powder of arjuna was shown to significantly reduce angina frequency and left ventricular mass, and improve left ventricular ejection fraction [43]. A 2001 randomized controlled trial revealed that arjuna was effective in reducing total cholesterol and LDL cholesterol in patients with coronary heart disease, even more so than Vitamin E, a known antioxidant [44]. In clinical trials arjuna bark extract was administered in 500 mg capsules every 8 h. As of yet, arjuna has not been found to produce negative side effects or interact negatively with other medications.

Grape Seed Extract

Grape seeds have highly concentrated levels of Vitamin E, flavonoids, linoleic acid, oligomeric proanthocyanidin complexes (OPCs), which may contribute to cardiovascular health. Randomized trials on the cardiovascular health benefits of grape seed extract in humans have yielded conflicting results, although evidence shows that grape seed extract may be effective in lowering blood pressure and heart rate. One study looked at the effect grape seed extract had on LDL cholesterol and oxidative stress in 24 male heavy smokers 50 years and older. The men were divided into two groups with one group receiving 2 capsules daily of 75 mg of grape procyanidin extracts and soy-phosphatidlcholine and the other group receiving a placebo. After 4 weeks, the group who took the grape seed extract had significantly lower levels of LDL cholesterol than the placebo group [45]. Grape seed extract may interact with medications that are broken down in the liver and it may act as a blood thinner, so it is not recommended for use with anticoagulants.

Green Tea

Green tea (*Camellia sinesis*) has been cultivated for centuries in Asia and parts of India, and traditional Chinese and Ayurvedic medical practitioners have been using it for nearly as long for numerous health conditions including cardiovascular disease. Green tea leaves contain a high concentration of powerful antioxidants as well as Epigallocatechin Gallate (EGCG), a polyphenol that is believed to protect against oxidation, lower LDL cholesterol, lower blood pressure and

increase HDL cholesterol. The Natural Medicines Comprehensive Database rates green tea as likely effective for lowering cholesterol and possibly effective for lowering blood pressure and reducing the risk of coronary artery disease. A Chinese randomized controlled trial found that regular green tea drinkers showed a 45–65% reduction in hypertension risk when compared to non-consumers of tea [46]. In another study of Japanese men, it was found that those who consumed a 3% concentration of green tea had lower mean values of fasting blood glucose and fructosamine than those who consumed a 1% concentration. Therefore, the researchers concluded that green tea at a high concentration has the potential to lower blood glucose levels [47]. The Natural Medicines Comprehensive Database rates green tea as likely safe for most adults when consumed in moderate amounts. However, in some cases green tea has been reported to cause stomach upset, constipation and in rare cases liver problems. The caffeine present in green tea may also cause side effects. In addition, green tea may have interactions with certain medicines including antibiotics and anticoagulants.

Spirulina

Spirulina is a free-floating blue-green algae found in alkaline waters that is often referred to as a superfood for its myriad of nutrients including vitamins B12, C, D, A and E, protein, potassium, beta-carotene, zinc, iron, selenium, calcium, essential amino acids and gamma linolenic acid. Data from animal and human clinical trials show that spirulina has hypolipidemic, antioxidant and anti-inflammatory activities. A 1998 study looked at the effect of spirulina on serum lipids in 30 male volunteers who had hyperlipidemia or mild hypertension, and they found that there was a marked reduction in serum cholesterol in those patients who were taking spirulina [48]. In a more recent study researchers at the Universidad Nacional Autonoma de Mexico found that spirulina was effective in increasing in the release of nitric oxide by the endothelium, decreasing the release of a vasoconstricting eicosanoid by the endothelium, and decreasing blood pressure and plasma lipid concentrations [49]. Spirulina appears safe even in high doses and the standard dose is 500 mg four to five times a day.

Raw Cacao

Historical evidence shows that the ancient Mayans and Aztecs used raw cacao in a medical capacity over 2000 years ago, and since then holistic healers have been espousing its wide range of health benefits. Pure cacao contains a wide variety of essential vitamins and minerals including vitamins A, B1, B2, B3, C, and E, magnesium, calcium, iron, zinc, copper, potassium, and manganese. Reports indicate that the flavonoids in cacao have beneficial activities including antioxidant protection and modulation of vascular homeostasis [50]. In addition, flavonoids encourage the activation of nitric oxide, which improves the elasticity of the blood vessels and circulation and decreases insulin resistance. A systematic review of a large number of trials found that cacao may have beneficial effects on cardiovascular risk including lowering blood pressure, anti-inflammation, anti-platelet function, higher HDL, decreased LDL oxidation. The researchers also conducted an updated meta-analysis of flavonoid intake and coronary heart disease (CHD) mortality and found that flavonoids likely lower the risk of death from coronary heart disease The Dutch Zutphen Study involved involving 470 healthy elderly men and found that not only was cocoa intake was inversely related to blood pressure, but that the risk for cardiovascular mortality for men in the highest tertile of cocoa intake was reduced by 50% compared with the lowest tertile [51].

Raw cacao differs from cocoa and chocolate in that it is the pure unroasted and unprocessed part of the cacao fruit. Cocoa is made by roasting the cacao beans at a high temperature, which changes the molecular structure of the cacao and eliminates many of the nutrients and flavonoids found in raw cacao. Milk chocolate has the lowest flavanol content while raw cacao has the highest. Moreover, cacao is very low in sugar and fat, while most commercially available chocolate has high sugar and fat content. Therefore raw cacao is recommended over heavily processed cocoa and chocolate.

Camu Camu

Camu camu is an Amazonian fruit that contains high levels of vitamin C. In a study focused on the anti-oxidative properties of camu camu, 20 male smokers considered to have an accelerated oxidative stress state were randomly assigned to take either 70 mL of 100% camu-camu juice daily or 1050 mg of vitamin C tablets daily. After 7 days the camu camu group showed a significant decrease in oxidative stress markers such as the levels of urinary 8-hydroxydeoxyguanosine and total reactive oxygen species, and inflammatory markers such as serum levels of high sensitivity C reactive protein, interleukin and IL-8, while the vitamin C group showed no changes [52]. This suggests that camu camu has powerful anti-oxidative and anti-inflammatory properties, which may be beneficial for cardiovascular health.

Orthomolecular Therapies

Orthomolecular therapies are based on the theory that restoring the optimal amount of substances normally present in the body can cure diseases and, in particular, mental

illnesses [53]. Their aim is to treat diseases with varying concentrations of chemicals, such as magnesium, zinc, selenium, melatonin, coenzymes, and megadoses of vitamins.

Coenzyme Q-10 (Ubiquinone)

Coenzyme Q-10, also known as ubiquinone, is a powerful antioxidant. The alternative name of ubiquinone is derived from the word *ubiquitous,* and it can be translated as "everywhere." Coenzyme Q-10 is a mitochondrial coenzyme that is present in every cell, and it is derived by endogenous synthesis from acetyl-coenzyme A and phenylalanine. The most common medicinal use of coenzyme Q-10 is for systolic congestive heart failure. Coenzyme Q-10 is also used for the treatment of coronary artery disease, diastolic heart failure, and hypertension and to prevent myocardial toxic effects of chemotherapeutic agents [54].

The rationale for use of coenzyme Q-10 for congestive heart failure is related to the fact that heart failure is characterized by chronic myocardial energy depletion and increased oxidative stress. Because coenzyme Q-10 is an obligatory component of the electron transport chain, and because it is essential for adenosine triphosphate generation during oxidative phosphorylation, dietary supplement could facilitate adenosine triphosphate generation and restore myocardial energy deposits. In addition, it has been proposed that, as a potent lipid soluble antioxidant, coenzyme Q-10 can act as free radical scavenger, thus counteracting the increased oxidative stress that characterizes congestive heart failure. Finally, a membrane-stabilizing property may also have a role in preventing arrhythmic death.

More than 30 studies that have suggested that coenzyme Q-10 can improve symptoms, quality of life, left ventricular function, and prognosis of patients with systolic congestive heart failure. Unfortunately, these studies have been limited by small sample size, lack of controls, suboptimal study design (no randomization or blinding), and inadequate measures of left ventricle systolic function.

More recently, Watson et al. [55] reported the result of a double-blind, randomized trial of 30 patients with congestive heart failure and who had an ejection fraction of less than 35%. Coenzyme Q-10, at a dose of 33 mg three times daily, or placebo was administered for 3 months. There were no significant differences in congestive heart failure–related quality of life and no improvement in left ventricular ejection fraction despite a more than twofold increase in serum levels of coenzyme Q-10. In addition, no changes in baseline left ventricular ejection fraction, peak exercise oxygen consumption, or exercise duration were reported from another double-blind placebo-controlled clinical trial in which 55 patients were randomly assigned to receive either placebo or coenzyme Q-10 at a dose of 200 mg daily and were monitored for 6 months [56]. Thus, according to the results of these two well-designed randomized clinical trials, it does not appear that coenzyme Q-10 is effective in the treatment of congestive heart failure.

Vitamin D

Vitamin D is a fat-soluble vitamin that acts as a hormone in the body. It can be absorbed through diet and dermal synthesis from sunlight. A large number of studies point to the fact that vitamin D deficiency could be a risk factor for heart attacks, strokes, congestive heart failure, and peripheral heart disease. The Health Professionals Follow-up Study followed over 18,000 healthy men over the age of 40 for 10 years and found that those who were deficient in vitamin D showed a significantly higher risk of myocardial infarction or fatal coronary heart disease than the men with sufficient levels of vitamin D [57]. Vitamin D may also prevent type 1 diabetes as evidence suggests from a 30-year study that followed over 10,000 Finnish children from birth to adulthood. The study showed that children who were given regular vitamin D supplements were nearly 90% less likely to develop type 1 diabetes [58]. Meta-analysis from five case-controlled studies also showed that the risk of type 1 diabetes was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented [59]. Although there is some evidence that vitamin D may strengthen the blood vessels and heart and lower blood pressure, further research is required. In a 2010 report the Institute of Medicine recommended a daily vitamin D intake of 600 IU for children and adults in North America. The report also stated that vitamin D was safe up to an intake of 4000 IU/day [60].

Vitamin K2

Vitamin K2 is a fat-soluble vitamin produced by bacteria and found in foods such as organ meats and fermented food products such as soy and dairy products. It is primarily responsible for moving calcium out of the arterial walls and moving it into the bones and manufacturing blood-clotting proteins. The two main forms of vitamin K are phylloquinone (vitamin K1) and menaquinones (vitamin K2). A Netherlands study involving healthy women between the ages of 49 and 70 found that the women who had a higher consumption of vitamin K2, particularly menaquinone 7, 8, and 9, exhibited significantly less risk of developing coronary heart disease [61]. The two primary forms of vitamin K2 available in supplement form are menaquinone-4 (MK-4), which is synthetic, and menaquinone-7 (MK-7), which occurs naturally in food. Data from the 2011–2012 National Health and Nutrition Examination Survey (NHANES) show that among children and teens aged 2–19 years, the average

daily vitamin K intake from foods is 66 mcg. In adults aged 20 and older, the average daily vitamin K intake from foods is 122 mcg for women and 138 mcg for men. When both foods and supplements are considered, the average daily vitamin K intake increases to 164 mcg for women and 182 mcg for men. (U.S. Department of Agriculture, Agricultural Research Service. What We Eat in America, 2009–2010.). The FNB has stated that vitamin K found in either food or supplements has no reported adverse effects in humans or animals. At this time more research is needed to identify the role of vitamin K and the prevention of coronary heart disease.

Vitamin E

Vitamin E includes at least eight compounds, of which alpha-tocopherol is the most active. The potential beneficial effect of alpha-tocopherol on the risk of coronary artery disease is related to its antioxidant effect on the metabolism of LDL. In addition, vitamin E has an antiplatelet effect [62], and it inhibits smooth muscle cell proliferation [63]. Available dietary supplements contain 200–800 IU, a dose that is significantly higher than the current recommended daily allowance (RDA) of 30 IU and significantly higher than the dose that could be achieved with diet alone. The data concerning the effect of vitamin E on the risk of coronary artery disease are conflicting; some studies show a beneficial effect, and some studies show no effect. Part of the conflicting results might be related to dosing, to study design, to duration of clinical follow-up, and to its use for "primary prevention" versus "secondary prevention." In the Nurses' Health Study, women in the fifth quintile of daily intake diet of vitamin E supplements had significant reductions in age- and smoking-adjusted risk of major adverse cardiac events, including myocardial infarction and cardiovascular death (relative risk, 0.66; 95% confidence interval, 0.50–0.87). The median dose of vitamin E in this group was 208 IU/day, and the total follow-up time was 679,485 person-years [64]. In another large prospective study of 39,910 men with 139,883 person-years of follow-up, men in the highest quintile had a significant reduction in major adverse cardiac events in comparison with men in the lowest quintile of dietary vitamin E intake (relative risk, 0.60; 95% confidence interval, 0.44–0.81) [65]. Both studies evaluated patients who were free of cardiovascular disease at the time of the enrollment. A third nonrandomized prospective study also showed an inverse relationship between dietary intake of vitamin E and the risk of death from coronary disease in 34,486 postmenopausal women, from lowest quintile of less than 5.68 IU/day to the highest quintile of >35.59 IU/day. In that study, no additional benefit from vitamin E supplement was identified. However, no information was available on the duration of dietary supplements use, and only 12.9% of women reported a supplemental intake of more than 100 IU/day [66].

Several randomized controlled clinical trials have evaluated the use of vitamin E for secondary prevention. In the Heart Outcome Prevention Evaluation, patients with existing coronary artery disease or at high risk of coronary events because of a history of diabetes and other risk factors were randomly assigned to receive placebo or to vitamin E, 400 IU/day, and to ramipril or matching placebo. Treatment with vitamin E for a mean of 4.5 years did not result in a reduction of cardiovascular events [67]. Also, no significant effect of vitamin E supplement on the incidence of major cardiac events was reported by the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [68]. However, in that study, a reduction in deaths from cardiac causes was observed.

The Cambridge Heart Antioxidant Study randomly assigned 2002 patients with coronary atherosclerosis to receive either vitamin E (400 or 800 IU/day) or placebo [69]. At a median follow-up of 1.4 years, there was a significant reduction in the incidence of nonfatal myocardial infarction in the vitamin E recipients in comparison with the placebo recipients (relative risk, 0.53), but there was no significant difference in rates of mortality from cardiovascular causes. A small number of events and differences in baseline clinical characteristics were potential limitations of that study. In another randomized clinical trial of primary prevention, no significant effects were observed in patients at high risk [70]. Against this negative body of evidence, in the Women's Health Study evaluating the long term use of vitamin E in the prevention of colon cancer, vitamin E administration was found to be associated with a reduction in cardiovascular death, which was particularly pronounced in older women [71].

In summary, although vitamin E, particularly long-term high dietary intake of vitamin E, might have a role in primary prevention of coronary artery disease, current available data do not support short-term use of vitamin E supplements for secondary prevention.

Vitamin C

Available data do not support the use of vitamin C supplements for the prevention of coronary artery disease [72]. Some studies have suggested an inverse relationship between dietary intake of vitamin C and the risk of coronary disease and of stomach cancer. Except for one study that did not adjust for supplemental intake of vitamin E, no study has so far shown a benefit from higher dietary or supplemental intake. Tissue saturation at high level of intake may explain the lack of effect observed with supplements [73]. The current recommended dietary allowance is 60 mg/day.

Vitamin A and Carotenoids

The generic term *vitamin A* is used to denote a family of fat-soluble compounds that have the same biologic properties as retinol, the most active form of vitamin A. The observation that vitamin A content in plants varies with the degree of pigmentation led to the discovery of carotenoids (provitamin A) [74]. The group of carotenoids includes beta-carotene, alpha-carotene, lycopene, lutein, and zeaxanthin. Beta-carotene and alpha-carotene are important sources of vitamin A; the other carotenoids cannot be converted into retinol but nonetheless have important antioxidant effects. Vitamin A plays an essential role in the function of the retina, has an antioxidant effect, and regulates cell differentiation [74]. In view of these effects, several investigators have assessed the relationship between vitamin A intake and the risks of cancer and coronary artery disease. Unfortunately, although observational studies have suggested an inverse relationship between carotenoid intake and the risk of coronary artery disease [75], randomized clinical trials have consistently failed to demonstrate a beneficial effect of supplemental doses of beta-carotene on the risk of cancer or of coronary artery disease [76–80]. It has been suggested that this discrepancy between observational studies and clinical trials might be due to the fact that clinical trials have used beta-carotene as a supplement, but the effect of dietary intake of vitamin A might be attributable to other carotenoids [72, 81].

Lutein

Lutein is a carotenoid found in dark green leafy vegetables and in egg yolks. In one study, an inverse relationship was found between lutein concentration and progression of intima-media thickness of the carotid artery in 480 middle-aged men and women who were monitored for 18 months [82]. In that study, just one portion of dark green leafy vegetables a day increased plasma concentration of lutein to the highest level. In vitro experiments showed inhibition by lutein of LDL-induced migration of monocytes in arterial walls, and in apolipoprotein E–null and in LDL receptor–null mice, addition of lutein in the diet decreased the development of atherosclerotic lesions [82]. Although, as in other observational studies, a direct causal relationship between lutein levels and the observed progression of intima-media thickness cannot be inferred, these results are promising and support the need for further investigation of carotenoids other than beta-carotene in the prevention of atherosclerotic vascular disease.

Folic Acid

The term *folate* was coined by Mitchell and coworkers in 1941 after its isolation from leafy vegetables. *Folic acid* refers to the synthetic form of this vitamin. The folate-cobalamin (vitamin B_{12}) interaction plays a pivotal role for the normal synthesis of purines, pyrimidines, and deoxyribonucleic acid. Folate deficiency has been unquestionably associated in a causative relationship with the development of neural tube defects and of megaloblastic anemia, and folic acid supplementation has been shown in randomized clinical trials to reduce the incidence of neural tube defects by up to 70% [83]. In addition, there is now substantial evidence linking a low intake of folic acid to an increase risk of cancer and of coronary artery disease. The relationship between folate and risk of coronary disease is further strengthened by the identification of high homocysteine levels as a risk factor for coronary artery disease. High folate intake has been shown to be associated with lower homocysteine levels [84]. In addition, randomized clinical trials have shown that folic acid administration in patients with high pretreatment homocysteine levels results in a 25% reduction of plasma homocysteine levels. The addition of vitamin B_{12} results in an additional 7% reduction [85]. The absolute reduction is related to pretreatment homocysteine levels; higher reductions are observed in patients with higher levels. The current Recommended Daily Allowance of folate is 400 μg/day. This dose is adequate for reducing plasma homocysteine levels in most patients, but higher doses might be required. Thus, daily dosages of 1 mg of folate and of 0.5 mg of vitamin B_{12} have been suggested for patients with persistently elevated homocysteine levels [86]. Because the estimated daily intake of folate with the average diet is 200 μg/day, routine folate supplementation with at least the RDA appears advisable.

High plasma homocysteine levels have been found to be also associated with a higher risk of restenosis after coronary angioplasty [87]. As a follow-up of this finding, a randomized placebo-controlled clinical trial showed that administration of a combination of folic acid (1 mg/day), vitamin B_{12} (400 μg/day), and pyridoxine (10 mg/day) significantly reduced homocysteine levels, and decreased restenosis and the need of target lesion revascularization in patients undergoing percutaneous transluminal angioplasty [88]. However, more recent studies have failed to show a benefit of folic acid and of B vitamins in the prevention of further cardiovascular events in patients with prior history of myocardial infarction [89, 90]. In addition, one study has suggested a possible harmful effect of combined administration of B vitamins [90].

Astaxanthin

Astaxanthin is a xanthophyll carotenoid that can be found naturally in salmon, shrimp, lobster, krill, microalgae and fungi. In a number of experimental studies on various species, astaxanthin has shown to have cardiovascular benefits, however, as of yet there have been no conclusive clinical

trials on humans. In a number of experimental studies the researchers used an ischemia-reperfusion myocardial model on rats, rabbits and dogs and found that astaxanthin protects the myocardium when administered both orally or intravenously prior to the induction of the ischemic event. In another study on hypertensive rats, investigators found that there was a significant reduction in blood pressure after 14 days of oral astaxanthin administration, which did not occur in normotensive Wistar Kyoto rats. Diabetic mice also benefited from astaxanthin supplements with a significant reduction in blood glucose levels, a significantly decreased relative mesangial area in the kidneys, and less glomerular 8-OHdG immunoreactive cells [91]. While results from the experimental studies seem promising, further investigation is needed into the cardiovascular benefits of astaxanthin on humans.

Magnesium

Magnesium is the fourth most abundant mineral in the human body, and it is responsible for a large number of biochemical reactions in the body and enzyme systems including cell growth, energy production, muscle control and nerve function. Magnesium also plays a role in regulating blood glucose levels, blood pressure, homocysteine levels and heart rhythm. Studies show that low levels of magnesium are associated with cardiovascular risk factors like hypertension and atherosclerosis, while magnesium supplements may lower blood pressure and reduce the risk of heart disease, stroke and diabetes. A National Health and Nutrition Examination study found that serum Mg below 0.8 mmol/L was associated with a higher risk of ischaemic heart disease [92]. A more recent study showed that there is a robust relationship between low serum magnesium levels in patients who undergo coronary artery bypass graft surgery and the incidence of major adverse cardiac events. They found that patients with low magnesium were twice as likely to suffer heart attacks even up to 1 year after the surgery when compared to patients with normal magnesium levels [93]. There is evidence to support the use magnesium supplementation for cardiovascular health. A meta-analysis of 22 clinical trials concluded that magnesium supplementation for 3–24 weeks decreased systolic blood pressure by 3–4 mmHg and diastolic blood pressure by 2–3 mmHg, which is a small but significant reduction [94]. Another meta-analysis on dietary magnesium intake and the risk of stroke found that there was a modest but statistically significant inverse association between magnesium intake and the risk of stroke. The results showed that an intake increment of 100 mg Mg/day was associated with an 8% reduction in risk of total stroke, and that magnesium intake was inversely associated with risk of ischemic stroke but not intracerebral hemorrhage or subarachnoid hemorrhage [95]. When taken as a food ingredient, magnesium shows little to no adverse affects, and as a supplement it is considered generally safe and toxicity is rare. However, magnesium may interact with several medicines, especially those that affect the filtration process of the kidneys. The Food and Nutrition Board (FNB) set the tolerable upper intake level (UL) for magnesium supplementation at 350 mg a day.

Probiotics

Probiotics are microorganisms in the form of bacteria and yeasts that are found naturally in the body as well as in some foods and supplements. Since the 1990s many medical professionals have been recommending probiotics for gastrointestinal ailments, however, recent research shows that probiotics may also have cardioprotective activities. In a review of 26 clinical studies and two meta-analyses investigators found that the probiotic strain L. *reuteri* NCIMB 30242 was effective in significantly reducing LDL cholesterol and improving other coronary heart disease risk factors such as inflammatory biomarkers [96]. In addition, one study revealed that *L. reuteri* supplementation in hypercholesterolemic adults increased levels of 25-hydroxyvitamin D by nearly 26% [97] The FDA rates *Lactobacillus* bacteria as generally recognized as safe, and randomized clinical trial demonstrated L. reuteri has no adverse side effects and that a twice daily dose of 2.9×10^9 CFU was safe and well tolerated in the general population [98].

Chelation Therapy

The concept of chelation as a way to sequester metal ions into chemical structures was developed initially by Alfred Werner, who received the Nobel Prize in 1913. G.T. Morgan coined the term *chelation* in 1920 from the Greek word *chela*, or "claw." Natural chelators such as tartrate and citrate were used between the 1920s and 1950s to treat iron overload, treat lead poisoning, and reduce the toxicity of antiparasitic agents containing antimonium. During the same period, synthetic chelators were developed to treat lead poisoning [ethylenediaminetetraacetic acid (EDTA)], arsenic poisoning (dimercaprol or British antilewisite) and iron overload (deferoxamine).

EDTA is a synthetic chelator that exists in two forms: a sodium salt (Na_2 EDTA) and a calcium salt ($CaNa_2$ EDTA). The activity and the toxicity of the chelating agent depend on the affinity of the metal ion for the chelator. Na_2 EDTA binds calcium and can cause hypocalcemic tetany, whereas $CaNa_2$ EDTA can be used to treat poisoning by metal ions that have higher affinity than calcium for the chelating

agents. EDTA was introduced in the early 1950s for the treatment of lead poisoning, and since then it has been used as an analytical tool and to treat a series of conditions, including hypercalcemia, digoxin toxicity, and radiation toxicity from plutonium. A reduction in the frequency of angina during EDTA therapy in patients with coronary disease was anecdotally reported in 1955 by Clarke et al. [99]. Since then, there have been at least 22 case reports and small case series and five clinical trials suggesting a marked benefit of chelation therapy in patients with coronary or peripheral vascular disease. Unfortunately, the reported case series and clinical trials have been flawed by lack of blinding of patients and of investigators, lack of standardization of medical therapy, nonuniformity in applied clinical end points within the same study, and insufficient sample size. Thus, although in the United States chelation therapy is advocated for the treatment of coronary artery disease and peripheral vascular disease, there is currently no solid scientific evidence to support such use.

The proposed mechanism of action of chelation therapy includes chelation of calcium directly from atherosclerotic plaque, induction of parathyroid hormone secretion, a reduction in serum cholesterol through an unknown mechanism, chelation of transitional metals with consequent reduction in free radical formation, and inhibition of platelet aggregation. Current chelation therapy protocols involve repeated intravenous administration of EDTA, usually in combination with vitamins, trace elements, and iron supplementation, and the standardized regimen includes two treatments per week, 20–30 or more treatments total.

Chelation therapy is associated with significant adverse effects (Table 34.3), and several deaths clearly related to chelation have been reported. However, in studies in which the recommended standardized regimen is not exceeded, no deaths have been reported, and the adverse events are rare.

Chelation therapy is popular, with a currently estimated $40 million annual market in the United States alone. This popularity despite the lack of solid scientific evidence, and the questions raised by the numerous case reports and small case series, has led the NIH to sponsor a large, well-designed randomized clinical trial [20]. The Trial to Assess Chelation Therapy (TACT) is a large, multicenter, placebo-controlled, double-blind study enrolling participants age 50 years and older with prior history of myocardial infarction. In the trial, patients receive 30 weekly intravenous treatments, followed by 10 more treatments given bimonthly, over a 28-month period. The effect of high dose vitamins was also evaluated in this trial. The study was completed in 2010, and the results were revealed at the American Heart Association Scientific Sessions in 2012. The results showed that post–myocardial infarction patients with diabetes mellitus aged 50 years or older demonstrated a significant reduction in cardiovascular events with EDTA chelation [100]. Although the findings are positive, further research is needed to support the routine use of EDTA chelation in all post-myocardial patients with diabetes mellitus in this age group [100].

Table 34.3 Adverse effects of chelation therapy

Renal failure
Arrhythmias
Tetany
Hypocalcemia
Hypoglycemia
Hypotension
Bone marrow depression
Prolonged bleeding time
Seizures
Respiratory arrest

Fish Oil

There is currently extensive evidence of beneficial effects of omega 3 fatty acid and fish oil in patients with cardiovascular disease. These effects include a reduction in the risk of fatal myocardial infarction, a reduction in the risk of ischemic stroke, and a reduction in the risk of sudden death. Pooled analysis have shown that the reduction in the risk of death from coronary heart disease and of sudden death occurs with modest consumption of fish oil (250–500 mg/day of EPA and DHA). Higher consumption does not appear to result in further relative risk reduction, thus suggesting a threshold effect. However, higher doses appear to reduce triglycerides levels. A recent study shows that omega 3 fatty acids may also prevent blood clotting by reducing levels of thromboxane A2, a chemical that contributes to platelet activation and aggregation. In this study 85 participants were separated into three groups and given a different dose of fish oil per day over a 30-day period. The results showed that the group who received between 1600 g EPA and 800 mg DHA per day had a significant decrease in thromboxane levels. This led the researchers to conclude that a dose of at least 800 mg eicosapentaenoic acid (EPA) and 400 mg docosahexaenoic acid (DHA) will lower AA:EPA ratios in healthy individuals [101].

It is important to note that fish by them self do not produce fish oil. The oil accumulates in fish tissue through the food chain, with higher concentrations present in predatory fish like salmon, mackerel, lake trout, and albacore tuna. Unfortunately, these predatory fish also accumulate toxic contaminants such as mercury, dioxin, PCBs and chlordane. There have been recent concerns that the beneficial effect of fish oil in preventing CHD death might be offset by an increase risk of cancer from toxic contaminants, and by other adverse effects secondary to mercury. It has been however estimated that with moderate consumption, the benefits

currently outweigh the risk. Several companies producing dietary supplements of fish oil have developed a process for removing contaminants. From a consumer standpoint, it is recommended that only product certified as "molecularly distilled" are used.

Adverse Effects of Herbal Supplements and Orthomolecular Therapies Commonly Used in Cardiovascular Cases

Many medicinal herbs have biologically active compounds that can have toxic effects and can interact with commonly used drugs. As stated before, herbal supplements are currently not regulated for purity, potency, standardization, and formulation. Thus, there might be significant variability in efficacy between different manufactures but also within batches from the same manufacturer [102]. Labeling of products may also not reflect their content. For example, cases of nephrotoxicity from a weight loss preparation initially attributed to fang-ji (*Stephania tetrandra*) were later found to be caused by the presence in the preparation of guang-fang-ji (*Aristolochia fangchi*), an herb that contains a known nephrotoxin. The confusion in that case was attributed to the similarity between the two names [103]. The importance of variability among products has been well documented by a study of St. John's wort products that was commissioned by the *Los Angeles Times* [104]. The result of the study showed that there were significant differences between the potency of the product and the claims on labels. Other potential problems related to herbal products include contamination with heavy metals in several Asian herbal products and the addition of pharmaceutical compounds, including caffeine, acetaminophen, indomethacin, hydrochlorothiazide, and prednisolone to proprietary "herbal" Chinese products [105–108].

Adverse effects and herb-drug interactions for the most commonly used herbal products are listed in Table 34.4 [24, 33, 34, 109–125].

Table 34.4 Herb-drug interactions for the ten most popular herbs in 1998

Herbal product	Use	Adverse events	Drug class	Drug interaction	Evidence
Ginkgo biloba	–	–	Antidiabetic agents	Possible increased risk of hypoglycemia	Theoretical
			Aspirin [26, 64]	Possible increased risk of bleeding due to decreased platelet aggregation	Case report
			Nonsteroidal antiinflammatory drugs	Possible increased risk of bleeding due to decreased platelet aggregation	Theoretical
			Trazodone [65]	Increased risk of sedation	Case report
			Warfarin [66]	Increased risk of bleeding	
St. John's wort	–	–	Cyclosporine [67–69]	Cyclosporine levels may be reduced, resulting in a decrease in efficacy (e.g., possible organ rejection)	Case report
			Digoxin [70–72]	Decreased plasma levels and clinical efficacy of digoxin	Controlled study in healthy volunteers
			Iron	Decreased iron absorption	Theoretical
			Oral contraceptives [73]	Possible decreased efficacy of the oral contraceptive due to increased hepatic metabolism	Case report
			Protease inhibitors [74, 75]	Decreased plasma levels and efficacy of protease inhibitor	Open-label study
			Serotonin reuptake inhibitors [76, 77]	Possible increased sedative effects or serotonin syndrome	Case report
			Theophylline	Decreased plasma levels and efficacy of theophylline	Case report
			Tricyclic antidepressants	Decreased plasma levels and efficacy of tricyclic antidepressants	Open-label study
			Warfarin	Anticoagulant effect may be decreased	Case report
Ginseng	–	–	Loop diuretics	Decrease in pharmacologic effect of the loop diuretic	Case report
			Monoamine oxidase inhibitors	Insomnia, irritability, visual hallucinations, and headache	Case report
			Antidiabetics [78, 79]	Hypoglycemia	
			Warfarin80	Anticoagulant effect may be decreased	Case report
Garlic	–	–	Warfarin	Possible increased risk of bleeding	Theoretical
			Antiretrovirals [17]	Decreased plasma concentration	Clinical study
Echinacea	–	–	Corticosteroids; cyclosporine	Possible interference with immunosuppressive effect of the drug	Theoretical

(continued)

Table 34.4 (continued)

Herbal product	Use	Adverse events	Drug class	Drug interaction	Evidence
Saw palmetto	–	–	Estrogens and oral contraceptives	Possible increased risk of adverse effects	Theoretical
			Iron	Decreased iron absorption	Theoretical
Kava kava	–	–	Alprazolam [81]	Possible additive or synergistic CNS effects, leading to lethargy	Case report
Pycnogenol and grape seed[a]	–	–	No documented interactions	N/A	N/A
Cranberry	–	–	No documented interactions	N/A	N/A
Valerian	–	–	Barbiturates; benzodiazepines; opiates	Possible prolongation of sleep or sedative effects	Theoretical
			Iron	Decreased iron absorption	Theoretical

CNS central nervous system, *N/A* not available

Conclusion

CAM therapies are commonly used by patients with cardiovascular diseases treated by conventionally trained physicians. It is therefore important for practitioners to be familiar with CAM therapies, with their proposed mechanism of action and effectiveness, and with the potential risks of adverse effects and drug interactions. It is likely that the rising interest of the medical community and of regulatory and funding agencies in CAM therapies will soon lead to a better understanding of their role in cardiovascular care.

Practical Points

- CAM therapies are commonly used by patients with cardiovascular diseases treated by conventionally trained physicians.
- Major domains of CAM therapy include (a) alternative medical systems, (b) mind-body interventions, (c) manipulative and body-based methods, (d) energy therapies, and (e) biologically based treatments.
- Data on the effect of garlic or garlic supplements have been conflicting. Variation in the concentration of the active compound in formulations may explain some of the differences between clinical trials.
- Cholestin (red rice yeast) has been shown in a randomized clinical trial to be effective in reducing total cholesterol (15% reduction) and LDL cholesterol (22% reduction). Because cholestin contains several statin-like compounds, its use requires the same precautions as with prescription statins.
- According to the results of two well-designed randomized clinical trials, it does not appear that coenzyme Q-10 is effective in the treatment of congestive heart failure.
- Hawthorn contains several active components that appear beneficial in patients with congestive heart failure. Two recent randomized clinical trials investigating its effectiveness in congestive heart failure (the HERB CHF study and the SPICE trial) unfortunately failed to show a beneficial effect in patients with heart failure.
- Soy protein has been shown to be effective in lowering lipids (mild reduction).
- Vitamin E, particularly long-term high dietary intake of vitamin E, might have a role in primary prevention of coronary artery disease. However, available data do not support short-term use of vitamin E supplements for secondary prevention.
- Randomized clinical trials have failed to demonstrate a beneficial effect of supplemental dosages of beta-carotene and vitamin A on the risk of cancer or of coronary artery disease.
- There is substantial evidence linking a low intake of folic acid to an increase risk of cancer and of coronary artery disease. In addition, a randomized placebo-controlled clinical trial showed that administration of a combination of folic acid, vitamin B_{12}, and pyridoxine significantly reduced homocysteine levels and decreased restenosis and the need of target lesion revascularization in patients undergoing percutaneous transluminal angioplasty. However, recent clinical trials evaluating folic acid in secondary prevention have been unable to show any significant benefit of folic acid in reducing adverse cardiovascular events.

- Because the estimated daily intake of folate with the average diet is 200 μg/day, routine folate supplementation with at least the RDA appears advisable.
- Lutein is a carotenoid found in dark green leafy vegetables and in egg yolks. Preliminary results support the need for further investigation of lutein and of carotenoids other than beta-carotene in the prevention of atherosclerotic vascular disease.
- Chelation therapy is advocated in the United States for the treatment of coronary artery disease and peripheral vascular disease. However, there is currently no solid scientific evidence to support such use.
- Herbal supplements are not regulated for purity, potency, standardization, and formulation. Thus, there might be significant variability in efficacy between different manufacturers and within batches from the same manufacturer.
- Many medicinal herbs have biologically active compounds that can have toxic effects and can interact with commonly used drugs.

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Elina Yamada

Cardiovascular disease and cancer are the most prevalent disease in the current era, and they both continue to be in rise, according to recent database. According to estimates from the National Cancer Institute and the Center for Disease Control and Prevention, there were more than ten million cancer survivors in the United States alone in 2002 [1]. More than two million survivors of breast cancer in US are believed to be at risk for cardiotoxicity. As treatment of cancer has become more effective, allowing longevity in survivors, cardiac disease in these patients has become common, and has affected not only the quality of life but the course of cancer treatment. Data from a Childhood Cancer Survivor Cohort study showed that more than half of all patients exposed to anthracycline will develop some degree of cardiac dysfunction 10–20 years after cancer treatment, 5% will develop overt heart failure, and 40% will experience arrhythmias [2]. This population showed an eightfold higher cardiovascular mortality when compared to the general population [3]. Therefore, it is in the best interest of the patients that both Cardiologists and Oncologists collaborate in the care of cancer patients with potential cardiac complications.

The goal of Cardiology-Oncology partnership is to eliminate cardiovascular complications as a barrier to effective treatment of cancer patients, by:

- Providing risk stratification for early detection of patients at risk of cardiac complications;
- Allowing prompt access to Cardiology consultation to identify and/or treat patients at risk;
- Monitoring for cardiac toxicity of new chemotherapeutic agents, at clinical and cellular level;
- Developing strategies to prevent future cardiotoxicity

Many antineoplastic agents are associated with cardiotoxicity, which can be divided into 5 categories: direct cytotoxic effects of chemotherapy causing cardiac dysfunction, cardiac ischemia, arrhythmias, long QTc on EKGs, hypotension, hypertension, and pericarditis. Radiation therapy can also lead to coronary artery disease and fibrotic changes to the valves, pericardium, and myocardium.

Patients being considered for cancer treatment with potentially cardiotoxic drugs, especially those who have cardiovascular risk factors or prior cardiac history should undergo detailed cardiovascular evaluation to optimize their treatment. Cardiotoxicity can be prevented by screening and modifying risk factors, and closely monitoring for cardiac complications by regular cardiac evaluation during the course of chemotherapy. Evaluation of cardiac risks prior to treatment, serial assessment of left ventricular systolic function by echocardiogram or radionuclide angiography, EKG, stress test for at risk patients, cardiac biomarkers such as troponin I, BNP, and serum electrolytes should be considered in selected patient populations.

Preliminary studies have shown that LV systolic dysfunction caused by anthracyclines and trastuzumab may improve by prompt treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and/or beta-blockers [4–7]. Myocardial ischemia, long QTc, and hypo/hypertension as results of chemotherapy should be promptly treated to avoid further cardiovascular complications. Open dialogue between both Cardiologists and Oncologists will be required for optimal patient care.

Cardiotoxicity from Cancer Treatment Drugs

Table 35.1 summarizes the cardiotoxic effects of different classes of cancer drugs and its incidence.

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Table 35.1 Cardiotoxic effects of cancer treatment drugs and incidence

Cancer treatment drugs and cardiotoxicity	Incidence
Myocardial dysfunction	
Anthacyclines (AC)	3–26%
Mitoxantrone (Novantrone)	<5%
Cyclophosphamide (Cytoxan)	7–28%
Mitomycin (Mutamycin)	1–5%
Ifosfamide (Ifex)	17%
Paclitaxel (Taxol) in combination with AC	5–15%
Docetaxel (Taxotere)	2.3–8%
Bevacizumab (Avastin)	1.7–3%
Trastuzumab (Herceptin)	2–28%
Sunitinib (Sutent)	2.7–11%
Imatinib (Gleevac)	0.5–1.7%
Myocardial ischemia	
Fluorouracil (5-FU)	1–68%
Capecitabine (Xeloda)	3–9%
Paclitaxel (Taxol)	5%
Docetaxel (Taxotere)	1.7%
Cisplatin (Platinol)	1–5%
Bevacizumab (Avastin)	0.6–1.5%
Sorafenib (Nexavar)	2.7–3%
Vinca alkaloids	1–5%
Hypertension	
Bavacizumab (Avastin)	4–35%
Sorafenib (Nexavar)	17–43%
Sunitinib (Sutent)	5–24%
Cisplatin (Platinol)	>10%
Hypotension	
Etoposide (Vepeside)	1–5%
Rituximab (Rituxan)	1–10%
Interleukin-2 (IL-2)	3%
Thalidomide (Thalomid)	<1%
Interferon—α	6–10%
All-trans Retinoic Acid (Tretinoin)	1–26%
Arrhythmias	
Rituximab (Rituxan)	1–5%
Paclitaxel (Taxol)	<1%
Ifosfamide (Ifex)	1–5%
Bradycardia	
Thalidomide (Thalomid)	5–55%
Paclitaxel (Taxol)	<0.1–31%
QTc Prolonagation	
Vorinostat (Zolinza)	3.5–6%
Arsenic trioxide (Trisenox)	26–93%
Desatinib (Sprycel)	<1–3%
Lapatinib (Tykerb)	16%
Nilotinib (Tasigna)	1–10%

Data from Edward et al. [33, 34]

Cardiomyopathy and Heart Failure

Patients receiving potentially cardiotoxic agents should have serial echocardiograms, or MUGA scan if the echocardiogram is non-diagnostic, to assess LV/RV systolic function. Recent studies have shown that assessment of myocardial global longitudinal strain using speckle tracking imaging with echocardiogram can detect myocardial toxicity at least 3 months prior to deterioration of LV systolic function assessed by LV EF, and studies have shown that this technique may allow early detection and medical intervention to prevent further deterioration of myocardial function [8].

Cardinale et al. [9, 10] demonstrated that measurement of troponin I during chemotherapy detected cardiotoxicity in the pre-clinical setting, at least 3 months before deterioration of LVEF, and served as a prognostic marker for future recovery of LV function. This finding was corroborated on the study by Sawaya et al. [8]

BNP has been used to differentiate shortness of breath caused by decrease in functional capacity due to cancer from one caused by increased filling pressures in the heart due to cardiotoxicity. Elevated BNP levels within 72 h of chemotherapy have been shown to predict LV dysfunction [11].

Small studies have shown that ACEi and ARBs, as well as beta-blockers, when started early as cardiotoxicity was detected, led to recovery of LV function [4–7].

Preliminary studies have shown that discontinuation of these heart failure medications led to deterioration of heart function. Therefore, it was suggested that once the heart failure medications were started for deterioration of heart function, they should be continued throughout life, if well tolerated.

Anthracycline/Anthraquinolones

Effects of anthracycline (doxorubicin, daunorubicin, epirubicin) on cardiovascular system can lead to cardiomyopathy and HF, and the occurrence of CHF is dose and schedule dependent; more common in women, prior cardiac disease and after mediastinal radiation therapy. The risk of cardiotoxicity increases when administered concurrently or prior to trastuzumab (Herceptin). Anthracycline results in direct cardiomyocyte loss, decreased contractility, and compromise of the microvasculature. Furthermore, the effect of anthracycline on cardiac progenitor cells and fibroblasts reduces the ability of the already-compromised heart to recover from additional cardiac stressors or cardiac injuries.

There is significant increase in the prevalence of cardiotoxicity with cumulative dose above 500 mg/m^2 (16–48%). However, review of data from the Childhood Cancer Survival Study Cohort revealed that even doses of 250 mg/m^2 were related to development of heart failure.

Mechanism of cardiotoxicity is believed to be due to impaired synthesis of myofilament proteins causing apoptosis and necrosis; resulting in direct cardiomyocyte loss, decreased contractility, and compromise of the microvasculature. Furthermore, the effect of anthracycline on cardiac progenitor cells and fibroblasts reduces the ability of the already-compromised heart to recover from additional cardiac stressors or cardiac injuries.

Cardiomyopathy caused by antracyclines can be divided in acute, early-onset and late-onset chronic progressive form. The acute onset occurs within 24 h of infusion and presents as myocarditis/pericarditis. The early onset usually occurs within the first year of treatment and is related to apoptosis. It can happen in <5% when used alone, and in up to 27% of patients when trastuzumab is associated with or is given after anthracycline therapy. The late-onset CMP occurs 1 year after exposure and biopsy has shown loss of myofibers and vacuolar degeneration.

Mitoxantrone, an anthraquinolone derivative, may cause free radical production causing myocarditis and arrhythmia with infusion in 1–5% of cases.

Dexrazoxane has been shown to reduce cardiac toxicity from AC and has been shown to be safe when administered with AC, and not to affect efficacy of treatment of malignance in a pediatric population [12].

Tyrosine Kinase Inhibitors

Tyrosine Kinase Inhibitors (TKI) are agents that fall into two classes: humanized monoclonal antibodies directed against receptor tyrosine kinases or their ligands, and small-molecule TKIs. They are used to treat chronic myelogenous leukemia and gastrointestinal stromal tumors (imatinib); and renal cell carcinoma (sunitinib), among other solid tumors. Some of these drugs have been associated with cardiotoxicity and may cause symptomatic congestive heart failure and, in others, asymptomatic LV dysfunction. Rates of cardiotoxicity associated with TKIs are not known because clinical trials have not included predefined cardiac endpoints. Identification of cardiotoxicity and CHF has been based largely on medical history and physical examination, which are unreliable, as dyspnea, fatigue and edema are common symptoms and signs of cancer therapy and heart failure, and LV dysfunction may develop without cardiac symptoms. Furthermore, rates of heart failure determined in trials before the approval of a drug by the US Food and Drug Administration could be underestimated as patients with cardiovascular disease are often excluded [13–17].

Cases of heart failure have been reported with imatinib (1.7–10%) and adverse cardiac effects are mentioned in the prescribing information for dasatinib (Sprycel—2%), sunitinib (Sutent—2.7–8%), sorafenib (Nexavar—1.9%)) and bevacizumab (Avastin—1.7%). It is clear, however, that cardiotoxicity is not a TKI 'class effect' because it seems to be uncommon with certain other TKIs, such as those that target the epidermal growth factor receptor (EGFR); also known as ERBB1. Although in most cases the overall cardiac risk of TKI therapy does not seem to be excessive, the precise clinical magnitude of the problem is not clear and the potential reversibility of the dysfunction is unknown. Recently, progress has been made in determining basic mechanisms underlying the cardiotoxicity of these drugs.

Alkylating Agents

Cyclophosphamide can cause cardiomyopathy in 7–28% of patients. It is dose related (> 150 mg/kg and 1.5 g/m^2/day) and observed within 1–10 days of initiation of therapy. Ifosfamide may also lead to LV dysfunction in up to 17% of patients, especially when given with other cardiotoxic drugs, and can be seen within 6–23 days after the first dose.

Monoclonal Antibody Tyrosine Kinase Inhibitors

Trastuzumab and bevacizumab have shown to potentially cause deterioration of LV systolic function. The incidence of trastuzumab related cardiomyopathy ranges from 2 to 28%, with higher risk when its use follows anthracycline therapy. Most of the cases are reversible after discontinuation of therapy and with institution of therapy for heart failure, such as ACEi or ARBs, and beta-blockers.

Mechanism of toxicity is likely due to inhibition of cardiomyocyte human epidermal growth factor receptor 2 (ErbB2) signaling, which impairs normal cell growth and repair. It may also cause ATP depletion, with subsequent contractile dysfunction by affecting mitochondrial integrity.

Myocardial Ischemia

Antimetabolites

Fluorouracil (5-FU) may cause angina-type chest pain in 1–68% of cases. High doses (>800 mg/m^2) and continuous infusion have been associated with higher incidence (7.6%) as compared to bolus injections (2%). It was observed within 2–5 days of starting therapy. In rare cases, it can cause myocardial infarction, heart failure and arrhythmias, with case reports of cardiogenic shock and sudden death [18–20].

There have been case reports of myocardial ischemia/infarct with capecitabine with incidence ranging 3–9%, with doses ranging 1500–2500 mg/m^2/day, and angina symptoms observed 3 h to 4 days after therapy [21, 22]. In most of the cases, EKG changes, such as ST elevations, were seen without elevation of cardiac enzymes, and coronary angiograms showed no significant stenosis. These findings suggest that angina symptoms and ischemic EKG changes are due to coronary vasospasm.

In case of development of angina/ischemia, the above agents should be discontinued and anti-anginal therapy

initiated along with work-up for ischemia. In patients with cardiovascular risk factors, coronary artery disease should be ruled-out before starting therapy with above agents, and they should be monitored carefully for ischemia. Restarting these drugs in patients who developed myocardial ischemia is controversial and should only be done if there is no better alternative for treatment of their malignancy. In this instance, nitrates or calcium channel blocker should be instituted, and the drug should be administered in a supervised hospital environment, with close monitorization for ischemia with telemetry and serial EKGs.

Antimicrotubule Agents

Paclitaxel has been associated with ischemia in 5% of cases and most of them occurred in patient with known coronary artery disease or hypertension, during treatment up to 14 days after therapy. Docetaxel related ischemia is rare (1.7%). The mechanism of ischemia with these drugs is unknown.

Bevacizumab may cause arterial thrombotic events and myocardial ischemia/infarct anytime during therapy, up to 3 months and has been observed in 1.5% of cases. Endothelial dysfunction due to the anti-VEGF properties of this drug has been speculated as mechanism of ischemia. Inhibition of VEGF causes reduction in nitric oxide and prostacyclin production, and increases hematocrit and blood viscosity by overproduction of erythropoietin, predisposing to thromboembolic events [23–29].

Hypertension

Hypertension is one of the most common comorbidities in cancer patient registry. New targeted cancer treatment drugs such as Vascular Endothelial Growth Factor inhibitors (VEGFi) disrupt angiogenesis to prevent tumor growth, and hypertension is a common adverse effect.

Early and aggressive initiation of antihypertensive therapy is indicated to maintain treatment schedule and reduce the risk of cardiovascular complications. Although there are studies showing different pathways that leads to hypertension with VEGF inhibitors, prospective clinical trial data is lacking regarding the most effective antihypertensive treatment. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics and dihydropyridine calcium channel blockers have been shown to be effective, without affecting cancer treatment course. Until clinical data is available, the choice of antihypertensive medication should be based on each patient's comorbidities. Studies have shown that hypertension is a pharmacodynamic marker of response to anti-VEGF therapy.

Monoclonal Antibody Based Tyrosine Kinase Inhibitor

Bevacizumab is related to causing hypertension in 4–35% of patients [23–26], with severe poorly controlled cases occurring in up to 18%, and hospitalization or discontinuation of therapy was necessary on 1.7% in clinical trials, with complications such as hypertensive encephalopathy and intra-cranial hemorrhage. Bevacizumab decreases endothelial nitric oxide synthase activity, possibly stimulating plasminogen activator inhibitor-1 expression, leading to risk of hypertension. VEGF may have effect on the renin-angiotensin system [27], and also may be responsible for cholesterol emboli syndrome [28].

Small Molecule Tyrosine Kinase Inhibitor

Sorafenib (17–43%) and sunitinib (5–24%) have been associated with hypertension, which occurred within 4 weeks of therapy. The mechanism of hypertension is thought to be due to VEGF inhibition, with decrease in nitric oxide production in the walls of arterioles and other resistance vessels [29].

Alkylating Agents

Cisplatin can lead to late cardiovascular complications with hypertension and myocardial ischemia even 10–20 years after the remission of metastatic testicular cancer [18].

Hypotension

Cytokines

High-dose interleukin-2 may cause hemodynamic changes similar to septic shock and can lead to hypotension and vascular leaky syndrome with respiratory insufficiency, requiring pressors and mechanic ventilation. Slowing or discontinuation of infusion, premedication with steroids and antihistamines can prevent these events. Interferon-α also has been seen to cause hypotension in the first 2–8 h of administration [30].

Miscellaneous

All-trans retinoic acid syndrome has been reported in 26% of cases, which can occur in the first 21 days of treatment. Symptoms and signs are hypotension associated with fever, dyspnea, pericardial and pleural effusion [31].

Monoclonal Antibody

Rituximab, widely used in non-Hodgkin lymphomas, may cause hypotension, angioedema, hypoxia and bronchospasm in up to 10% of cases during the first hours of infusion [32].

Arrhythmias

Many drugs as shown in Table 35.1 may cause atrial or ventricular arrhythmias. Patients should be advised to report if palpitations, dizziness or syncope, and rhythm monitoring performed with EKG, Holter or event monitor while receiving cancer treatment drugs.

QTc Prolongation

Drugs used to treat cancer such as arsenic trioxide, paclitaxel, and some of the tyrosine kinase inhibitors may cause QTc prolongation, increasing the risk of ventricular arrhythmias such as Torsade de Pointes (TP). Because cancer patients are usually taking multiple medications that can potentially cause QTc prolongation such as antiemetic, antibiotics, or drugs that may cause low potassium or magnesium, the risk of TP may increase further. Review of all patient's medications, and close monitoring of QTc should be done with serial EKGs during treatment. Risk and benefit assessment should be done before continuing the cancer drug if QTc > 500 ms, after replacing non-cancer drugs that cause long QTc and correcting electrolyte abnormalities.

Practical Points

- Many cancer treatment drugs have potential cardiotoxicities, including myocardial dysfunction, pericarditis, hypertension, hypotension, ischemia, arrhythmias, and long QTc.
- It is very important to know the potential cardiac adverse effects of each drug, and monitor for them.
- Educating Oncologists and patients about the signs and symptoms of potential cardiac toxicities of cancer treatment drugs will assist in early diagnosis.
- Prompt referral to Cardio-Oncologist when cardiotoxicity is suspected is recommended.
- Early diagnosis of cardiotoxicity with the appropriate testing and treatment will prevent progression of cardiac problems, leading to less interruptions or changes in cancer treatment

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