SECTION II

Heart Failure and Transplant

EDITOR

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CHAPTER 8

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Heart Failure with Systolic Dysfunction

I. INTRODUCTION

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

B. Terminology

1. Based on the hemodynamic model, **systolic heart failure** has been defined by the presence of impaired contractility of the left ventricle, most commonly conveyed in an ejection fraction (EF) of < 40% to 50%. This drop in contractility may be associated with chamber dilation and a decreased stroke volume (Fig. 8.1). There is a growing appreciation for the limitations of this classification. The threshold for systolic dysfunction is arbitrary and it is now clear that patients with heart failure with preserved EF suffer similar morbidity and mortality. There is substantial variability in EF determinations made by different imaging modalities. Most importantly, EF correlates poorly with symptoms, cardiac indices, and potential response to pharmacotherapy.
2. In practice, heart failure is a bedside diagnosis that is defined by clinical assessment. Patients may have cardiac dysfunction without symptoms, often referred to as **asymptomatic left ventricular (LV) dysfunction**. Others may have preserved LV systolic function with typical signs and symptoms of heart failure, best referred to as **heart failure with preserved EF** (see Chapter 9).
3. The major pathophysiologic process in the progression of heart failure is **cardiac remodeling**, in the form of progressive chamber enlargement with an obligatory reduction in EF. Histopathologically, this is associated with myocyte hypertrophy, apoptosis, and necrosis. Molecular alterations including reexpression of a fetal gene program and alterations in excitation–contraction coupling and regulatory proteins occur.
4. In some cases, **myocardial recovery** or **reverse remodeling** is possible with pharmacologic and device therapy.
5. The term **congestive heart failure** is overused and nonspecific, often being applied to states of hypervolemia unrelated to cardiac dysfunction. Conversely, not all patients with heart failure have signs and symptoms of congestion.
6. The term **right heart failure** is used to describe patients with predominantly peripheral signs and symptoms of heart failure with a relative paucity of pulmonary congestion.
7. **Acute decompensated heart failure** or **AHFS** refer to episodes of acute or subacute deterioration of heart failure due to a wide range of precipitants. The vast majority of these events are marked by systemic and pulmonary congestion.

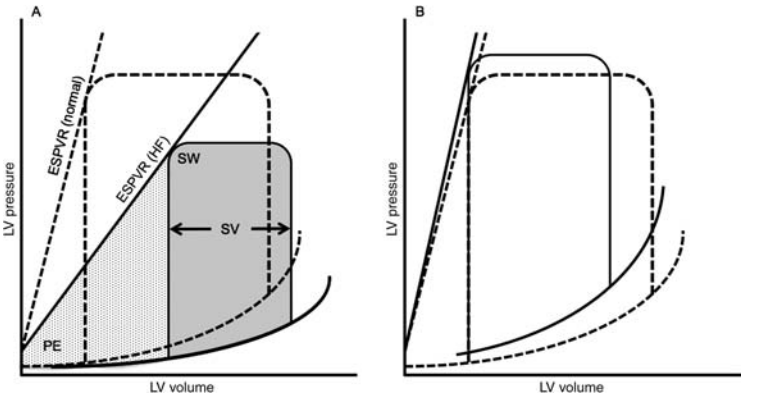

FIGURE 8.1 Pressure–volume loops in normal (dashed line) and heart failure (HF; solid line) patients. **A:** Pressure–volume loops in HF with impaired ejection fraction typically demonstrate a reduction in the end-systolic pressure–volume relationship (ESPVR; i.e., the end-systolic elastance), a representation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

II. PATHOGENESIS

A. Heart failure is a progressive disorder initiated by some form of myocardial injury. This injury may range from acute disruptions in myocardial function (myocardial infarction or myocarditis) to one of a number of chronic derangements including familial and metabolic cardiomyopathies or chronic volume or pressure loading related to valvulopathies, intracardiac shunts, or systemic hypertension. Regardless of the initial insult, the compensatory mechanisms that may be beneficial acutely ultimately become maladaptive in the chronic phase.

B. Neurohormonal activation

1. **Activation of the sympathetic nervous system.** Chronic activation of the sympathetic nervous system ultimately results in decreased β-adrenergic receptor responsiveness and decreased norepinephrine stores and sympathetic innervation of the myocardium. Chronically, these changes contribute to myocyte hypertrophy, fibrosis, and necrosis. Extracardiac effects include increased tubular reabsorption of sodium, activation of the renin–angiotensin system (RAS), neurogenic vasoconstriction, and vascular hypertrophy.
2. **Activation of the RAS.** As heart failure progresses, renal hypoperfusion and sympathetic stimulation of the kidneys result in increased production of renin by the juxtaglomerular apparatus. Renin cleaves circulating angiotensinogen into the biologically inactive angiotensin I, which is subsequently cleaved by angiotensin-converting enzyme (ACE) to the biologically active angiotensin II. Importantly, angiotensin II can be generated in renin and ACE-independent pathways as well. In addition to direct cardiovascular effects, angiotensin II stimulates aldosterone production by the zona glomerulosa of the adrenal cortex, which in turn promotes reabsorption of sodium in exchange for

potassium in the distal nephron. Chronically, aldosterone results in the promotion of hypertrophy and fibrosis in the vasculature and myocardium, endothelial dysfunction, and inhibition of norepinephrine uptake.

3. **Other neurohormonal derangements.** Inappropriate production of arginine vasopressin has an antidiuretic effect contributing and worsens vasoconstriction. Endothelin, neuropeptide Y, and other peripheral vasoconstrictors further enhance vascular tone.

III. CLASSIFICATION

A. The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines currently classify heart failure on the basis of the evolution of the disease across a continuum:
   1. **Stage A:** patients at high risk for developing heart failure without structural heart disease or symptomatic heart failure.
   2. **Stage B:** patients with structural heart disease who have not yet developed symptoms of heart failure.
   3. **Stage C:** patients with structural heart disease with prior or current symptoms of heart failure.
   4. **Stage D:** patients with refractory end-stage heart failure who require specialized advanced treatment.

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

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

VI. ETIOLOGY.

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

TABLE 8.1 New York Heart Association Functional Classification

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

TABLE 8.2 Etiologies of Heart Failure

- Dilated cardiomyopathy
  - Idiopathic
  - Familial
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Unclassified cardiomyopathies
  - Fibroelastosis
  - Mitochondrial cardiomyopathy
  - Left ventricular noncompaction
- Specific cardiomyopathies
  - Ischemic cardiomyopathy
  - Stress-induced cardiomyopathy
  - Valvular obstruction or insufficiency
  - Hypertensive
  - Inflammatory (lymphocytic, eosinophilic, giant cell myocarditis)
  - Infectious (Chagas disease, Lyme disease, HIV, enterovirus, adenovirus, CMV, bacterial or fungal infections)
- Metabolic
  - Endocrine (thyroid diseases, adrenal insufficiency, pheochromocytoma, acromegaly, diabetes mellitus)
  - Familial storage disease (hemochromatosis, glycogen storage disease, Hurler's syndrome, Anderson-Fabry disease)
  - Electrolyte deficiency syndromes (hypokalemia, hypomagnesemia)
  - Nutritional deficiencies (kwashiorkor, anemia, beriberi, carnitine and selenium deficiency)
  - Amyloid
  - Familial Mediterranean fever
- Systemic diseases
  - Connective tissue disorders (SLE, polyarteritis nodosa, rheumatoid arthritis, scleroderma, dermatomyositis, polymyositis, sarcoidosis)
  - Muscular dystrophies (Duchenne's, Becker's, myotonic, limb girdle)
  - Neuromuscular (Friedreich's ataxia, Noonan's disease)
  - Toxins (alcohol, catecholamines, cocaine, anthracyclines and other chemotherapeutics, radiation)

CMV, cytomegalovirus; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.
Modified from WHO Classification.

A. Ischemic cardiomyopathy is the cause of 60% to 75% of cases of systolic heart failure in industrialized countries. It is defined as **cardiomyopathy in the presence of prior extensive myocardial infarction, hibernating myocardium, or severe coronary artery disease**. However, the mere ***presence of obstructive coronary artery disease does not equal ischemic cardiomyopathy as it is possible to have coronary artery disease superimposed with a nonischemic etiology of heart failure***. A careful assessment of the coronary anatomy, the burden of ischemia, and the presence of infarcted and viable myocardium must be made and an assessment of the proportionality of these findings to the degree of myocardial dysfunction should be made. The risks and benefits of percutaneous or surgical revascularization should be assessed in all patients with ischemic cardiomyopathy. Extensive observational data have suggested a benefit for coronary artery bypass grafting (CABG) compared with medical therapy alone in moderate to severe LV systolic dysfunction. Registry data suggest that CABG is superior to percutaneous coronary intervention in patients with reduced EF. However, recently released 5-year data from the Surgical Treatment for Ischemic Heart Failure (STICH) trial demonstrated no difference in 5-year mortality for patients with left ventricular ejection fraction (LVEF) < 35% undergoing CABG in addition to optimal medical therapy versus optimal medical therapy alone. Furthermore, a substudy of STICH demonstrated that preoperative viability testing did not effectively predict whether patients derived benefit from CABG. Notably, patients with left main trunk disease and severe angina were excluded from the study and these patients should continue to be treated aggressively with revascularization.

B. Dilated cardiomyopathy. In 20% to 30% of cases of heart failure with systolic dysfunction, the precise etiology is not established and a diagnosis of nonischemic, dilated, or idiopathic cardiomyopathy is made. Patients with **dilated cardiomyopathy typically have a better prognosis than their ischemic counterparts**.

1. Dilated cardiomyopathy is frequently attributed to the residual effects of **subclinical viral myocarditis**. Reverse transcription polymerase chain reaction analysis of endomyocardial biopsies from patients with dilated cardiomyopathy demonstrates amplification of viral genomes in approximately two-thirds of cases. Any virus can cause myocarditis, but, owing to its ubiquity, coxsackie B virus is the most epidemiologically important.
2. **Familial dilated cardiomyopathy.** It is now recognized that 25% to 50% of cases of dilated cardiomyopathy may have a genetic basis. Conditions are typically autosomal dominant and show variable penetrance. A detailed three-generation family history is essential at the time of initial evaluation. If the family history suggests a genetic predisposition, clinical screening of family members is appropriate and genetic testing can be performed following referral to a genetic counselor. Importantly, only 15% to 25% of presumed familial dilated cardiomyopathies have identifiable genetic alterations.

C. Hypertensive and diabetic cardiomyopathy are seldom considered as stand-alone diagnoses. Progression from LV hypertrophy to overt dysfunction in hypertensive patients (the so-called burnt-out hypertensive heart) most likely results from progressive microvascular ischemia. Hypertension and diabetes also contribute significantly to the development of coronary artery disease and ischemic cardiomyopathy.

D. Cardiotoxic agents. The list of toxins that can produce cardiomyopathy is extensive. Identification of the toxin and removal of the offending agent may halt the progression of or even reverse LV dysfunction.

1. **Chemotherapeutic agents. Anthracycline** toxicity can cause myocyte destruction and cardiomyopathy. Patients who receive a cumulative doxorubicin equivalent dose of < 400 mg/m^2 are at low risk for this syndrome, while those receiving a cumulative dose > 700 mg/m^2 have an approximately 20% lifetime risk of developing cardiomyopathy. Other cardiotoxic drugs that require careful cardiac monitoring include **cyclophosphamide** and **trastuzumab**. Trastuzumab

(Herceptin) is now frequently used in the treatment of human epidermal growth factor receptor 2 positive breast cancer and has been associated with a reversible cardiomyopathy in 2% to 7% of patients undergoing treatment. Antiangiogenic drugs such as sunitinib can also cause cardiotoxicity and uncontrolled hypertension.

2. **Alcohol** consumption is thought to represent a common cause of toxin-mediated cardiomyopathy; however, there is limited observational data on the actual incidence of the cardiomyopathy or the volume of alcohol consumption necessary to induce it. Total abstinence from alcohol may result in complete resolution, whereas continued use is associated with a 3- to 6-year mortality exceeding 50%.
3. **Stimulant drugs** including cocaine and methamphetamine may result in the development of heart failure via multiple derangements including progressive concentric hypertrophy and recurrent myocardial infarction.
4. **Toxin exposures** including lead, arsenic, and cobalt can result in progressive myocardial dysfunction.

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

F. Tachyarrhythmia-induced cardiomyopathy can complicate the course of atrial fibrillation, atrial flutter, ectopic atrial tachycardia, and even occult sustained ventricular tachycardia and frequent premature ventricular contractions (> 20% to 30% of beats). In general, it is thought that persistent tachycardia in excess of 110 bpm is required to induce LV dysfunction. This is a critical diagnosis to make, as treatment of the underlying tachyarrhythmia generally results in complete resolution of the cardiomyopathy.

G. Peripartum cardiomyopathy is defined as a dilated cardiomyopathy occurring between the last month of pregnancy and up to 5 months postpartum. The majority of peripartum cardiomyopathy patients improve with standard heart failure pharmacotherapy, with over 50% of patients experiencing complete normalization of cardiac function.

H. Valvular disorders are common causes of heart failure. Aortic regurgitation and mitral regurgitation (MR) result in chronic volume overload and ultimately culminate in dilated cardiomyopathy. Severe aortic stenosis and outflow tract obstruction commonly lead to progressive LV dysfunction (see Chapters 14 and 15). Surgical correction is the preferred management of severe valvular lesions.

I. Miscellaneous disorders

1. **Thyroid disorders**
   a. **Hypothyroidism** is common in patients with heart failure. Severe hypothyroidism (i.e., myxedema) may cause decreased cardiac output and heart failure. Bradycardia and pericardial effusion can develop in extreme cases of hypothyroidism.
   b. Heart failure may complicate **hyperthyroidism**, especially in elderly patients with low ventricular reserve. Atrial fibrillation is a common accompanying arrhythmia, occurring in 9% to 22% of patients with thyrotoxicosis. Nonspecific symptoms such as fatigue, weight loss, and insomnia predominate. Previously stable angina may become unstable. Patients treated with amiodarone may develop a wide range of thyroid disorders ranging from abnormal thyroid function tests to overt amiodarone-induced thyrotoxicosis or hypothyroidism. Both conditions can occur in otherwise normal thyroid glands.
2. **Thiamine deficiency (beriberi).** Although rare in industrialized countries, thiamine deficiency is still prevalent in the developing world. It can also occur in alcoholics or individuals observing fad diets. Wet beriberi includes features of **high-output cardiac failure such as marked edema, peripheral vasodilatation, and pulmonary congestion**. The signs and symptoms of dry beriberi include glossitis, hyperkeratosis, and peripheral neuropathy. The laboratory diagnosis is made using decreased RBC transketolase and 24-hour urine thiamine

levels. Severe cases can present with lactic acidosis. Intravenous therapy with 100 mg of thiamine followed by daily oral supplementation can result in dramatic clinical improvement. Chronic use of high-dose diuretics may be complicated by subclinical thiamine deficiency of unknown significance.

3. **Other nutritional deficiencies.** Carnitine and selenium deficiency may result in dilated cardiomyopathy complicating chronic parenteral nutrition.
4. **High-output heart failure from anemia.** Acute anemia caused by rapid blood loss is associated with decreased cardiac output due by hypovolemic shock. In contrast, chronic anemia can be associated with symptoms of heart failure due to compensatory mechanisms. These include fluid retention, increased cardiac output, decreased vascular resistance, and increased 2,3-diphosphoglycerate with a resultant rightward shift in the oxyhemoglobin dissociation curve. Moderate degrees of chronic anemia (hemoglobin < 9 g/dL) typically only result in heart failure symptoms in patients with preexisting cardiac disease. Chronic anemia of severe proportions (hemoglobin < 7 g/dL) may result in high-output heart failure even in individuals with normal hearts. Evaluation and management of the underlying cause and supportive care are advised. Thresholds for transfusion depend on the clinical context and rapidity of blood loss. Iron repletion should be considered in iron-deficient patients and in inpatients is most readily achieved with the daily administration of intravenous ferric gluconate 125 mg for 8 to 10 days.
5. While early in its course **hemochromatosis** may present with restrictive cardiomyopathy, it typically progresses to a mixed or dilated form. Treatment with chelating agents or phlebotomy may improve cardiac function in both primary and secondary forms.
6. **Inherited myopathies** such as Becker's and Duchenne's muscular dystrophies, limb girdle dystrophy, and myotonic dystrophy are associated with dilated cardiomyopathy. Friedreich's ataxia is most commonly associated with hypertrophic cardiomyopathy, but in rare instances can present with a dilated phenotype. Mitochondrial cardiomyopathies may also present with dilated cardiomyopathy.
7. **Cardiac sarcoidosis** can present with LV dysfunction with regional hypokinesis or aneurysmal dilatation. It is frequently associated with conduction abnormalities and ventricular tachyarrhythmias. The diagnosis can be supported with stereotypical findings on cardiac MRI and positron emission tomography (PET). The diagnosis is rare in the absence of extracardiac manifestations.
8. **Chagas disease** caused by the flagellate protozoan *Trypanosoma cruzi* remains a common cause of heart failure in patients from Latin America. In the chronic symptomatic phase, patients typically present with a syndrome of ventricular dysfunction with regional wall motion abnormalities in the absence of obstructive coronary artery disease. This pattern should prompt *T. cruzi* titers in patients from endemic regions.

V. SIGNS AND SYMPTOMS

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

1. The most common and earliest presenting symptom is **dyspnea**, typically with exertion. **Orthopnea** is typical with more advanced disease. It is amongst the most sensitive (90%) and specific (90%) signs of decompensated heart failure. As further decompensation occurs, **paroxysmal nocturnal dyspnea** and **Cheyne-Stokes respiratory patterns** may occur.
2. **Fatigue** and **exercise intolerance** are common complaints in patients with heart failure and may reflect diminished cardiac output. Seldom considered but highly prevalent symptoms include **nocturnal cough, insomnia, and depressed mood**.

3. **Palpitations** and **syncope** may occur in patients with underlying arrhythmia and require prompt evaluation.
4. **Anorexia** and **abdominal pain** are common in advanced right heart failure.

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

1. **Volume overload** is the hallmark of heart failure. Typical signs of volume overload include the following:
   a. **Weight gain** is a sensitive indicator of congestion.
   b. **Pulmonary rales** due to accumulation of fluid in the pulmonary interstitium and alveoli secondary to high left atrial pressure are commonly referred to as **acute cardiogenic pulmonary edema**. Importantly, rales may be absent in patients with chronic systolic heart failure who develop compensatory perivascular and lymphatic changes.
   c. **Jugular venous distention or elevated jugular venous pressure (JVP)** while not directly reflecting left-sided filling pressures can track these with a reasonable sensitivity (70%) and specificity (79%). JVP should be assessed at a 45° incline with the neck fully exposed. In cases of extreme JVP elevation, the patient may need to be seated upright in order to properly visualize. Five centimeters of water should be added to the vertical distance from the sternal angle to the meniscus of the JVP to account for the distance to the midpoint of the right atrium. Compression of the right upper quadrant and a resultant positive **hepatojugular reflex** (defined as a sustained increase in JVP of ≥4 cm) increase the sensitivity of the JVP for detecting congestion.
   d. **Pedal edema** by some estimates is only present in 30% of patients with decompensated heart failure and is somewhat nonspecific, as it may reflect venous insufficiency, nephrotic syndrome, cirrhosis, or concomitant treatment with calcium channel blockers or thiazolidinediones.
   e. **Ascites and hepatomegaly** may occur. When accompanied by a palpably pulsatile liver, hepatomegaly suggests severe tricuspid regurgitation.
   f. A holosystolic murmur of **MR** is often present in the setting of LV dilatation.
   g. **A third heart sound** (S_3 gallop) is best heard with the bell of the stethoscope in the left lateral position and signifies increased LV end-diastolic pressure.
2. Often neglected are the subtle signs of **peripheral hypoperfusion**.
   a. **Pulsus alternans** or a low-amplitude pulse in the absence of alternative explanations reflects severely impaired cardiac output.
   b. Tachycardia and narrow pulse pressure also suggest diminished cardiac output.
   c. Lethargy, pallor, mottled skin, cool extremities, and poor capillary refill are typical signs.
   d. **Hypotension** itself may be one of the most important clinical findings in heart failure. Several studies have demonstrated that a systolic blood pressure < 90 mm Hg is a strong predictor of morbidity and mortality.

VI. DIAGNOSTIC EVALUATION

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

1. A **comprehensive metabolic panel** should be assessed on initial evaluation and then subsequently based on clinical judgment. Particular attention should be paid to the presence of hyponatremia, which portends a worse prognosis. Hypokalemia is common in the setting of ongoing diuretic therapy. Hyperkalemia can be seen in the context of overaggressive potassium repletion and ongoing treatment with ACE or aldosterone inhibitors or in diabetic patients with

associated type IV renal tubular acidosis. Aside from the pragmatic considerations, many real-world registries have identified elevated blood urea nitrogen (BUN) and creatinine as powerful predictors of outcome. Renal function must also be taken into account when considering therapy with renally excreted drugs. Transaminitis and in some cases a cholestatic pattern of liver function test abnormalities may be seen in the context of right heart failure.

2. **Anemia** is present in up to 40% of heart failure patients and is associated with increased mortality and functional impairment. While frequently due to anemia of chronic disease, a thorough diagnostic evaluation should be performed.
3. The natriuretic peptides **B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP)** are released in the setting of increased ventricular dilation or wall stress. Normal ranges (BNP < 100 pg/mL; NT-proBNP < 125 pg/mL if age < 75 years and < 450 pg/mL if age ≥75 years) must be interpreted in the context of associated conditions known to alter levels. Increasing age and worsening renal function are associated with increased levels. There is an inverse relationship between natriuretic peptides and body mass index.
   a. **Screening for heart failure.** Although cardiac dysfunction has been associated with elevated natriuretic peptide levels, the sensitivity is relatively low in asymptomatic patients and is highly dependent on the cut-off levels chosen. In general, routine assessment of BNP is not recommended as a screening test for structural heart disease in asymptomatic patients.
   b. **Diagnosing heart failure.** The primary use of natriuretic peptides remains the diagnosis of heart failure in symptomatic patients particularly when the diagnosis is unclear. The high negative predictive value (up to 90%) in this setting allows BNP testing to be useful to rule out a cardiac cause of symptoms. With the growing epidemic of obesity, it is important to remember that ***normal natriuretic peptide levels may be present in morbidly obese patients with decompensated heart failure.***
   c. **Management of heart failure.** While still controversial, there is emerging evidence that serial measurements of natriuretic peptides may be beneficial in guiding outpatient heart failure management and may result in decreased heart failure–related mortality versus usual care.
   d. **Determining prognosis of heart failure.** Data now suggest that natriuretic peptide levels are closely correlated with morbidity and mortality in patients with both established heart failure and other cardiovascular diagnoses (e.g., stable coronary artery disease, acute coronary syndromes, pulmonary hypertension, and atrial fibrillation).
4. **Other biomarkers.** A growing list of biomarkers assessing systemic inflammation, oxidative stress, extracellular matrix remodeling, and myocyte injury is commercially available or in development. While some of these provide useful prognostic information, it is not clear how to best integrate them into the diagnosis and management of heart failure.
5. **Thyroid function testing** is warranted for all patients with a new diagnosis of heart failure.
6. Iron studies including ferritin, serum iron, and total iron binding capacity (with calculation of percent transferrin saturation) should be performed to screen for hemochromatosis and occult iron deficiency.
7. Standard laboratory screening for **modifiable cardiovascular risk factors** including fasting lipid panel and serum glucose should be obtained.

B. **The electrocardiogram (ECG)** may provide important information pertaining to the cause and management of heart failure and is a recommended component of the evaluation of any patient with a clinical diagnosis of heart failure.
   1. It is important to look for evidence of prior myocardial infarction, chamber enlargement and hypertrophy, conduction disease, and supraventricular or ventricular arrhythmias.

2. Specific diagnoses can be suggested in the ECG. Cardiac amyloidosis classically presents with low voltages and a pseudoinfarction pattern in the anterior leads in stark contrast to echocardiographically thickened walls. Arrhythmogenic right ventricular (RV) cardiomyopathy may present with epsilon waves or localized prolongation (> 110 milliseconds) of the QRS complex in the right precordial leads.
3. The ECG is an important means of assessing **dyssynchrony**. Marked first-degree atrioventricular (AV) block or very short AV delays in the presence of paced rhythms may contribute to AV dyssynchrony. The presence of QRS prolongation > 120 milliseconds (particularly left bundle branch block morphologies with QRS > 130 milliseconds) suggests interventricular dyssynchrony and remains the most important predictor of response to cardiac resynchronization therapy.
4. **Holter or event monitors** are often useful in identifying occult arrhythmia and arrhythmia burden.

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

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

1. **Etiology of heart failure.** Regional wall motion abnormalities occurring in an anatomic coronary artery distribution are suggestive of ischemic cardiomyopathy. However, regional wall motion abnormalities can also be seen in the context of nonischemic dilated cardiomyopathy, stress-induced cardiomyopathy, and infiltrative cardiomyopathies (with inferobasal wall motion abnormalities classically seen in the setting of cardiac sarcoidosis). The presence and severity of valvular stenosis or insufficiency can be assessed as can the relative dysfunction of the right and left ventricles.
2. **Prognosis in heart failure.** The following parameters are useful in assessing the risk of heart failure–associated morbidity and mortality.
   a. **EF and LV dimensions.** While correlating poorly with heart failure symptoms, exercise capacity, and oxygen consumption, the EF provides valuable prognostic information with morbidity and mortality closely linked to EF and LV volumes. The American Society of Echocardiography recommends that assessment of EF and LV volumes be made using the biplane Simpson's method of disks.
   b. **LV mass.** Remodeling in the failing heart results in increased LV mass due to eccentric hypertrophy, which worsens prognosis. Eccentric hypertrophy is defined echocardiographically as an LV mass > 95 g/m^2 in women and > 115 g/m^2 in men with a regional wall thickness (2 × posterior wall thickness/LV end-diastolic dimension) of ≤0.42.
   c. **The myocardial performance index (Tei index).** The Tei index provides a useful assessment of systolic and diastolic function and is equal to (the isovolumic contraction time + the isovolumic relaxation time)/the ejection time. All dimensions are obtained via pulse wave or tissue Doppler. A Tei index of > 0.77 in patients with dilated cardiomyopathy is highly predictive of cardiovascular morbidity and mortality.
   d. **Measures of diastolic dysfunction.** Many of the measures of diastolic dysfunction detailed in Chapter 9 have powerful prognostic ability in patients

with systolic heart failure. The presence of a restrictive filling pattern ($E/A > 2$, deceleration time < 115 to 150 milliseconds) persisting despite Valsalva maneuver is a particularly ominous finding.

E. Other imaging modalities

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

F. Right heart catheterization (see Chapter 60). Invasive hemodynamic monitoring is often helpful in the diagnosis and inpatient management of heart failure. Right heart catheterization can be combined with exercise testing or infusions of inotropic or vasodilatory agents to study their hemodynamic effects. Reasonable indications for right heart catheterization include short-term management of acute cardiogenic shock, evaluation of patients for cardiac transplantation or mechanical circulatory support, clarification of hemodynamics in the context-specific comorbidities (e.g., suspected RV infarction or mechanical complications of myocardial infarction), adjustment of therapy in patients with recurrent or refractory symptoms, and optimization of medical therapy in order to facilitate weaning from inotropes.

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

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

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

I. Cardiopulmonary exercise testing (metabolic stress testing) while not recommended as part of the routine evaluation of patients with heart failure should be considered in the context of symptoms out of proportion with objective measures of disease severity, discriminating between cardiac and pulmonary etiologies of dyspnea, or assessing candidacy for cardiac transplantation or mechanical circulatory support. Several routinely measured parameters are highly predictive of prognosis in patients with established heart failure.

1. **Peak oxygen consumption (Vo_2)** is perhaps the most important parameter in objectively describing functional capacity and prognosticating. Normal values based on age and sex are indexed to body weight, with a normal value being > 84% predicted. Patients being considered for heart transplantation undergo risk stratification with a metabolic stress test. Patients with a peak Vo_2 < 14 mL/kg/min or < 50% predicted are at increased risk for adverse cardiovascular events and if the limitation is deemed to be cardiac should be considered for transplantation. Interpretation of the peak Vo_2 is highly dependent on the adequacy of effort as assessed by the respiratory exchange ratio (RER). The RER is the ratio of Vco_2/Vo_2 and is at steady state an estimate of the respiratory quotient. It signifies the conversion to anaerobic metabolism and the sudden rise in co_2 production occurring with the onset of metabolic acidosis. Failure to achieve an RER > 1.05 suggests insufficient effort or premature termination of the study. Up to 50% of heart failure patients are incapable of achieving an adequate RER, with a modified Bruce treadmill protocol necessitating the use of alternative protocols.
2. **Ventilatory anaerobic threshold** is another means of assessing the adequacy of effort and represents the point at which minute ventilation (V_E) increases out of proportion with Vo_2 (typically occurring at 60% to 70% of peak Vo_2).
3. **V_E/Vco_2 slope** is a dimensionless ratio indicating the relationship between minute ventilation and CO_2 production. The slope is elevated in most patients with heart failure and is inversely related to cardiac output at peak exercise. A slope > 35 identifies higher risk individuals independently of peak Vo_2.

J. Sleep study. Obstructive sleep apnea and central sleep apnea are common comorbidities contributing adversely to the pathogenesis and prognosis of patients with heart failure. There should be a low threshold for appropriate testing.

VII. TREATMENT.

The effective management of heart failure relies on appreciating the distinction between acute and chronic therapies.

A. Acute heart failure syndromes. In the United States, AHFS continue to constitute the most common indication for hospital admission in adults over age 65 years. These hospitalizations represent an inflection point in the course and prognosis of the chronic disease, with 90-day and 1-year postdischarge mortality as high as 14%

TABLE 8.3 Precipitants of Acute Decompensated Heart Failure

Medication nonadherence
Myocardial ischemia, infarction
Arrhythmias (tachyarrhythmias, bradycardia)
Infection
Anemia
Alcohol consumption
Pregnancy
Worsening hypertension
Acute valvular insufficiency
Drugs that can acutely worsen HF symptoms
Calcium channel antagonists
β-Blockers
Nonsteroidal anti-inflammatory drugs
Thiazolidinediones
Antiarrhythmic agents (all class I agents, sotalol)

and 37%, respectively. Only 20% of AHFS represent patients with de novo heart failure. The majority are patients with worsening chronic heart failure. The initial management goals include symptom improvement, decongestion, and hemodynamic stabilization with optimization of tissue perfusion. It is important to attempt to identify and correct any precipitating factors (Table 8.3).

1. **Invasive hemodynamic monitoring**
   a. **Pulmonary artery catheter.** The **ESCAPE** trial demonstrated that the routine use of a pulmonary artery catheter in the management of patients with AHFS did not result in a reduction in subsequent hospitalizations or mortality but did result in an increase in anticipated complications. The use of a pulmonary artery catheter should therefore be restricted to the scenarios detailed above where there is need for clarification of cardiac indices or filling pressures and in critically ill patients failing to respond to standard therapies. When available, a PCWP of > 18 mm Hg suggests cardiogenic pulmonary edema and a cardiac index of < 2.0 L/min/m^2 is consistent with cardiogenic shock.
   b. **Arterial catheter.** Continuous blood pressure monitoring with an arterial catheter can be useful in cases with marginal blood pressure and allows for optimal titration of intravenous vasodilators.
2. **Maximizing oxygenation** is vital. All patients with acute cardiogenic pulmonary edema should be positioned upright and receive supplemental oxygen. **Noninvasive positive pressure ventilation (NIPPV)** should be considered in those with ongoing increased work of breathing, respiratory acidosis, or persistent hypoxemia. The Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema (**3CPOE**) trial demonstrated that NIPPV results in more rapid resolution of symptoms and metabolic derangements than continuous positive airway pressure (CPAP) ventilation or standard oxygen therapy. While there was no evidence of a reduction in short-term mortality, this can be an invaluable tool

often forestalling intubation. Patients who fail to respond to NIPPV should be promptly intubated. The use of positive end-expiratory pressure (PEEP) can be effective in improving oxygenation, but high levels of PEEP come at the cost of reduced systemic venous return and cardiac output, which may be problematic in patients in shock.

3. **Vasodilators.** In the absence of symptomatic hypotension, intravenous vasodilators are the first-line therapy for the management of cardiogenic pulmonary edema.
   a. **Nitroglycerin** reduces LV filling pressures via venodilation and to a lesser extent via systemic afterload reduction. It may be given rapidly in the emergency setting (0.4 to 0.8 mg, given sublingually every 3 to 5 minutes) and by means of intravenous infusion in the subacute setting (starting dosage of 0.2 to 0.4 μg/kg/min), with titration every 5 minutes on the basis of symptoms or mean arterial pressure (MAP). While there is no maximal dose, increasing beyond 300 to 400 μg/min likely yields no additional benefit and should prompt the addition of another vasodilator. Tachyphylaxis can occur with high-dose infusions. Headache is the most common side effect, and use is contraindicated in the setting of recent use of phosphodiesterase-5 (PDE-5) inhibitors.
   c. **Sodium nitroprusside** is a potent vasodilator with balanced venous and arteriolar effects. It requires careful hemodynamic monitoring (typically by arterial line). A starting dosage of 0.1 to 0.2 μg/kg/min is used and titrated every 5 minutes to achieve a clinical response while maintaining an MAP > 65 mm Hg. Nitroprusside is particularly useful in instances where a rapid and large reduction in afterload is desired (e.g., cardiogenic shock and acute severe aortic regurgitation or MR). While cyanide and thiocyanate toxicity is exceedingly rare with short durations of therapy, nitroprusside should be used with caution in patients with severe renal dysfunction. Long-term, high-dose infusions should be avoided. In patients with myocardial ischemia, nitroglycerin or a combination of nitroglycerine and nitroprusside is preferred to avoid the theoretical risk of coronary steal.
   d. **Nesiritide** is an intravenous vasodilator that gained popularity in the acute care setting because of its ease of use in the absence of invasive hemodynamic monitoring. Typical dosing starts with 2 mg/kg delivered by intravenous bolus followed by an infusion at a rate of 0.01 mg/kg/min for up to 48 hours. The recently published Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (**ASCEND-HF**) trial demonstrated that nesiritide had no effect on death or rehospitalization for heart failure at 30 days when compared with conventional therapy. While providing some reassurance regarding previous safety concerns, these results have led most experts to discourage its use on the basis of lack of efficacy.
4. **Diuretics.** In addition to their ability to gradually reduce intravascular volume, diuretics have an immediate vasodilatory effect, which may be responsible for their prompt symptom relief. Reductions in filling pressures may be associated with augmented forward flow due to optimization of LV and RV mechanics and interventricular interaction. Because many patients with acute cardiogenic pulmonary edema do not have total body salt and water excess, the judicious use of diuretics is recommended. Often, filling pressures normalize with the use of vasodilators alone. Patients without chronic exposure to loop diuretics usually respond to 20 to 40 mg of intravenous furosemide. Patients undergoing long-term furosemide therapy typically need an intravenous bolus dose at least equivalent to their oral dose. Rather than an arbitrary therapeutic goal of net fluid balance or an estimated dry weight, frequent clinical assessments of volume status should

guide therapy and define the point at which conversion to an oral maintenance regimen should occur. Nevertheless, up to 30% of patients with AHFS continue to have symptoms of congestion at the time of discharge. Important adverse effects include hypotension, hypokalemia, hypomagnesemia, and hypocalcemia. There is also extensive evidence suggesting that intravenous diuretics may result in at least transient neurohormonal activation which is theoretically disadvantageous. Electrolyte repletion is best achieved with scheduled doses of potassium and magnesium supplements to prevent severe deficits. Results of the recently published Diuretic Optimization Strategies Evaluation (**DOSE**) trial demonstrate no benefit of continuous or bolus dose intravenous diuretic administration and no detriment from high doses (an intravenous dose 2.5 times the patients' chronic oral dose of furosemide). If a continuous diuretic infusion is opted for, it should be preceded by a bolus dose, as should any subsequent titration in the continuous rate. Diuretic resistance can be addressed with escalating doses of loop diuretics and subsequently with the addition of a thiazide diuretic (hydrochlorothiazide, metolazone, or chlorothiazide). Some degree of worsening renal function must often be tolerated in order to achieve adequate decongestion. However, if progressive renal failure occurs despite persistent congestion, ultrafiltration or the addition of an intravenous vasodilator or inotrope needs to be considered.

5. **Inotropic therapy.** When signs and symptoms of decompensated heart failure persist despite administration of vasodilators and diuretics, intravenous inotropes may be considered. Their use should be restricted to patients with clear clinical or direct hemodynamic evidence of refractory elevated filling pressures and reduced cardiac output. For patients without significant hypotension, the intravenous inodilators dobutamine or milrinone can be used to augment cardiac output. Both drugs are associated with increased myocardial oxygen demand and cardiac arrhythmias and should be used with extreme caution in patients with ischemia and preexisting arrhythmias. Both drugs may cause hypotension, although this is more common with loading doses of milrinone. ***There is no evidence to support benefit with the use of chronic or intermittent infusion of inotropic agents, and in fact, there is extensive observational data suggesting a trend toward increased postdischarge mortality.*** Use is typically confined to the acute care setting and as a bridge to transplant/mechanical circulatory support or palliation in patients who are not candidates for advanced therapies. In cases of severe hypotension (especially as a result of administration of vasodilators or β-blockers), temporary use of vasopressors such as dopamine, norepinephrine, and phenylephrine may be necessary. In contrast to the conventional wisdom, recent prospective data suggest that norepinephrine is not inferior to dopamine in the setting of cardiogenic shock.
   a. **Dobutamine** acts on β-1 and to a lesser extent on β-2 and α-1 adrenergic receptors. It has a shorter half-life than milrinone and usually is the drug of choice in the acute setting. Infusions are usually started at 2.5 to 5.0 μg/kg/min. On the basis of hemodynamic response, it may be titrated by 1 to 2 μg/kg/min every 30 minutes until the desired effect or a dosage of 10 μg/kg/min is reached.
   b. **Milrinone** is a PDE inhibitor that increases myocardial inotropy by inhibiting the degradation of cyclic adenosine monophosphate. It is a potent systemic and pulmonary vasodilator due to its effects on vascular PDE. For patients who need an immediate inotropic response, a loading dose of 50 μg/kg over 10 minutes is followed by an infusion of 0.125 to 0.75 μg/kg/min. Because it does not target β-receptors, milrinone may be more effective than dobutamine in the setting of recent or ongoing β-blocker therapy.
6. **Ultrafiltration** has been used as an alternative to pharmacologic diuresis in acute decompensated heart failure. The Ultrafiltration vs. Intravenous Diuretics

for patients hospitalized for Acute Decompensated Congestive Heart Failure (**UNLOAD**) study demonstrated that ultrafiltration was safe and resulted in a reduced need for intravenous diuretics and inotropes. Whether ultrafiltration should be considered a first-line alternative to standard intravenous diuretics will depend on the outcome of future trials assessing the relative safety, efficacy, and cost-effectiveness. Currently the use of ultrafiltration is reserved for patients refractory to intravenous diuretic therapy or with diuresis complicated by worsening renal function.

7. **Vasopressin antagonists.** The oral vasopressin receptor 2 antagonist tolvaptan was shown to be safe and results in short-term symptom improvement in patients hospitalized with acute decompensated heart failure in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (**EVEREST**) trial. This occurred without a reduction in long-term heart failure morbidity or mortality. Tolvaptan and the nonselective intravenous vasopressin receptor inhibitor conivaptan are both approved for the management of hypervolemic or euvolemic hyponatremia that can accompany decompensated heart failure.
8. **Temporary mechanical circulatory support.** The use of temporary and permanent mechanical circulatory support is described in detail in Chapter 12. Patients with refractory cardiogenic shock and cardiogenic pulmonary edema may benefit from the temporary use of intraaortic balloon counterpulsation or an alternative temporary means of mechanical circulatory support (i.e., veno-arterial extracorporeal membrane oxygenation, Impella, or TandemHeart) may facilitate bridging to stabilization or further decision making.
9. Diagnosis and management of atrial and ventricular tachyarrhythmias is critical to the care of patients with acute decompensated heart failure, as these frequently precipitate exacerbations and alter the disease course. Their management is discussed in detail in Chapter 21.
10. **Transition to chronic pharmacotherapy** is implemented once clinical stability is achieved. Generally, vasodilators (ACE inhibitors, angiotensin II receptor blockers [ARBs], or hydralazine/isosorbide dinitrate) are reintroduced first in concert with weaning of intravenous vasodilators. If β-blockers were held due to cardiogenic shock, they can be cautiously reintroduced in stable, euvolemic patients.

B. Chronic medical therapies. The goals of chronic medical therapy are to prolong survival and to improve symptoms and functional status. While there have been few recent major advancements in pharmacotherapy, the evolution of therapies with profound survival benefit for patients with heart failure represents a triumph of modern medicine.

1. **ACE inhibitors** have been shown to reduce morbidity and mortality among patients with systolic heart failure. The mechanism of long-term benefit is related to attenuation of the RAS. In addition, ACE inhibitors improve symptoms, clinical status, and exercise capacity.
   a. **Use of an ACE inhibitor is the first-line therapy for asymptomatic and symptomatic LV dysfunction.** The dose of the ACE inhibitor should be increased to the target doses demonstrating clinical benefits in trials (Table 8.4). Although there are theoretical benefits of using "tissue" ACE inhibitors (e.g., quinapril and ramipril), there are no data to support their preferential use. Relative contraindications include hyperkalemia (potassium > 5.5 mEq/L), renal insufficiency (creatinine > 3.0 mg/dL), and hypotension (systolic blood pressure < 90 mm Hg) and should be gauged on a case-by-case basis. It is not advisable to stop ACE inhibitors in patients with systolic heart failure, even when there is complete resolution of symptoms.

TABLE 8.4 Drug Dosing for Common Medical Therapies for Chronic Heart Failure

Drug	Start (mg)	Target (mg)	Max (mg)
ACE inhibitors			
Captopril (Capoten)	6.25–12.5 tid	50 tid	100 tid
Enalapril (Vasotec)	2.5–5 bid	10 bid	20 bid
Lisinopril (Prinivil, Zestril)	2.5–5 qd	20 qd	40 qd
Ramipril (Altace)	1.25–2.5 bid	5 bid	10 bid
Quinapril (Accupril)	5 bid	20 bid	20 bid
Fosinopril (Monopril)	2.5 or 5 bid	20 bid	20 bid
Benazepril (Lotensin)[a]	2.5 or 5 bid	20 bid	20 bid
Moexipril (Univasc)[a]	7.5 qd	30 qd	30 qd
Trandolapril (Mavik)	1 qd	4 qd	4 qd
Angiotensin receptor blockers			
Candesartan (Atacand)	16 qd	32 qd	32 qd
Valsartan (Diovan)	80 qd	160 qd	320 qd
Losartan (Cozaar)[a]	12.5–25 qd	50 qd	100 qd
Irbesartan (Avapro)[a]	150 qd	300 qd	300 qd
Telmisartan (Micardis)[a]	40 qd	80 qd	80 qd
Hydralazine/isosorbide dinitrate			
Hydralazine	25 qid	50–75 qid	100 qid
Isosorbide dinitrate	10–20 tid	20–80 tid	80 tid
Hydralazine–isosorbide dinitrate (BiDil)	25/37.5 tid	50/75 tid	50/75 tid
Aldosterone antagonists			
Spironolactone (Aldactone)	12.5–25 qd	25 qd	50 bid
Eplerenone (Inspra)	25 qd	50 qd	100 qd
Diuretics[b]			
Furosemide (Lasix)	10 qd (IV) 20 qd (po)	As required	1,000 qd (IV) 240 bid (po)
Bumetanide (Bumex)	1 qd	As required	10 qd
Torsemide (Demadex)	10 qd	As required	200 qd
Ethacrynic acid (Edecrin)	50 qd	As required	200 bid
Hydrochlorothiazide (HCTZ)	25 qd	As required	50 qd
Triamterene (Maxzide)	50 qd	As required	100 bid
Metolazone (Zaroxolyn)	2.5 qd	As required	10 qd

TABLE 8.4 Drug Dosing for Common Medical Therapies for Chronic Heart Failure (*Continued*)

Drug	Start (mg)	Target (mg)	Max (mg)
β-Blockers			
Carvedilol (Coreg)	3.125 bid	25 bid	50 bid
Carvedilol phosphate (Coreg CR)	10 qd	40 qd	80 qd
Metoprolol succinate (Toprol XL)	25 qd	150–200 qd	200 qd
Bisoprolol (Zebeta)[a]	1.25 qd	10 qd	20 qd

ACE, angiotensin-converting enzyme.

[a]Not yet approved by the FDA for management of heart failure.

[b]Oral to IV conversion for furosemide is approximately 2:1. Oral to IV conversion for all other loop diuretics is 1:1.

b. After initiation, close monitoring for **hyperkalemia** and **renal insufficiency** is warranted.

(1) Hypotension is common, especially with first dose in a volume-depleted patient (e.g., after aggressive diuresis). This may require downtitration of diuretic doses and other vasodilator therapy. Due to its short half-life, captopril is usually used in the acute setting (e.g., after myocardial infarction).

(2) Renal insufficiency and **hyperkalemia** may occur when ACE inhibitors are given in the setting of volume depletion. **It is crucial to discontinue other nephrotoxic agents (e.g., nonsteroidal anti-inflammatory agents)** and ensure adequate kidney perfusion. **If BUN or creatinine levels increase by < 50%, ACE inhibitors can be continued safely; if they increase by > 50%, the ACE inhibitor dose should be halved; if they increase by > 100%, the ACE inhibitor should be held and switched to hydralazine and isosorbide dinitrate**. In the case of hyperkalemia, discontinuation of potassium supplementation and reducing the ACE inhibitor dose is usually effective.

c. Unique side effects of ACE inhibitors are cough and angioedema.

(1) The **cough** associated with ACE inhibitors is related to increased levels of bradykinin. It tends to be nonproductive and involuntary, rarely resolving with altering the dose or specific agent. All attempts should be made to identify an alternative cause of cough before discontinuing ACE inhibitors.

(2) Angioedema is a rare complication of ACE inhibitors (0.4%). It involves soft tissue edema of the lips, face, tongue, and, occasionally, the oropharynx and epiglottis. Angioedema typically begins within 2 weeks of initiation of ACE inhibitor therapy, but some patients present with this complication months to years after starting therapy. **Angioedema is an absolute contraindication to the use of any type of ACE inhibitor**.

2. Angiotensin II receptor blockers are specific receptor antagonists to the angiotensin II type 1 receptors. Although they theoretically provide more complete inhibition of the deleterious effects of angiotensin II than do ACE inhibitors, clinical trials have not demonstrated superiority in patients with heart failure. In general, ARBs are used and monitored in the same manner as ACE inhibitors. These drugs are reserved for patients who are ACE inhibitor intolerant, although in practice, they are used extensively. ARBs have a similar side-effect profile to ACE inhibitors (e.g., hypotension, renal insufficiency, and hyperkalemia). There appears to be a < 10% incidence of cross-reactivity for ACE inhibitor–associated

angioedema in patients receiving ARBs. However, consideration for the use of these agents must be weighed against the life-threatening nature of this complication. Whether ARBs can produce additional benefit when added to ACE inhibitors is still being debated. While the addition of an ARB is reasonable in patients on maximal medical therapy including target doses of ACE inhibitors and β-blockers with persistent symptoms, it is preferable to add an aldosterone antagonist in this setting. ARBs should not be added to an ACE inhibitor in the postmyocardial infarction period. Valsartan and candesartan are the best studied ARBs in patients with heart failure and should be used preferentially.

3. The combination of **hydralazine** and **isosorbide dinitrate** may provide a reduction in morbidity and mortality in selected heart failure patients. A fixed dose combination of hydralazine and isosorbide dinitrate (BiDil) demonstrated a substantial reduction in mortality when added to African American patients on optimal medical therapy including ACE inhibitors and β-blockers in the African-American Heart Failure Trial (A-HeFT). This combination is also indicated in patients intolerant of ACE inhibitors or ARBs. Side effects of hydralazine may include reflex tachycardia and rarely drug-induced lupus erythematosus.
4. **β-Adrenergic blockers (β-blockers).** Once considered to be contraindicated in patients with heart failure, β-blockers are now considered **first-line therapy for symptomatic patients with heart failure (NYHA class II, III, or stable class IV)** because of their consistent mortality benefits.
   a. It is often customary to start ACE inhibitors before β-blockers. This in part reflects the fact that all major β-blocker trials demonstrated their benefit on a background of therapy with ACE inhibition. Furthermore, while ACE inhibitors provide immediate beneficial hemodynamic effects, β-blockers may acutely result in diminished LVEF and cardiac output, which may be poorly tolerated in decompensated patients. In some instances (e.g., postmyocardial infarction and comorbid tachyarrhythmias), β-blockers may be particularly beneficial and should be started before or concurrently with ACE inhibitors. β-Blockers should generally not be initiated or titrated in the setting of acutely decompensated heart failure whether due to congestion or severely impaired cardiac output.
   b. Only carvedilol, bisoprolol, and metoprolol succinate have been approved for the medical treatment of chronic heart failure. Although atenolol and metoprolol tartrate are widely available and relatively inexpensive, there is no evidence to support their use in this population. β-Blockers with intrinsic sympathomimetic activity (pindolol and acebutolol) in particular should be avoided.
   c. Relative contraindications to β-blocker therapy are a heart rate < 60 bpm, symptomatic hypotension, more than minimal pulmonary or systemic congestion, signs of peripheral hypoperfusion, a PR interval > 0.24 seconds, second- or third-degree AV block, a history of severe reactive airway disease, and peripheral arterial disease with resting limb ischemia. It is important to note that these are relative contraindications and particularly in the setting of reactive airway disease and peripheral arterial disease, the risks of β-blocker therapy must be weighed against their known benefits.
   d. Current recommendations are to start β-blockers in those who are clinically euvolemic. The general principle is to "start low and go slow." The initial dose is **slowly up-titrated every 2 to 4 weeks over 3 to 4 months to achieve target doses**, provided that the patient can tolerate side effects. It is imperative to maintain contact with the patient and adjust vasodilator or diuretic therapy during titration. It is not advisable to stop β-blockers in patients with a history of heart failure, even if there is complete resolution of symptoms and LV dysfunction.

e. Every effort should be made to achieve target doses, but it is clear that even low doses of these drugs provide benefit. While the degree of β-blockade appears to be the best predictor of long-term response, there is no evidence to support titration to a given resting heart rate.

f. Side effects are common when using β-blockers. Patients should understand that these drugs are used to prolong survival and often do not improve symptoms.

(1) Dizziness and **light-headedness** are common and may be related to hypotension or heart block. **Significant bradycardia** mandates dose reduction of β-blockers and other rate-lowering agents such as digoxin and amiodarone. **Advanced heart block** is a contraindication to β-blockers unless a permanent pacemaker is present. **Hypotension** can be managed by staggering the timing of drug administration. In practice, carvedilol (with its nonselective, α_1-blocking vasodilator effects) may have greater blood pressure lowering than selective β_1 agents such as metoprolol succinate. Both drugs are well tolerated in up to 70% of heart failure patients in our clinics.

(2) Worsening heart failure is still an important adverse effect of β-blockers. Intensification of diuretic therapy and dose reduction or slower titration may be necessary.

5. Aldosterone receptor antagonists have long been used as weak, potassium-sparing diuretics in patients with heart failure. The concept of incomplete blockade of the RAS by ACE inhibitors led to studies demonstrating significant pleiotropic effects of aldosterone antagonism in patients with advanced heart failure including antifibrotic effects and a reduction in sudden cardiac death. Results from the Randomized Aldactone Evaluation Study (**RALES**), Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (**EPHESUS**), and now Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (**EMPHASIS-HF**) trial have demonstrated substantial mortality benefit in all stages of heart failure.

a. Aldosterone inhibitors are indicated in patients with NYHA class II symptoms and an LVEF ≤ 30% or NYHA class III or IV patients with an LVEF ≤ 35% already treated with ACE inhibitors and β-blockers and without significant renal dysfunction (creatinine > 2.5 mg/dL) or hyperkalemia (potassium > 5 mEq/L). Their use is also indicated in patients with postinfarction LV dysfunction (LVEF ≤ 40%) with any heart failure symptoms or diabetes mellitus.

b. In most cases, potassium supplementation should be reduced or discontinued. A basic metabolic panel should be checked within 1 week after initiation and monitored at regular intervals.

c. The most common and life-threatening side effect of aldosterone antagonists is **hyperkalemia**, which is particularly problematic in patients with concomitant **renal insufficiency** and diabetes mellitus (type IV renal tubular acidosis). **Painful gynecomastia** and **galactorrhea** may occur when using spironolactone.

d. While studies were typically performed with either spironolactone (RALES) or eplerenone (EPHESUS and EMPHASIS-HF), most experts believe that aldosterone inhibitors work via a class effect. Our approach is to initiate treatment with spironolactone due to its low cost and to transition to eplerenone only in the setting of significant gynecomastia.

6. Diuretics are used to maintain euvolemia and to improve symptoms, but their overuse can result in volume contraction, hypotension, and renal dysfunction.

a. An effective and inexpensive initial regimen includes 20 to 120 mg of furosemide taken orally each day. If furosemide doses higher than 120 mg/d are

needed, a second evening dose is typically prescribed. If this regimen fails, a daily dose of a thiazide diuretic such as metolazone or hydrochlorothiazide can be added 30 minutes prior to furosemide dosing.

   b. More expensive loop diuretics (e.g., torsemide and bumetanide) may have superior bioavailability and may be more effective in diuretic-resistant patients. Torsemide in particular may have unique benefits in the form of antifibrotic effects and minimization of the postdiuretic sodium retention that complicates the use of loop diuretics with shorter half-lives.
   c. The concept of **diuretic resistance** is evolving. Very often, this is contributed to by a failure to adhere to a low-sodium (< 2,000 mg/d) diet.
   d. The goal of chronic diuretic therapy is maintenance of euvolemia. This is most reliably achieved in patients who record daily weights and make physician-supported changes in diuretic dosing on an as-needed basis.

7. **Digoxin** is reasonable to use in patients with persistent heart failure symptoms despite appropriate medical therapy including ACE inhibitors and β-blockers and in patients with atrial fibrillation to control ventricular rate.
   a. Despite a fairly narrow therapeutic window, digoxin is safe and significantly reduces heart failure hospitalizations. A typical starting dose of 0.125 mg of digoxin daily is appropriate in patients with normal renal function.
   b. While the **Digitalis Investigation Group (DIG) trial** demonstrated the best clinical outcomes in patients with a serum digoxin concentration of 0.5 to 0.8 ng/mL, routine measurement of levels is not recommended in the absence of concern for toxicity.
8. **Other drugs of importance. Statins** should be used in the secondary prevention of atherosclerotic cardiovascular disease without regard to the presence of heart failure. There is no evidence of benefit in heart failure patients without coronary artery disease. While **aspirin** clearly prevents reinfarction and other vascular events in patients with known coronary artery disease, there is growing evidence from observational and randomized studies that it may worsen outcomes in heart failure patients via inhibition of prostaglandin synthesis and the resultant adverse hemodynamic and renal effects. This remains a controversial subject and the decision of whether to use aspirin or not should be made on a case-by-case basis. It should likely be avoided in patients without coronary disease who have refractory heart failure symptoms.
9. **Electrolyte supplementation** is among the most important and least emphasized areas in chronic heart failure management. Potassium depletion is common with diuretic therapy, whereas hyperkalemia can be caused by ACE inhibitors, spironolactone, or worsening renal insufficiency. In general, oral potassium supplementation is necessary to maintain serum potassium level in the ideal range of 4.0 to 5.0 mEq/L. Magnesium, thiamine, and calcium depletion are also common with long-standing diuretic therapy.
10. **Device therapy.** Chapters 55 and 56 provide detailed coverage of the indications, contraindications, and clinical issues related to implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT-D).
11. **Device monitoring.** Currently implanted electrical cardiovascular devices including ICD and CRT-Ds have the capability to remotely monitor a variety of electrophysiologic (e.g., heart rate variability, atrial arrhythmia burden and rate, ventricular tachycardia, % biventricular pacing, and average heart rate) and physiologic (e.g., patient activity and intrathoracic impedance) parameters with prognostic value. Several implantable hemodynamic monitors are under development for use in patients with advanced heart failure. How to best integrate device monitoring into a comprehensive approach to heart failure disease management remains to be established.

12. **Novel therapies**
    a. **ω-3 polyunsaturated fatty acids (PUFA)** have demonstrated an ability to reduce heart failure–associated morbidity and mortality and are now considered a reasonable intervention in patients with NYHA functional class II–IV symptoms by the Heart Failure Society of America. The **Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure (GISSI-HF)** trial demonstrated that 1 g/d of PUFAs resulted in a reduction in all-cause mortality. Recent data suggest that higher doses of PUFAs used in patients with milder heart failure symptoms due to nonischemic cardiomyopathy may result in a dramatic reduction in heart failure hospitalizations. The formulation of PUFA used is important, as there does appear to be a dose–response effect. Formulations containing at least 1 g of eicosapentaenoic acid and docosahexaenoic acid appear to be required for benefit.

C. Chronic nonmedical therapies

1. **Patient education and disease management programs** remain the most effective treatment strategy for patients with systolic heart failure. Sodium restriction (< 2,000 mg daily) and medication compliance are crucial to reducing hospitalizations. Control of blood pressure, serum glucose, and lipid levels should be emphasized. Some highly motivated patients can perform self-monitoring (i.e., daily weights and symptom assessment) and care (i.e., titration of diuretics) analogous to the chronic management of diabetes.
2. **Exercise training.** There is a clear body of evidence supporting the fact that exercise training improves endothelial function and functional capacity in patients with chronic heart failure. A supervised cardiac rehabilitation program should be advised when available.

D. Advanced therapies. Mechanical circulatory support and orthotopic heart transplantation are therapies currently reserved for patients with ACC/AHA stage D heart failure refractory to other therapies. These are described in detail in Chapters 12 and 13, respectively.

VIII. PROGNOSIS. Heart failure is associated with high rates of morbidity and mortality. In the Framingham Heart study, patients with heart failure had mortality rates four to eight times those of age-matched controls. A patient with NYHA class IV heart failure has a 1-year survival between 30% and 50%—a mortality rate comparable to that of advanced malignancies. Several risk scores have been developed to characterize the risk of heart failure hospitalization and mortality. The Seattle Heart Failure Model is perhaps the most widely used of these and incorporates demographic, clinical, pharmacologic, and laboratory data to provide accurate 1-, 2-, and 3-year survival estimates. Table 8.5 lists some common clinical predictors of poor survival in systolic heart failure.

TABLE 8.5 Common Clinical Predictors of Poor Prognosis in Systolic Heart Failure

- Increased age
- Male gender
- Increased New York Heart Association functional class
- Severely reduced LV ejection fraction (< 25%), extensive cardiac remodeling (LVIDd > 65 mm), or reduced cardiac index (< 2.5)
- Concomitant diastolic dysfunction (particularly irreversible restrictive filling, stage IV diastolic dysfunction)
- Reduced right ventricular function

(Continued)

TABLE 8.5 Common Clinical Predictors of Poor Prognosis in Systolic Heart Failure (*Continued*)

- Atrial fibrillation, elevated average heart rate, and reduced heart rate variability
- Low peak Vo_2 with maximal exercise (14 mL/min/kg), low heart rate response to exercise, increased peripheral chemosensitivity (ventilatory response to hypoxia), and high V_E/Vco_2
- High plasma BNP and N-terminal proBNP levels
- High levels of other cardiac and neurohormonal biomarkers including norepinephrine, renin, arginine vasopressin, aldosterone, endothelin-1, tumor necrosis factor, cardiac troponin T and I, and C-reactive protein
- Anemia
- Markers of reduced tissue perfusion:
  - Low mean arterial pressure
  - Renal insufficiency (creatinine clearance < 60 mL/min)
  - Attenuated response to diuretics and lack of hemodynamic and structural improvement (reverse remodeling) with medical therapy
  - Persistent signs of congestion and fluid retention or failure to normalize filling pressures (PCWP < 16 mm Hg, CVP < 8 mm Hg) with medical therapy
  - Serum sodium < 135 mg/dL
- Cardiac dyssynchrony (QRS > 130 milliseconds, left bundle branch block)
- Depression
- Nocturnal Cheyne-Stokes respiration and obstructive sleep apnea

BNP, B-type natriuretic peptide; CVP, central venous pressure; LV, left ventricular; LVIDd, left ventricular internal dimension at diastole; PCWP, pulmonary capillary wedge pressure.

ACKNOWLEDGMENTS: *The authors would like to thank Dr. Brian Hardaway for his contributions to earlier editions of this chapter.*

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USEFUL WEB SITES

Seattle Heart Failure Model: http://depts.washington.edu/shfm/
HFSA Heart Failure Guidelines: http://www.heartfailureguidelines.org/

CHAPTER 9

Evan Lau
W.H. Wilson Tang

Heart Failure with Preserved Ejection Fraction and Restrictive Cardiomyopathy

I. INTRODUCTION

A. Epidemiologic studies suggest that nearly one-half of patients with heart failure have a normal ejection fraction; the proportion in those hospitalized has been reported to range from 24% to 55%. The survival of patients with heart failure and preserved ejection fraction was once thought to be better than those with a decreased ejection fraction, but recent evidence suggests similar mortality rates.

Heart failure with preserved ejection fraction (HFpEF) has become the preferred term in the literature. This clinical entity has also been referred to as diastolic heart failure and heart failure with preserved ejection fraction. In this chapter, we focus on HFpEF and provide a brief discussion of the restrictive cardiomyopathies, which are important differential diagnoses in patients presenting with heart failure and a normal ejection fraction.

B. Definition. In the latest consensus document (by the European Working Group), HFpEF is defined as **(1) signs *and* symptoms of congestive heart failure; (2) left ventricular ejection fraction (LVEF) > 50% and a nondilated left ventricle (< 97 mL/m^2); (3) and evidence of elevated left ventricular (LV) filling pressures (Table 9.1)**. The last criterion is fulfilled in one of three ways: (1) invasive hemodynamics (pulmonary capillary wedge pressure [PCWP] > 12 mm Hg or left ventricular end-diastolic pressure [LVEDP] > 16 mm Hg), (2) unequivocal echocardiographic evidence of elevated LV filling pressure (E/e' > 15), or (3) equivocal echocardiographic evidence (E/e' > 8 but < 15) **and** a positive β-natriuretic peptide (BNP) (NT-BNP > 220 pg/mL or BNP > 200 pg/mL).

C. Pathophysiology. Most pathophysiologic abnormalities in patients with HFpEF are related to diastolic function. There are two major determinants of diastolic function: LV relaxation and LV stiffness. LV relaxation relates to the cellular mechanisms involved with actin–myosin crossbridge detachment. This requires intracellular calcium uptake into the sarcoplasmic reticulum, an energy- or adenosine triphosphate (ATP)-dependent process. Thus, ischemia, which would decrease intracellular availability of ATP, would prolong the time required for ventricular relaxation. LV stiffness relates to the compliance of the myocardial tissue. One determinant of this is the extracellular matrix. For example, increase in fibrosis and collage deposition, as in patients with hypertensive heart disease, leads to an increase in LV stiffness. Restrictive cardiomyopathies share a similar pathophysiology, with increased LV stiffness; however, these differ in the pathology underlying the change in ventricular compliance: extracellular amyloid deposition (cardiac amyloidosis); endocardial fibrosis from eosinophilic injury (Loeffler's endocarditis and endomyocardial fibrosis); intracellular lysosomal engorgement with sphingolipids (Fabry's disease); and others.

TABLE 9.1 Diagnostic Criteria for Heart Failure with Preserved Ejection Fraction

Clinical	Signs and symptoms of CHF
Left ventricular size and function	Nondilated (< 97 mL/m^2), EF > 50%
Hemodynamics (one of the following conditions must be met)	1. LVEDP > 16 mm Hg or PCWP > 12 mm Hg 2. E/e' > 15 3. If E/e' > 8 but < 15, then BNP must be elevated (NT-BNP > 220 pg/mL or BNP > 200 pg/mL)

CHF, congestive heart failure; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; BNP, β-natriuretic peptide.

A number of other pathophysiologic mechanisms have been implicated in patients with HFpEF. These include arterial stiffness, the relationship between arterial and ventricular stiffness, and chronotropic incompetence. The implications and relative importance of these mechanisms are still unclear.

II. CLINICAL PRESENTATION

A. Demographics. When compared with patients with systolic dysfunction, those with HFpEF tend to be older and are more likely to be female. Associated comorbidities include hypertension, diabetes, obesity, and chronic kidney disease.

B. Symptoms. Analogous to systolic dysfunction, diastolic dysfunction spans the spectrum of asymptomatic or subclinical disease to those with an established clinical syndrome of congestive heart failure. The symptoms of diastolic heart failure are indistinguishable from those of systolic heart failure. It may present with only exertional fatigue or dyspnea symptoms. Other patients will have more overt symptoms of left-sided (dyspnea, orthopnea, and paroxysmal nocturnal dyspnea) and right-sided (edema and abdominal bloating) heart failure.

C. Signs. The signs of HFpEF are similar to those for systolic heart failure. One should look for the typical signs of right-sided (elevated jugular venous pressure, hepatic congestion, ascites, and lower extremity edema) and left-sided (rales) congestion. The presence of an S4 usually signifies a stiff left ventricle. As opposed to those patients with dilated cardiomyopathies, the location of the apical impulse is usually close to the midclavicular line, signifying a normal-sized ventricle. One should also pay attention to the strength of the impulse; in patients who do not have thick chest walls, a hypertrophied ventricle will often have a stronger impulse than the one without left ventricular hypertrophy (LVH). In patients with exertional symptoms alone, the above signs may not be present as the manifestation of their diastolic dysfunction may occur only during exercise.

In patients who present with impressive right-sided heart failure features, particularly ascites and hepatic congestion, restrictive cardiomyopathy or constrictive pericarditis or a combination should be considered. In these patients, clinical findings of multiorgan disease may indicate specific etiologies of restrictive cardiomyopathy. The cardiac examination may demonstrate more specific findings, including Kussmaul's sign: a paradoxical elevation in the mean jugular venous pressure during inspiration. This is classically described in constrictive pericarditis but can be seen in patients with restrictive cardiomyopathy as well as other pathologies (severe right ventricular failure and tricuspid regurgitation).

III. LABORATORY EXAMINATION AND BASIC INVESTIGATIONS

A. Electrocardiogram (ECG). ECG is an insensitive test for HFpEF. In this scenario, the most important finding is the amplitude of QRS voltage. The presence of elevated voltages and other criteria for LVH would support this as a possible cause of HFpEF. Conversely, in a patient who has increased wall thickness (typically by echocardiography) but has low voltage or infarction patterns on ECG (in this case, "pseudoinfarction"), infiltrative or restrictive cardiomyopathy should be considered.

B. Chest radiograph. The chest x-ray has few specific findings for HFpEF. In a posterior–anterior film, a normal-sized heart (lateral heart width < 2/3 of a hemithorax) may be a clue to a normal-sized left ventricle. Otherwise, the findings are the same as in systolic dysfunction: fluffy alveolar opacities (alveolar pulmonary edema), increased interstitial markings (increased interstitial fluid), pulmonary vascular redistribution (increased pulmonary venous pressures), and pleural effusions.

C. Specific laboratory investigations. BNP can be helpful in establishing the diagnosis of HFpEF (as stated above). When compared with patients with systolic heart failure, the elevation in BNP is generally lower. In patients with undifferentiated dyspnea, a normal BNP would argue against the presence of any heart failure syndrome.

IV. DIFFERENTIAL DIAGNOSIS.

For the purposes of our discussion, there are two clinical presentations to consider: exertional dyspnea (without findings of heart failure) and congestive heart failure. In a patient presenting primarily with exercise intolerance or exertional dyspnea, HFpEF should be considered, in addition to silent coronary artery disease, primary lung disease, anemia, etc.

In a patient who has an established clinical syndrome of heart failure, the differential diagnosis is typically narrowed following echocardiography. In a patient with preserved ejection fraction and a normal-sized left ventricle, HFpEF is the most likely cause. Other entities to consider include restrictive cardiomyopathies, hypertrophic cardiomyopathy (HCM), valvular heart disease, and constrictive pericarditis. Here, we primarily discuss HFpEF and restrictive cardiomyopathies.

A. HFpEF. Heart failure without another obvious cause, particularly in the context of advanced age, hypertension, obesity, chronic kidney disease, and diabetes, should lead to an early consideration for HFpEF. In such patients, myocardial ischemia may play some role in the manifestation of heart failure. This is particularly true for patients presenting with acute heart failure or flash pulmonary edema. In the absence of dynamic valvular regurgitation, ischemia leading to pulmonary edema usually denotes a large amount of myocardium at risk. This type of presentation certainly warrants aggressive investigation for obstructive coronary disease and when applicable, revascularization. Whether or not ischemia plays a role in patients with more subacute or chronic heart failure presentations is debatable.

B. Hypertrophic cardiomyopathy. The diagnosis of HCM is usually made in the presence of LVH, without concomitant hypertension or aortic stenosis. There are many manifestations of HCM, one of which is a "restrictive" phenotype that presents predominantly with diastolic heart failure. Distinction between HCM and other restrictive cardiomyopathies is not always clear, but it should be considered in certain scenarios: examples of this would include family members with HCM (particularly with an identified gene mutation), the typical reverse curve morphology of the interventricular septum, predilection for sudden death or ventricular tachyarrhythmia, and/or the presence of LV outflow tract obstruction.

C. Restrictive cardiomyopathies. Restrictive cardiomyopathies represent a group of disorders in which ventricular stiffness is increased by mechanisms/pathologies other than those related to the more garden-variety HFpEF patients. This may be a result of infiltrative, inflammatory, or metabolic diseases. The most common etiology of restrictive cardiomyopathy is cardiac amyloidosis.

1. **Cardiac amyloidosis.** Amyloidosis refers to the deposition of amyloid, or an abnormal protein, in organ tissue. There are several causes, and the following are the most important ones that manifest with cardiac involvement.
   a. Primary amyloidosis is caused by a primary hematologic malignancy. Monoclonal plasma cells produce a light-chain immunoglobulin; deposition into cardiac tissue is variable. Early stages show subclinical diastolic dysfunction (usually seen on echocardiography); later stages show severe restrictive cardiomyopathy. Traditionally, patients presenting with heart failure are felt to have a very poor prognosis with limited treatment options. However, anecdotal experience suggests that achieving remission of the malignancy with chemotherapeutics may positively impact patient's heart failure symptoms.
   b. Familial amyloidosis involves the inheritance of a gene that produces a mutant form of transthyretin, a serum protein carrier of thyroxine and retinol. The protein is produced in the liver and is deposited in the kidneys, the heart, and the nerves. Some centers may offer cardiac transplantation to selected patients.
   c. Senile amyloidosis is similar to familial amyloidosis in that it is related to the deposition of a pathologic variant of transthyretin. This usually occurs in older men.
2. **Endomyocardial fibrosis.** Endomyocardial fibrosis occurs in areas close to the equator, such as equatorial Africa, South America, and Asia. It usually affects children and young adults. Histologically it is characterized by granulation tissue, collagen, and extensive connective tissue lining the endocardium. It affects both ventricles (50%), left ventricle (40%), or isolated right (10%) ventricle and is associated with a 2-year mortality rate of up to 50%. Atrial fibrillation, mitral regurgitation, and thromboembolism are common. The response to medical treatment is poor. Endocardial decortication may be beneficial for those with New York Heart Association (NYHA) class III or IV symptoms. This technique has high operative mortality (15% to 20%), but when successful, reduces symptoms and may favorably affect the survival.
3. **Loeffler's (eosinophilic) endocarditis.** Loeffler's endocarditis is more commonly seen in temperate climates and generally occurs as part of the idiopathic hypereosinophilic syndrome. It typically manifests in middle age. Features include eosinophilia, restrictive cardiomyopathy, and nervous system and marrow involvement. Left ventricular mural thrombus frequently occurs. Aside from conventional heart failure medications (including anticoagulation), corticosteroids and hydroxyurea are useful treatment options. Surgery may be required for advanced fibrotic disease.
4. **Idiopathic restrictive cardiomyopathy.** Idiopathic restrictive cardiomyopathy is a diagnosis of exclusion. It usually occurs sporadically, but may be inherited with an autosomal dominant pattern in association with distal skeletal myopathy and occasionally a heart block. Echocardiography reveals near-normal LV dimensions and function, biatrial enlargement, and variable hypertrophy. Endomyocardial biopsy is unremarkable or shows nonspecific changes. The condition may manifest at any age throughout childhood or adult life. Survival time varies, with a mean survival of 9 years. Cardiac transplantation may be indicated in selected patients.
5. **Sarcoidosis.** Cardiac sarcoidosis can present with restrictive cardiomyopathy, but much more commonly it produces a dilated cardiomyopathy phenotype. Associated cardiac manifestations include conduction disease and ventricular tachyarrhythmia.
6. **Radiation carditis.** Radiation heart disease affects almost all components of the heart. Direct myocardial involvement, usually in the form of diastolic dysfunction, can be underappreciated, particularly when there is concomitant valvular, coronary, and/or pericardial disease. Separating the relative contributions of multiple pathophysiologic mechanisms in a given radiation patient is extraordinarily challenging. This is particularly evident when these patients go to surgery for

correction of valvular, coronary, and/or pericardial disease; suboptimal outcomes despite these corrections may be related to residual myocardial disease.

7. **Metabolic storage diseases** are characterized by intracellular deposition of substances within the myocyte, resulting in increased myocardial stiffness.
   a. **Hemochromatosis**, or iron overload, is listed as a storage disorder that can cause restrictive cardiomyopathy. However, when cardiac manifestations occur, the phenotype is usually a dilated cardiomyopathy.
   b. **Glycogen storage diseases.** Types II, III, IV, and V glycogen storage diseases may present with cardiac manifestations, usually as asymptomatic increase in LV thickness.
   c. **Gaucher's disease.** Gaucher's disease is caused by a deficiency in β-glucosidase, which leads to cerebroside deposition into multiple organs (spleen, liver, brain, bone marrow, lymph nodes, and heart). In the heart, this can cause increased ventricular thickness with diastolic dysfunction, LV systolic dysfunction, pericardial effusion, and valvular disease. This can be treated with enzyme replacement.
   d. **Fabry's disease** is a lysosomal storage disease caused by a deficiency in α-galactosidase (X-linked, recessive trait). This leads to glycosphingolipid accumulation in the kidney, the skin, and the heart. Cardiac manifestations include increased LV thickness, diastolic dysfunction, AV block, and mitral regurgitation. This can be treated with enzyme replacement.

V. DIAGNOSTIC TESTING

A. **Echocardiography** is the primary modality in evaluating a patient with a clinical syndrome of congestive heart failure. It is the modality of choice when evaluating LV diastolic function (Fig. 9.1). The most commonly used parameter in clinical practice is the Doppler interrogation of the transmitral flow pattern and tissue Doppler evaluation of annular velocity to determine the E/e' ratio. There are numerous other 2D and Doppler findings that are critical to diagnosis, including chamber size and wall thickness.
   1. **Transmitral flow pattern.** In sinus rhythm, using pulsed wave Doppler across the mitral inflow tract generates two waves: the early E wave, corresponding to rapid ventricular filling as the mitral valve opens, and the A wave, which reflects atrial contraction. In healthy people younger than 50 years, E is larger than A (i.e., E/A ratio > 1). The E-wave deceleration time is the time from peak E inflow

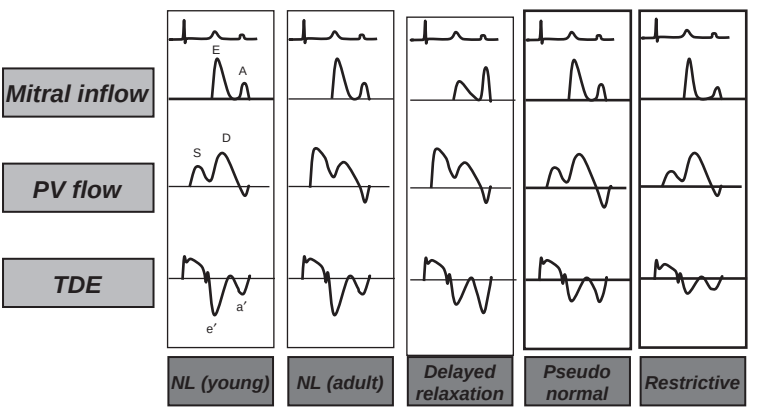

FIGURE 9.1 Patterns of diastolic function. PV flow, pulmonary vein flow; TDE, tissue Doppler (mitral annulus); NL, normal.

velocity to decay to zero. With age, hypertension, or ischemia, the viscoelastic properties of the ventricle decrease, and the E wave decreases in amplitude, has a gentler slope, and has a longer deceleration time. The atrial kick is proportionately greater, and E–A reversal occurs, with an E/A ratio < 1 (grade 1 diastolic dysfunction). With progression of diastolic dysfunction, left atrial (LA) pressure rises further to compensate, and the E wave becomes more prominent than the A wave (i.e., pseudonormalization or grade 2 diastolic dysfunction). As diastolic dysfunction progresses, the LV stiffness increases and the deceleration time shortens, reflecting rapid equilibration of LA/LV pressures during early diastole. When the deceleration time is < 160 milliseconds and the E/A ratio is > 2, the patient is considered to have grade 3 diastolic dysfunction.

Although the transmitral flow pattern is one of the primary ways of evaluating diastolic function, it has several limitations. It can be difficult to differentiate normal diastolic function from the "pseudonormal" pattern of grade 2 diastolic dysfunction, as they both have E/A ratios > 1. Because of this, American Society of Echocardiography guidelines have assigned stronger weight to other findings, including tissue Doppler imaging (TDI) and LA chamber size. Also, the transmitral flow pattern can often be difficult to interpret or uninterpretable in common scenarios, including atrial fibrillation, tachycardia (fusion of E and A waves), and mitral valve disease (MR ≥ 3+, mitral stenosis, and mitral prosthesis).

2. **Tissue Doppler imaging (TDI) of the mitral annular velocity.** In the evaluation of LV diastolic function, TDI is used to measure the velocity of movement of the septal and lateral aspects of the mitral annulus. The myocardial velocities have three main components: systolic wave (S'), early diastolic wave (e'), and the late diastolic wave (a'). In the earliest stages of diastolic dysfunction, the diastolic velocities of annular motion decrease. Normally, the lateral annulus tends to have higher velocities than the septal mitral annulus. Septal e' < 8 cm/s and/or a lateral e' < 10 cm/s suggests the presence of diastolic dysfunction.

   Unlike the transmitral flow pattern, there is no "pseudonormalization" pattern with annular velocity, making it easier to differentiate normal from abnormal diastolic function. The mitral annular TDI should be used with caution when other conditions coexist that may affect annular velocity independent of ventricular relaxation such as infarction of the septum or lateral wall or constriction with pericardial adhesion of the lateral wall.

3. **E/e'.** The ratio of the E velocity (obtained from the transmitral flow pattern) and the e' (obtained from TDI primarily of the lateral mitral annulus) can be used to estimate filling pressure, as there is a rough correlation with invasive hemodynamics (PCWP). This correlation is better with patients with depressed ejection fraction but is reasonable in patients with normal ejection fraction. Extreme values are most helpful. E/e' < 8 correlates with normal LV filling pressures. E/e' > 15 correlates with PCWP > 12 mm Hg; higher values are more specific for this. Unfortunately, there are many patients that fall into the intermediate zone, where E/e' > 8 but < 15. For these patients, the presence of elevated filling pressure cannot be determined by this method alone. Echocardiographic guidelines suggest using the presence of LA enlargement (LA volume index > 34 mL/m^2). Plasma BNP may be helpful in equivocal cases to determine whether or not there is corroborating evidence for elevated pressures.

   In patients with predominantly **exertional** symptoms, it may be useful to perform exercise echocardiography to determine the presence of diastolic dysfunction during exertion, particularly when this is not evident at rest. The sonographer should obtain LV images in multiple views following stress. Once the 2D information has been acquired, Doppler studies, including the transmitral flow pattern and the TDI of the septal and lateral mitral annulus, should be recorded. The diastolic abnormalities usually persist after tachycardia subsides, so

it is recommended that the data are recorded for a period of time following stress to reduce the likelihood of E- and A-wave fusion, which would make the E-wave velocity difficult to interpret. The most important parameter is E/e' following stress; if it is > 15, exertional increase in LV filling pressures is likely.

B. Invasive hemodynamic assessment. Invasive hemodynamic assessment is not routinely performed but is indicated when it is unclear whether elevated filling pressures are present on noninvasive studies. The PCWP (> 12 mm Hg) or LVEDP (> 16 mm Hg) should be measured. Other diastolic parameters, including Tau (τ), the time constant of isovolumic relaxation, are rarely measured in clinical practice.

When restrictive cardiomyopathy is considered, detailed hemodynamics may be of greatest value in directing management but are often less helpful in differentiating between possible diagnoses. Findings such as elevated and equalized diastolic pressures in four chambers (within 5 mm Hg), M pattern of the right atrial pressure waveform, "dip and plateau" of the ventricular diastolic pressures, equalization of LVEDP/RVEDP, and Kussmaul's sign occur in a number of pathologies, including restrictive cardiomyopathy, constrictive pericarditis, severe right ventricular failure, and severe tricuspid regurgitation.

C. Magnetic resonance imaging (MRI). In most patients with a diagnosis of HFpEF, cardiac MRI is rarely needed. It is useful to measure ventricular function, mass, and volumes when echocardiography is not diagnostic. It is also helpful in establishing or excluding specific conditions such as constrictive pericarditis, sarcoidosis, amyloidosis, or hemachromatosis (see Chapter 51).

D. Endomyocardial biopsy. Endomyocardial biopsy is used in selected circumstances, particularly when there is a high suspicion of a disorder whose diagnosis will profoundly impact management and prognosis. The most common indication is when cardiac amyloidosis is suspected. Biopsy in this setting can determine the presence of amyloid as well as differentiate between the different types of amyloid. The yield of endomyocardial biopsy for patchy diseases, such as sarcoidosis, is low.

VI. THERAPY. A handful of trials have attempted to look at the role of a variety of agents, including angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and β-blockers in patients with HFpEF. Unfortunately, **none of these trials have shown mortality benefit**. There has been variable effect of these medications on morbidity end points, including heart failure hospitalizations, symptoms, and LVH regression. The relevance of some of these trials is in question, as their entry criteria included patients with LV dilation and LVEF < 50%, likely a population quite different from our current conception of HFpEF patients. As the literature currently stands, no specific treatment has clearly demonstrated mortality benefit in patients with HFpEF. Treatment of hypertension should be in accordance with JNC VII guidelines (the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). Otherwise, treatment should be aimed toward symptomatic relief. The current ACC/AHA 2009 guidelines are listed in Table 9.2.

A. Salt restriction. Patients should be placed on a salt-restricted diet, usually 2,000 mg of sodium daily.

B. Diuretics. Diuretics should be used for symptomatic treatment of edema and pulmonary congestion. Chronic use of loop diuretics may lead to diuretic resistance; in this scenario, a thiazide- or potassium-sparing diuretic may be used to augment diuresis. For this indication, hydrochlorothiazide (usually 50 mg dosage, given once or intermittently) is effective within the first day. In extreme cases, patients may have significant bowel edema, rendering diuretics with poor oral absorption ineffective. In these patients, torsemide, which has a better oral absorption profile, is a reasonable option. Diuresis is often limited by the occurrence of prerenal azotemia. This is particularly common in those HFpEF or restrictive cardiomyopathy patients with

TABLE 9.2 Guidelines Adapted from ACC/AHA 2009 Update

Class I guidelines	
Control systolic and diastolic hypertension	Physicians should control hypertension in accordance with published guidelines (level of evidence: A)
Diuretics	Physicians should use diuretics to control pulmonary congestion and peripheral edema (level of evidence: C)
Ventricular rate should be controlled in the presence of AF	Physicians should control ventricular rate in AF (level of evidence: C)
Class IIa guidelines	
Coronary revascularization	In patients with CAD in whom ischemia is having an adverse effect on cardiac function (level of evidence: C)
Class IIb guidelines	
Restoration and maintenance of sinus rhythm	May be useful in improving symptoms (level of evidence: C)
Digoxin	Usefulness in reducing symptoms is not well established (level of evidence: C)
β-Blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists and controlled hypertension	Might be effective in minimizing symptoms (level of evidence: C)

AF, atrial fibrillation; CAD, coronary artery disease.

systemic disorders that have concomitant effects on the kidney, including hypertension, diabetes, or amyloidosis. In these cases, balancing congestive symptoms and azotemia can be challenging. On occasion, the patient may only achieve symptomatic relief after aggressive diuresis, even to the point where the blood urea nitrogen and/or creatinine are at levels higher than baseline values.

C. **Angiotensin receptor blockers.** Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Programme (CHARM-P) and Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) are two trials that evaluated the use of ARBs in the HFpEF population. I-PRESERVE is arguably the most relevant trial, as it enrolled patients with LVEF ≥ 45% and randomized patients to irbesartan versus placebo. This trial showed no difference in the primary end point of mortality and heart failure hospitalizations between the active and placebo groups. CHARM-P, which randomized candesartan versus placebo also failed to show a difference in a similar primary end point; the secondary end point of heart failure hospitalizations did seem to be reduced in the candesartan arm.

D. **ACE inhibitors**. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial randomized patients with LVEF > 40% to perindopril versus placebo. The primary end point was not met, but after 1 year, there appeared to be a statistically significant decrease in heart failure hospitalizations in the active treatment arm.

E. **Beta-blockers.** The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial randomized

nebivolol versus placebo in all-comers with congestive heart failure. Thirty-five percent of the patients had LVEF > 35%. In the overall trial, the nebivolol group demonstrated a significant decrease in the primary end point of mortality and heart failure mortality. In the subgroup analysis, the improvement appeared to hold in the group with LVEF > 35%.

F. Digoxin. The Digitalis Investigation Group (DIG) trial evaluated the use of digoxin in patients with heart failure. A subgroup of that trial examined patients with LVEF > 45%. There was no significant difference in mortality in this subgroup. There was a nonsignificant trend toward decreased heart failure hospitalizations but an increased trend toward unstable angina hospitalizations in those treated with digoxin.

G. Spironolactone. In patients with depressed ejection fraction, aldosterone antagonists have been demonstrated to have beneficial effects, likely working through antifibrotic mechanisms. There are two ongoing pivotal trials, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) and Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-HF), designed to evaluate the use of spironolactone in patients with HFpEF.

H. Sildenafil. Currently, there is no indication for phosphodiesterase 5 inhibitors in HFpEF, and mechanistic studies are ongoing.

VII. PRACTICAL APPROACH TO HFpEF AND RESTRICTIVE CARDIOMYOPATHIES

A. Exertional dyspnea only. In these patients, HFpEF should be on the differential diagnosis. Resting echocardiogram should be performed, with particular attention paid toward the presence of resting diastolic dysfunction. If this is absent, one can consider exercise echocardiography to determine exercise-induced diastolic dysfunction. Even in the presence of this diagnosis, specific treatment or change in management is uncertain.

B. Congestive heart failure. For patients presenting with overt signs of congestive heart failure, echocardiography should be used to narrow the differential diagnosis. In the absence of findings to support LV systolic dysfunction, valvular disease, or constrictive pericarditis, one should consider HFpEF as the diagnosis if there is evidence of diastolic dysfunction and elevated LV filling pressures. This is determined by unequivocal echocardiographic evidence ($E/e' > 15$); equivocal echocardiographic evidence ($E/e' > 8$ and < 15) + elevated BNP (NT-BNP > 200 pg/mL or BNP > 200 pg/mL); or invasive hemodynamics (PCWP > 12 mm Hg, LVEDP > 16 mm Hg). If the above findings are met and the patient fits the appropriate demographic (elderly, female, hypertension, chronic kidney disease, diabetes, and obese), then HFpEF is a reasonable diagnosis.

Restrictive cardiomyopathy should be entertained when patients present with significant right-sided heart failure symptoms (ascites, hepatic congestion, and severe edema), have multiorgan presentations (amyloidosis—orthostasis and renal failure; Fabry's—renal and skin involvement), or do not fit the typical demographic for HFpEF (young and no hypertension). In these patients, additional, focused testing should be performed to establish the etiologic diagnosis. This may include cardiac MRI and, in selected circumstances, endomyocardial biopsy.

C. Treatment. To date, there has been no class of medications that has been clearly established to have mortality benefit for patients with HFpEF. As it is believed that hypertension is the underlying etiology in most patients with HFpEF, blood pressure in these should be treated according to the established guidelines. However, particular agents do not have a priority as they do in patients with depressed ejection fraction, because they have not yet been demonstrated to have the same mortality and morbidity benefits. Otherwise, diuretics should be used for symptomatic benefit. The importance of concomitant obstructive coronary artery disease is debatable in asymptomatic patients. Likewise, revascularization should be reserved for patients in which ischemia is thought to play a major, adverse role in cardiac function (Table 9.2).

For those patients with restrictive cardiomyopathy, treatment should be directed toward the specific etiology. Oftentimes, there are no therapies that can reverse the severity of the restrictive cardiomyopathy, and the presence of congestive heart failure portends a poor prognosis. In these patients, diuretics are used for symptomatic relief. In selected candidates, cardiac transplantation may be entertained.

VIII. PROGNOSIS. HFpEF was once thought to confer a better prognosis than systolic dysfunction. Recent evidence demonstrates that the survival rates in both cases are similar. Twenty-two percent to 29% of patients with HFpEF die within 1 year of being discharged from their first hospitalization; 65% die within 5 years. Unlike patients with systolic dysfunction, no effective treatment has been found to improve this dismal outcome. The two groups have also been found to have similar rates of readmission for heart failure.

ACKNOWLEDGMENTS: *The authors thank Drs. Ryan P. Daly, John G. Peterson, and W.H. Wilson Tang for their contributions to earlier editions of this chapter. Special thanks to Dr. Allan Klein for his contributions to the figures of this chapter.*

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CHAPTER 10

Anthony Hart
Eiran Z. Gorodeski

Hypertrophic Cardiomyopathy

I. INTRODUCTION. The generally accepted definition of hypertrophic cardiomyopathy (HCM) is left ventricular (LV) hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself could produce such hypertrophy. There are many causes of LV wall thickening (Table 10.1), including long-standing hypertension, aortic stenosis, and infiltrative cardiomyopathies. However, these diseases can typically be identified by noninvasive markers, such as a history of significant hypertension and severe aortic stenosis. Other diseases will be identified by multisystem organ involvement (e.g., skeletal muscle weakness in Danon disease). HCM can be identified by a constellation of abnormalities, including gene mutations, marked LV thickness (> 25 mm), the presence of left ventricular outflow tract (LVOT) obstruction, and/or the presence of systolic anterior motion (SAM).

While there are many alternative names for HCM, including *idiopathic hypertrophic subaortic stenosis, hypertrophic obstructive cardiomyopathy, and muscular subaortic stenosis*, the World Health Organization (WHO) recommends that HCM should be used. It is the preferred term because it does not imply that obstruction (present in only approximately 25% of cases) is an invariable component of the disease.

II. CLINICAL PRESENTATION

A. Natural history

1. The **histological features** of HCM are disarray of cell-to-cell arrangement, disorganization of cellular architecture, and fibrosis. The most common sites of ventricular involvement are, in decreasing order, the septum, apex, and midventricle. One-third of patients have wall thickening limited to one segment. These morphologic and histological features, which vary in phenotypic and clinical expression, give rise to the characteristically unpredictable natural history of HCM.
2. The **prevalence** of HCM is approximately 1 in 500, and the condition appears to be familial in origin. This makes HCM one of the most common genetically transmitted cardiovascular diseases. It is found among 0.5% of unselected patients referred for echocardiographic examination and is a leading cause of sudden death among athletes younger than 35 years.

B. Signs and symptoms

1. **Heart failure.** Symptoms, which include dyspnea, dyspnea on exertion, paroxysmal nocturnal dyspnea, and fatigue, are largely a consequence of two processes: elevated LV diastolic pressure caused by diastolic dysfunction and dynamic LV outflow obstruction.
   a. Events that accelerate heart rate, decrease preload, shorten diastolic filling time, increase LV outflow obstruction (i.e., exercise and tachyarrhythmias), or worsen compliance (i.e., ischemia) exacerbate these symptoms.

TABLE 10.1 Differential Diagnosis of Left Ventricular Wall Thickening

Long-standing hypertension
Athlete's heart
Aortic stenosis
Amyloidosis
Mitochondrial disease
Fabry disease
Friedreich's ataxia
Danon disease
Noonan syndrome
Pompe disease

b. Between 5% and 10% of patients with HCM progress to severe LV systolic dysfunction, characterized by progressive LV wall thinning and cavity enlargement.

2. **Myocardial ischemia.** Myocardial ischemia occurs in obstructive and nonobstructive HCM.
   a. The **clinical and electrocardiographic** presentation is similar to that of ischemic syndromes in persons without HCM. Ischemia has been demonstrated with thallium perfusion studies, elevated myocardial lactate levels during rapid atrial pacing, and positron emission tomography.
   b. While epicardial artery obstruction is less common, **mismatch of supply and demand** due to thickened vessels and small vessel disease from increased collagen deposition in the intima and media are the most likely pathophysiologies of ischemia. Contributing factors include the following:
      (1) Small vessel coronary disease with decreased vasodilator capacity
      (2) Elevated myocardial wall tension as a consequence of delayed diastolic relaxation time and obstruction to LV outflow
      (3) Decreased capillary-to-myocardial fiber ratio
      (4) Decreased coronary perfusion pressure
3. **Syncope and presyncope** are usually a consequence of diminished cerebral perfusion caused by inadequate cardiac output. These episodes are commonly associated with exertion or cardiac arrhythmia.
4. **Sudden death.** The annual mortality rate for HCM is **1%**. Most deaths are sudden or unexpected.
   a. Not all patients with HCM are at equal **risk for sudden death**. Twenty-two percent of patients with sudden death have no symptoms. **Sudden death appears to be most common among older children and young adults**; it is rare in the first decade of life. Approximately 60% of deaths occur during periods of inactivity; the remaining deaths occur after vigorous physical exertion.
   b. **Arrhythmogenic and ischemic mechanisms** can initiate a clinical spiral of hypotension, decreased diastolic filling time, and increased outflow obstruction that often culminates in death.

III. PHYSICAL EXAMINATION

A. Inspection of the jugular venous system may reveal a prominent *a* wave that indicates hypertrophy and lack of compliance of the right ventricle. A precordial heave, representing right ventricular (RV) strain, can be found in persons with concomitant pulmonary hypertension.

B. Palpation

1. The **apical precordial pulse is usually laterally displaced and diffuse**. LV hypertrophy may cause a presystolic apical impulse or palpable fourth heart sound (S_4). A three-component apical impulse may occur, with the third impulse resulting from a late systolic bulge of the left ventricle.
2. The carotid pulse has been classically described as bifid. This **rapid carotid upstroke followed by a second peak** is caused by a hyperdynamic left ventricle. This is in contrast to the *parvus et tardus* pulse of fixed aortic or subvalvular aortic stenosis, which is a carotid pulse characterized by a delayed amplitude and upstroke.

C. Auscultation

1. S_1 (first heart sound) is usually normal and is preceded by S_4.
2. S_2 (second heart sound) can be normal or paradoxically split as the result of the prolonged ejection time of patients with severe outflow obstruction.
3. The **harsh, crescendo–decrescendo systolic murmur** associated with HCM is best heard at the left sternal border. It radiates to the lower sternal border but not to the neck vessels or axilla.
   a. An important aspect of the murmur is its **variation in intensity and duration** with ventricular loading conditions. During periods of increased venous return, the murmur is of shorter duration and is less intense. In the underfilled ventricle and during periods of increased contractility, the murmur is harsh and of a longer duration.
      (1) The **concomitant murmur of mitral insufficiency** can be differentiated because of its holosystolic, blowing quality that radiates to the axilla.
      (2) A soft, early, decrescendo, **diastolic murmur of aortic insufficiency** is found in approximately 10% of patients with HCM.
   b. **Maneuvers that affect preload and afterload** can be helpful in diagnosing HCM and differentiating it from other systolic murmurs (Table 10.2).

TABLE 10.2 Effects of Maneuvers or Pharmacologic Intervention to Differentiate Murmur of Hypertrophic Cardiomyopathy from Aortic Stenosis

Maneuver	Physiologic effect	HCM	AS	MR
Valsalva and standing	Decreases VR, SVR, and CO	↑	↓	↓
Squat and handgrip	Increases VR, SVR, and CO	↓	↑	↑
Amyl nitrite	Increases VR Decreases SVR and LV volume	↑	↑	↓
Phenylephrine	Increases SVR and VR	↓	↑	↑
Extrasystole	Decreased LV volume	↑	↓	No change
Post-Valsalva release	Increased LV volume	↓	↑	No change

AS, aortic stenosis; CO, cardiac output; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MR, mitral regurgitation; SVR, systemic vascular resistance; VR, venous return; ↓, decrease; ↑, increase.

TABLE 10.3 Molecular Genetics of Hypertrophic Cardiomyopathy

Gene symbol	Protein name	% of HCM caused by mutations in this gene
MYH7	Myosin heavy chain	40
MYBPC3	Myosin-binding protein C	40
TNNT2	Troponin T	5
TNNI3	Troponin I	5
TPM1	Tropomyosin 1	2
ACTC1	Actin, α	Unknown
MYL2	Myosin regulatory light chain 2	Unknown
MYL3	Myosin light polypeptide 3	1

HCM, hypertrophic cardiomyopathy.

IV. GENETIC ASPECTS OF HCM. Familial HCM is caused by mutation in one of the genes currently known to encode different components of sarcomere proteins or sarcomere-associated proteins that are inherited in an autosomal dominant manner (see Chapter 42). To date, familial HCM is known to be caused by over 1,400 different mutations in at least 8 genes (Table 10.3). Multiple analyses suggest that these common genetic subtypes are essentially phenotypically indistinguishable.

HCM genotype does not necessarily imply that subjects will have the phenotypic traits of HCM as variable penetrance exists, and environmental factors as well as modifier genes affect whether a particular subject will manifest HCM phenotypically.

Patients with an **identified pathogenic mutation** are at an increased risk for cardiovascular death, nonfatal stroke, or progression to NYHA functional class III or IV compared with patients with no identified mutations.

V. DIAGNOSTIC TESTING

A. Electrocardiogram (ECG). Although most patients have electrocardiographic evidence of disease, no changes are pathognomonic for HCM. Common electrocardiographic findings in HCM are listed in Table 10.4. These abnormalities do not correlate with disease severity or pattern of hypertrophy.

B. Echocardiography is the preferred diagnostic method because of its high sensitivity and low risk profile. It also allows characterization of the site of obstruction. Careful

TABLE 10.4 Electrocardiographic Findings in Hypertrophic Cardiomyopathy

Evidence of right and left atrial enlargement
Q waves in the inferolateral leads
Voltage criteria for large negative precordial T waves (associated with Japanese variant)
Left-axis deviation
Short PR interval with slurred upstroke

TABLE 10.5 Two-Dimensional, M-Mode, and Doppler Echocardiographic Findings in Hypertrophic Cardiomyopathy

Asymmetric septal hypertrophy (> 13 mm)
Systolic anterior motion of the mitral valve
Small left ventricular cavity
Septal immobility
Premature closure of the aortic valve
Resting gradients > 30 mm Hg
Provocable gradients > 50 mm Hg
Normal or increased motion of the posterior wall
Reduced rate of closure of the mitral valve in mid-diastole
Mitral valve prolapse with regurgitation
Maximal left ventricular diastolic wall thickness > 15 mm

assessment for conditions that can also cause secondary hypertrophy (aortic or subaortic stenosis, hypertension, infiltrative diseases, etc.) should also be done.

1. **M-mode and two-dimensional** echocardiographic findings in HCM are listed in Table 10.5. Close evaluation of the extent of hypertrophy should be done given the role of septal thickness in risk stratification for sudden cardiac death (SCD).
2. **Doppler echocardiography** enables recognition and quantification of dynamic LVOT obstruction as well as the response to various maneuvers.
   a. Approximately one-fourth of patients with HCM have a resting pressure gradient between the body and LVOT; others have only provocable gradients.
   b. The **diagnosis of HCM with obstruction** is based on resting peak instantaneous gradient > 30 mm Hg. These gradients correlate directly with the time of onset and duration of contact between the mitral leaflet and the septum, as occurs during SAM of the mitral leaflet. The earlier and longer the contact occurs, the higher the pressure gradient.
      (1) Inducing obstruction and, therefore, gradients, in patients believed to have latent obstruction, can be accomplished with substances (e.g., amyl nitrite, isoproterenol, and dobutamine) or maneuvers (e.g., Valsalva maneuver and exercise) that decrease LV preload or increase contractility.
      (2) Although the **clinical relevance of outflow obstruction has been debated, relief by means of surgical or pharmacologic technique is associated with clinical improvement** among many patients. Echocardiographic recognition of HCM and of HCM with outflow obstruction is, therefore, important.
   c. **Recognition of mitral regurgitation (MR).** Echocardiographic evaluation of MR and the detection of valve anomalies may have a considerable effect on medical and surgical strategies in the care of patients with HCM.
      (1) Approximately **60% of patients with HCM have structural abnormalities of the mitral valve**, including increased leaflet area, elongation of leaflets, and anomalous insertion of papillary muscles directly into the anterior mitral leaflet.

(2) When there is no leaflet abnormality, the degree of MR is directly related to the severity of obstruction and lack of leaflet coaptation.

C. Magnetic resonance imaging (MRI). Advantages of MRI in the evaluation of HCM include excellent resolution, lack of radiation, inherent contrast, three-dimensional imaging, and tissue characterization. Disadvantages are cost, length of study, and exclusion of patients with contraindications to exposure to magnetism, such as patients with implantable cardioverter–defibrillators (ICDs) or pacemakers.

1. MRI can detect **LV hypertrophy** missed by echocardiography, specifically in the anterolateral and basal LV free walls.
2. **Myocardial scar**, often found in patients with HCM, can be detected as **delayed hyperenhancement with gadolinium-contrast MRI**. Some small studies have suggested that the amount of hyperenhancement may be a predictor of SCD in this patient population.
3. Improved identification of MR, SAM, abnormal papillary muscles, and diastolic dysfunction.
4. Differentiate from alternative causes of LV thickening such as Fabry disease and amyloidosis.

D. Cardiac catheterization is used primarily for defining coronary anatomy before myectomy or a mitral valve operation and evaluation of ischemic symptoms. The characteristic findings of HCM during hemodynamic assessment are listed in Table 10.6 and illustrated in Figure 10.1.

1. Patients with normal coronary arteries may have **typical ischemic symptoms**. These symptoms may indicate myocardial bridges, phasic narrowing during systole, reduced coronary flow reserve, or systolic reversal of flow in the epicardial vessels.
2. **Left ventriculography** usually reveals a hypertrophied ventricle, prominent septal bulge, nearly complete obliteration of the ventricular cavity during systole, SAM, and MR. The **spadelike** appearance of the ventricular cavity is confined to ventricles with **apical involvement**.

VI. MANAGEMENT STRATEGIES

A. Priority of therapy. Effective therapy must include pathways for the **prevention and management of heart failure** caused by diastolic and systolic dysfunction, arrhythmias, ischemia, and failed medical therapy and the **prevention of sudden death**. The specific strategies for patients with HCM can be as heterogeneous as the clinical presentation and evolution. See Figure 10.2 for a simplified treatment algorithm.

TABLE 10.6 Hemodynamic Findings during Cardiac Catheterization

Subaortic or mid-ventricular outflow gradient on catheter pullback
Spike-and-dome pattern of aortic pressure tracing[a]
Elevated right and left ventricular end-diastolic pressures
Elevated pulmonary capillary wedge pressure
Increased V wave on wedge tracing[b]
Elevated pulmonary arterial pressure

[a]A consequence of outlet obstruction.
[b]May result from either mitral regurgitation or elevated left atrial pressure.

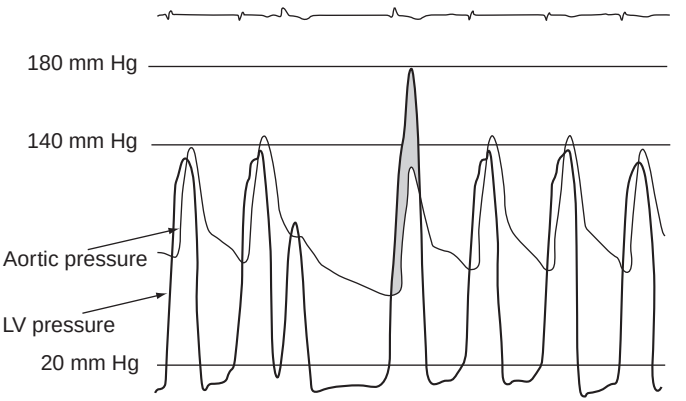

FIGURE 10.1 Severe increase in the left ventricular (LV) aortic gradient in the beat after a premature ventricular contraction (PVC) (Brockenbrough-Braunwald-Morrow sign) due to an increase in contractility and decrease in afterload during the post-PVC beat.

B. Medical therapy. Although never proven to reduce mortality in clinical trials, **β-blockers are the first-line therapy** for HCM, regardless of the presence of LV outflow obstruction.

1. **β-Blockers** improve symptoms and exercise tolerance. β-Blockers with additional α-blocking properties, such as carvedilol and labetalol, should probably not be used as first-line agents because of their additional vasodilatory properties.
   a. The mechanism of action of β-blockers is inhibition of sympathetic stimulation brought about by the negative inotropic and chronotropic properties of the drugs. β-Blockers diminish myocardial oxygen requirements and augment diastolic filling, which mitigate angina and the detrimental effects of LV outflow obstruction, respectively.
2. **Calcium channel blockers (CCBs)** are considered to be second-line agents that are also effective in reducing the common symptoms of HCM in patients who are intolerant of or have undergone unsuccessful treatment with β-blockers.
   a. **CCBs** have a negative inotropic effect and reduce the heart rate and blood pressure. They may also have beneficial effects on diastolic function by improving rapid diastolic filling, although possibly at the expense of higher LV end-diastolic pressures. The beneficial effects seem to be limited to the nondihydropyridines **verapamil** and **diltiazem** (Table 10.7). Conversely, dihydropyridine CCBs may be contraindicated (see below).
   b. Because of the unpredictable hemodynamic effects of their vasodilator properties, CCBs should be administered cautiously to patients with considerable outlet obstruction and elevated pulmonary pressures.
3. **Disopyramide**, a class 1a antiarrhythmic agent, may be an effective alternative or adjunct to β-blocker and CCB therapy. Its strong negative inotropic qualities coupled with its ability to suppress ventricular and supraventricular arrhythmias make it an effective treatment when marked outflow obstruction or arrhythmias are manifested. Potential disadvantages are anticholinergic properties, accumulation in patients with hepatic or renal dysfunction, the possibility of augmenting atrioventricular (AV) nodal conduction in the presence of atrial fibrillation, and

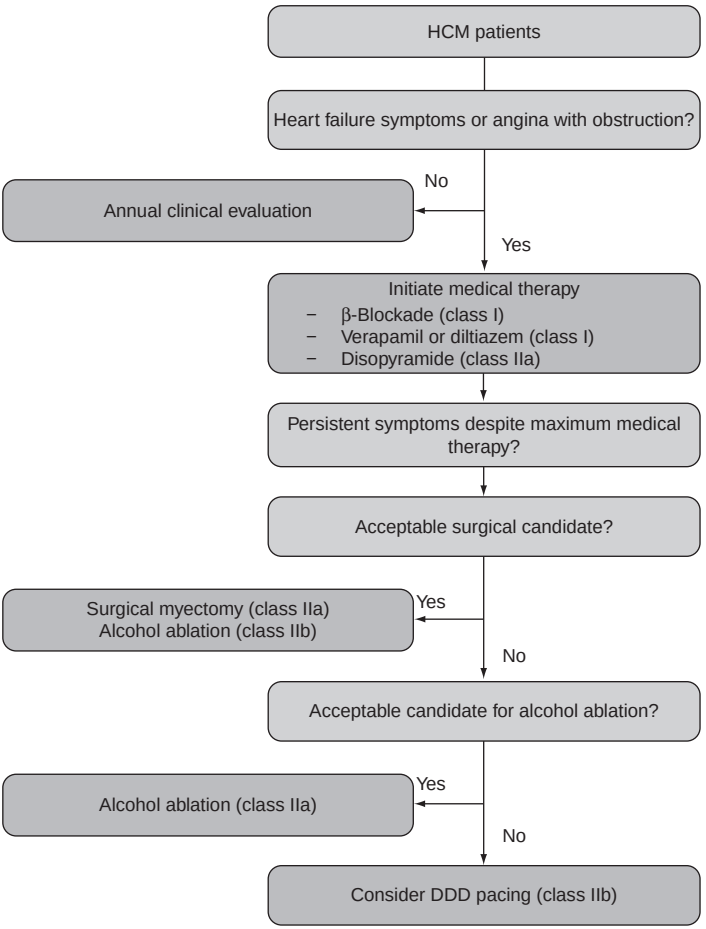

FIGURE 10.2 Management algorithm for hypertrophy cardiomyopathy. DDD, dual pacing for both chambers, dual chamber activity sensing, and dual response; HCM, hypertrophic cardiomyopathy. (Adapted from Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. *Circulation* 2011;124:e783–e831)

waning hemodynamic effects with time. It is because of these significant side effects that disopyramide is typically used in a very symptomatic patient when a more definitive procedure is being planned, such as surgical myectomy or alcohol septal ablation. It is not considered to be a long-term treatment for HCM.

4. **Dihydropyridine CCBs** (e.g., nifedipine and amlodipine), **angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers** should be avoided because they cause peripheral vasodilation, which may result in decreased LV filling and worsening of outflow tract obstruction.

TABLE 10.7 Pharmacologic Therapy for Hypertrophic Cardiomyopathy

Drug	Standard dose[a] (mg/d)
β-Blockers	
Metoprolol	50–200
Atenolol	50–100
Calcium channel antagonists	
Verapamil	120–360
Diltiazem	120–360
Antiarrhythmics	
Disopyramide	400–1,200
Amiodarone	200–400
Sotalol	160–320

[a]Doses can be increased to treat patients with persistent symptoms who have no evidence of an adverse response.

5. **Diuretics** should be used cautiously as high filling pressures are often necessary due to the stiff ventricle, and overdiuresis may reduce LV size and increase obstruction.
6. **Digoxin** should be avoided due to potential worsening of the LVOT obstruction secondary to the positive inotropic effect.
7. **Phenylephrine**, a pure α-agonist that causes vasoconstriction, can be considered in cases of refractory hypotension unresponsive to IV fluids. Pressors with positive inotropic effects, such as norepinephrine, dopamine, and dobutamine, can provoke LVOT obstruction and should be avoided.

C. **Nonpharmacologic treatment** is typically reserved for those patients with symptoms despite optimal medical therapy (Table 10.8). With severe symptomatic, nonobstructive HCM, cardiac transplantation remains the only option. However, persons with symptomatic obstruction and resting or latent gradient of 50 mm Hg or more despite optimal medical treatment are candidates for septal myectomy or alcohol septal ablation. Younger patients with gradients > 75 mm Hg and low surgical risk should be considered for septal myectomy even in the absence of symptoms.

1. **Septal myectomy** of HCM has been performed for more than 50 years and is the **procedure of choice for patients with progressive, drug-refractory functional limitation due to LVOT obstruction.**
   a. When performed by an experienced surgeon, septal myectomy is considered the most definitive treatment and is associated with a mortality rate of < 1% to 2%. It is effective in abolishing resting gradients in > 90% of patients, and most patients have long-lasting symptomatic relief. Enlargement of the LVOT has been found to reduce SAM, MR, LV systolic and end-diastolic pressures, left atrial pressure, and resting gradients. A retrospective study by Ommen et al. (1) from the Mayo Clinic published in 2005 demonstrated that patients who underwent myectomy had significantly longer survival and less incidence of SCD as compared with patients with obstruction who did not undergo surgery. In fact, after myectomy, survival was no different as compared with HCM patients who did not have obstruction at baseline.

TABLE 10.8 Excerpts from 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

Invasive therapies—recommendations

Class I

Septal reduction therapy should be performed only by experienced operators in the context of a comprehensive HCM clinical program and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction.

Class IIa

Consultation with centers experienced in performing both surgical septal myectomy and alcohol septal ablation is reasonable when discussing treatment options for eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. *(Level of Evidence: C)*

Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. *(Level of Evidence: B)*

Surgical septal myectomy, when performed at experienced centers, can be beneficial in symptomatic children with HCM and severe resting obstruction (> 50 mm Hg) for whom standard medical therapy has failed. *(Level of Evidence: C)*

When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms (usually NYHA functional class III or IV). *(Level of Evidence: B)*

Class IIb

Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation. *(Level of Evidence: B)*

The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked (i.e., > 30 mm) septal hypertrophy, and therefore the procedure is generally discouraged in such patients. *(Level of Evidence: C)*

Selection of patients for ICD

Class I

The decision to place an ICD in patients with HCM should include application of individual clinical judgment, as well as a thorough discussion of the strength of evidence, benefits, and risks to allow the informed patient's active participation in decision making. *(Level of Evidence: C)*

ICD placement is recommended for patients with HCM with prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant VT. *(Level of Evidence: C)*

Class IIa

It is reasonable to recommend an ICD for patients with HCM with

1. Sudden death presumably caused by HCM in one or more first-degree relatives. *(Level of Evidence: C)*
2. A maximum LV wall thickness ≥ 30 mm. *(Level of Evidence: C)*
3. One or more recent, unexplained syncopal episodes. *(Level of Evidence: C)*

(Continued)

TABLE 10.8 Excerpts from 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy (*Continued*)

An ICD can be useful in select patients with NSVT (particularly those < 30 years of age) in the presence of other SCD risk factors or modifiers. *(Level of Evidence: C)*

An ICD can be useful in select patients with HCM with an abnormal blood pressure response with exercise in the presence of other SCD risk factors or modifiers. *(Level of Evidence: C)*

It is reasonable to recommend an ICD for high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation. *(Level of Evidence: C)*

Class IIb

The usefulness of an ICD is uncertain in patients with HCM with isolated bursts of NSVT in the absence of any other SCD risk factors or modifiers. *(Level of Evidence: C)*

The usefulness of an ICD is uncertain in patients with HCM with an abnormal blood pressure response with exercise when in the absence of any other SCD risk factors or modifiers, particularly in the presence of significant outflow obstruction. *(Level of Evidence: C)*

Participation in competitive or recreational sports and physical activity

Class IIa

It is reasonable for patients with HCM to participate in low-intensity competitive sports (e.g., golf and bowling). *(Level of Evidence: C)*

Management of AF

Class I

Anticoagulation with vitamin K antagonists (i.e., warfarin, to an INR of 2.0 to 3.0) is indicated in patients with paroxysmal, persistent, or chronic AF and HCM. *(Level of Evidence: C)*

Ventricular rate control in patients with HCM with AF is indicated for rapid ventricular rates and can require high doses of β-antagonists and nondihydropyridine calcium channel blockers. *(Level of Evidence: C)*

Class IIa

Disopyramide (with ventricular rate-controlling agents) and amiodarone are reasonable antiarrhythmic agents for AF in patients with HCM. *(Level of Evidence: C)*

Radiofrequency ablation for AF can be beneficial in patients with HCM who have refractory symptoms or who are unable to take antiarrhythmic drugs. *(Level of Evidence: B)*

Maze procedure with closure of LA appendage is reasonable in patients with HCM with a history of AF, either during septal myectomy or as an isolated procedure in selected patients. *(Level of Evidence: C)*

Class IIb

Sotalol, dofetilide, and dronedarone might be considered alternative antiarrhythmic agents in patients with HCM, especially in those with an ICD, but clinical experience is limited. *(Level of Evidence: C)*

AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter–defibrillator; INR, international normalized ratio; LA, left atrial; LV, left ventricular; LVOT, left ventricular outflow tract ; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VT, ventricular tachycardia. From Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. *Circulation* 2011;124:e783–e831.

2. **Alcohol septal ablation**—essentially a controlled infarction of the septum—is an alternative to septal myectomy. Because it has a greater risk than myectomy of complications including complete heart block and extensive myocardial infarction, it is **generally used in patients who are not candidates for surgical myectomy**. There are no randomized trials comparing myectomy and septal ablation.
   a. **Technique.** In the cardiac catheterization laboratory, a guidewire is advanced through the left main trunk to probe the first or second septal perforator, or both. An angioplasty catheter is placed in the proximal portion of the septal branch for vessel isolation. Ultrasonic contrast agents are infused in the cannulated perforator to define the area at risk for infarction. Infusion of 1 to 4 mL of absolute alcohol causes infarction in the zone of septal myocardium served by the cannulated septal branch. In most centers, a temporary ventricular pacing catheter is placed into the RV apex before performing the ablation, in order to manage any transient conduction abnormalities.
   b. **Results.** In the majority of patients, there is a marked immediate decrease in the LVOT gradient. This gradient response is thought to be triphasic: immediate reduction (due to stunning), early reappearance, and sustained fall by 3 months after the procedure (due to remodeling). Within this initial period, most patients attain good symptomatic relief. Risks of the procedure include high-grade AV block, coronary dissection, large anterior wall myocardial infarction, pericarditis, and electrical instability of the scar that forms as a result of the infarction. In a Scandinavian study by Jensen et al. of 313 alcohol septal ablation procedures performed in 279 patients, mortality was low at 0.6%, but 20% of patients required implantation of a pacemaker (2).
3. **Dual-chamber pacing** has been previously used in hopes of alleviating symptoms by altering the timing of septal contraction, but studies have not confirmed any long-term benefit. Dual-chamber pacing should only be considered in patients with medically refractory symptoms who are not candidates for septal reduction therapy.
4. **Special management considerations**
   a. **Atrial fibrillation**, which occurs in up to a third of patients with HCM, can have devastating consequences. Atrial fibrillation decreases diastolic filling time and causes the loss of atrial systole. These changes can lead to acute hemodynamic decompensation and pulmonary edema given the stiff left ventricle of patients with HCM. Because of the increased risk of thromboembolism, all patients with HCM-associated atrial fibrillation (be it paroxysmal or permanent) should be strongly considered for anticoagulation therapy. Aggressive efforts should be made to maintain sinus rhythm given the increased morbidity and mortality associated with atrial fibrillation in patients with HCM.
      (1) **Acute paroxysms** of atrial fibrillation are best managed with prompt cardioversion with transesophageal echocardiogram (TEE). Data concerning the prevention of recurrence are lacking, but the 2006 ACC/AHA Guidelines for the Management of Patients with Atrial Fibrillation suggest disopyramide or amiodarone as possible agents. Other class III agents, such as dofetilide, sotalol, and dronedarone, should be reserved for use in patients with an ICD given the paucity of safety data.
      (2) **Chronic atrial fibrillation** may be well tolerated if the heart rate is controlled with β-blockers or calcium channel antagonists.
      (3) **Maze or radiofrequency ablation.** For patients who do not tolerate atrial fibrillation and cannot be maintained in sinus rhythm, AV nodal ablation and implantation of a dual-chamber pacemaker may be an option. Other options including catheter ablation or combined surgical myectomy–maze can be considered.

b. Risk stratification for sudden death remains one of the more challenging aspects for the management of HCM, especially for primary prevention. Table 10.9 lists the established factors for risk stratification. Additional risk factors (e.g., scar burden as determined by late gadolinium contrast on MRI) continue to be evaluated. Currently, the only effective means of preventing SCD is an ICD.

(1) Placement of an ICD carries several potential complications, including but not limited to infection, inappropriate firing, lead fracture, and generator depletion. The **decision to implant an ICD is highly individualized** and should take into consideration that younger patients will be subject to a higher risk of device-related complications due to the longer time the device will be present.

(2) Patients who survive an episode that might have ended in sudden death, have sustained ventricular arrhythmias, or have multiple risk factors for sudden death should be strongly considered for an ICD.

(3) Selection of patients for ICD implantation as primary prevention is difficult. A retrospective multicenter study from the Minneapolis Heart Institute Foundation (3) evaluated the incidence of appropriate ICD interventions in patients with HCM who previously received a device for one of four SCD risk factors: history of HCM-related SCD in a relative younger than 50 years, "massive" LV hypertrophy, nonsustained ventricular tachycardia on Holter monitoring, and prior unexplained syncope (nonneurocardiogenic). The study concluded that one risk factor may be enough for consideration of ICD implantation. Of note, there was no control group in this study.

VII. SPECIAL CONSIDERATIONS

A. Athlete's heart

1. Differentiating HCM from hypertrophy of athletes. Failure to diagnose HCM places an athlete at undue risk for sudden death while incorrect labeling of HCM often leads to irrational treatments, unnecessary fears, and inappropriate recommendations concerning exercise. Diagnostic uncertainty is greatest when maximal diastolic LV wall thickness exceeds the upper limit of normal (12 mm) but is less than the defined lower limit of expected hypertrophy (15 mm) for HCM and in the absence of SAM and LV outflow obstruction.

a. Characteristics that **substantiate the diagnosis of HCM** include unusual patterns of hypertrophy, an LV end-diastolic diameter of < 45 mm, septal thickening > 15 mm, left atrial enlargement, abnormal diastolic function, family history of HCM, and abnormal LV filling.

TABLE 10.9 Risk Factors for Sudden Cardiac Death

Previous cardiac arrest
Sustained ventricular tachycardia
Prolonged or repetitive episodes of nonsustained ventricular tachycardia on Holter monitor
Left ventricular wall thickness > 30 mm
Family history of SCD
No change or a decrease in blood pressure with exercise
Syncope or near-syncope

SCD, sudden cardiac death.

b. Findings more consistent with the **hypertrophied heart of an athlete** are LV end-diastolic diameter > 45 mm, septal thickening < 15 mm, left atrial size < 4 cm, LV end-diastolic diameter > 45 mm, and a decrease in LV thickness with deconditioning.

Should differentiation not be possible, the patient should stop training: after several months, ventricular hypertrophy will typically regress in the athlete but will persist in a patient with HCM.

2. Participation in sports. HCM is the most common cause of sudden death in young athletes. It appears that intense exercise, with its resulting rapid changes in hemodynamics, can increase the risk of death as well. The European Society of Cardiology recommends prohibiting athletes with HCM from participating in competitive high school and college sports. These recommendations remain in force after medical or surgical intervention.

a. Athletes with HCM with or without obstruction who are younger than 30 years should **not** participate in competitive, aerobically demanding sports.

b. Participation in recreational sports should take into consideration the intensity of the activity (with the resulting fluctuations in hemodynamics) and the danger to the individual should impaired consciousness occur. For instance, activities such as rock climbing and weightlifting carry a higher risk of morbidity and mortality than activities such as golf and bowling.

B. Infective endocarditis (IE)

1. Predisposing factors. Gastrointestinal and genitourinary tract surgical procedures place patients at increased risk for bacteremia. It is unclear if dental procedures place patients with HCM at risk.

2. Pathophysiology. Bacterial seeding of endomyocardial lesions is caused by repeated trauma associated with hemodynamic and intrinsic valvular abnormalities.

3. Prophylaxis. Guidelines on the prevention of IE published by the AHA in 2007 question the practice of treating patients with HCM with antibiotics prior to dental procedures and recommend against it except in the setting of prior endocarditis. However, there are no large, prospective, randomized double-blind trials testing the efficacy of IE prophylaxis. Given the catastrophic consequences of endocarditis in patients with HCM, routine antimicrobial prophylaxis for IE should be weighed on an individual basis.

C. Yamaguchi's or Apical HCM

1. Clinical presentation. Patients experience chest pain, dyspnea, fatigue, and, in rare instances, sudden death.

2. Prevalence. Within Japan, apical HCM constitutes 25% of all cases of HCM. Outside Japan, only 1% to 2% of cases are associated with isolated apical hypertrophy.

3. Diagnostic testing

a. An **ECG** reveals giant negative T waves in the precordial leads and LV hypertrophy (Fig. 10.3).

b. Echocardiographic findings include the following:

(1) Localized hypertrophy in the distal left ventricle beyond the origin of the chordae tendineae

(2) Wall thickness in the apical region of at least 15 mm or a ratio of maximal apical to posterobasal thickness > 1.5

(3) Exclusion of hypertrophy in other parts of the ventricular wall

(4) No LVOT obstruction or gradient

c. MRI demonstrates localized hypertrophy to the cardiac apex. MRI is useful in the care of patients with poor echocardiographic windows.

d. Cardiac catheterization reveals a spadelike configuration of the LV cavity at end diastole and apical end-systolic LV cavity obliteration.

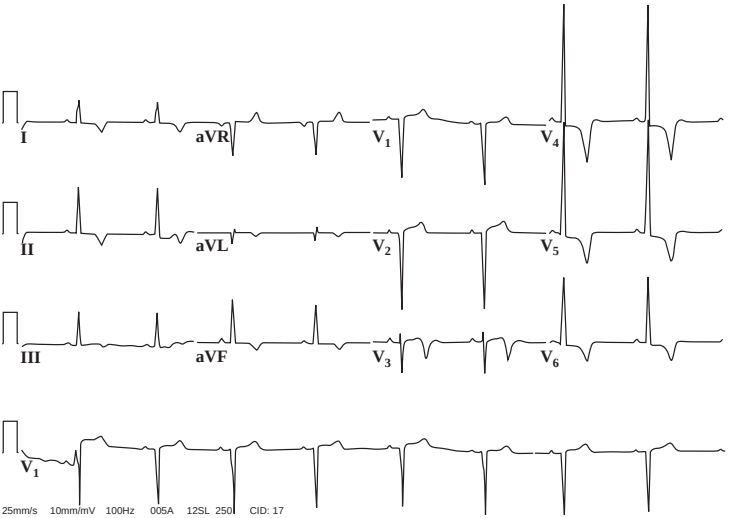

FIGURE 10.3 Electrocardiogram (ECG) in an apical hypertrophic cardiomyopathy (HCM, Yamaguchi). The classic ECG for apical HCM has deep anteroapical T-wave inversions.

4. **Prognosis** is favorable compared with that associated with other forms of HCM.
5. **Therapy.** Therapeutic efforts are limited to management of diastolic dysfunction with β-blockers and calcium channel antagonists.

D. HCM among the elderly

1. **Clinical presentation.** In addition to the signs and symptoms of other forms of HCM, hypertension is more common with HCM in the elderly population.
2. **Incidence.** Although the incidence is unknown, HCM among the elderly is probably more common than expected.
3. **Genetic aspects.** Reports have suggested that the delayed expression of mutations in the gene for cardiac myosin-binding protein C may play an important role in HCM in the elderly.
4. **Echocardiographic findings** for elderly patients (65 years or older) are compared with findings for young patients (40 years or younger) as follows:
   a. **Common findings**
      (1) LVOT gradient, both provocable and at rest
      (2) Asymmetric hypertrophy
      (3) SAM of the mitral valve
   b. **Differences pertaining to the elderly**
      (1) Less hypertrophy
      (2) Less RV involvement
      (3) Ovoid versus crescentic left ventricle
      (4) Prominent septal bulge (i.e., sigmoid septum)
      (5) More acute angle between the aorta and septum as the aorta uncoils with age
      (6) Management of HCM in the elderly is similar to that of other forms of HCM.
      (7) The **prognosis** is favorable compared with that for forms of HCM that occur at a younger age.

E. Screening of family members. With familial HCM, the dominant pattern of inheritance imparts a 50% chance of disease transmission to offspring.

- **a.** Serial 12-lead ECG and transthoracic echocardiogram are recommended **every 12 to 18 months in first-degree relatives** of HCM patients starting at age 12 during adolescence due to the propensity of HCM to worsen during growth spurts.
- **b.** Because of the possibility of late-onset phenotypic expression, **screening of first-degree relatives should continue into middle age**, but the frequency of screening can be scaled back to a minimum of every 5 years once full growth has been obtained.
- **c.** If genetic testing reveals a mutant HCM gene in the offspring, the high penetrance of the mutation imparts a > 95% lifetime risk of developing clinical and/or phenotypic evidence of disease. These gene-positive offspring should continue with serial examinations.
- **d.** First-degree relatives that are mutation negative have no risk of developing HCM and do not need further screening.

ACKNOWLEDGMENTS: *The author acknowledges the contributions of Eiran Gordeski, MD; Mark Robbins, MD; and A. Thomas McRae III, MD, to prior editions of this chapter.*

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CHAPTER 11

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Myocarditis

I. INTRODUCTION. Myocarditis is defined as an inflammatory infiltration of the myocardium with associated necrosis or degeneration, or both. The disease is also known as **inflammatory cardiomyopathy** (or myocarditis with cardiac dysfunction in the World Health Organization 1995 classification for cardiomyopathy). The incidence and prevalence of myocarditis are unclear; the syndrome is underdiagnosed because of the large number of asymptomatic cases. Myocarditis usually affects younger individuals; the median age of patients with lymphocytic myocarditis is 42 years.

A. Clinicopathologic classification of myocarditis is clinically oriented but not widely used.

1. **Fulminant myocarditis** (17%) usually has a distinct onset. It can result in either complete, spontaneous resolution or rapidly progressive deterioration and death due to severe cardiac compromise. Usually there are multiple active foci of inflammatory infiltrate on histology with complete resolution.
2. **Acute myocarditis** (65% of myocarditis cases) has an indistinct onset, with moderate cardiovascular compromise and incomplete recovery, often resulting in cardiac dysfunction or subsequent death. Histologically, there are active or borderline inflammatory infiltrates that resolve completely over time.
3. **Chronic active myocarditis** (11% of myocarditis cases) has a presentation similar to that of acute myocarditis, but the chronic form usually progresses to only mild or moderate cardiac dysfunction, occasionally with restrictive physiology. Histologic examination often shows ongoing fibrosis, suggesting chronic inflammatory changes.
4. **Chronic persistent myocarditis** (7% of myocarditis cases) has an indistinct onset, with nonresolving active or borderline inflammatory infiltrates seen on histologic examination. Usually, there is no cardiovascular compromise.

B. Histologic classification of myocarditis, also called the Dallas classification (1986)

1. Initial biopsy
   a. Myocarditis: myocardial necrosis or degeneration, or both, in the absence of significant coronary artery disease with adjacent inflammatory infiltrates or fibrosis, or both
   b. Borderline myocarditis: inflammatory infiltrates too sparse or myocyte damage not apparent
   c. No myocarditis: no inflammatory infiltrates or myocyte damage
2. Subsequent biopsy
   a. Ongoing (persistent) myocarditis or fibrosis, or both
   b. Resolving (healing) myocarditis or fibrosis, or both
   c. Resolved (healed) myocarditis or fibrosis, or both

C. World Health Organization (Marburg Criteria, 1996). A minimum of 14 infiltrating leukocytes per mm (1), preferably T lymphocytes, and up to 4 macrophages may be included.

II. CLINICAL PRESENTATION

A. Signs and symptoms

1. Myocarditis can be **totally asymptomatic** or can manifest with **chest pain syndromes** ranging from mild persistent chest pain of acute myopericarditis (35% of cases) to severe symptoms that mimic acute myocardial infarction. Chest pain associated with coronary artery vasospasm may rarely occur in patients with myocarditis. Alternatively, chest pain may be more typical for pericarditis, suggesting pericardial involvement.
2. About 60% of patients may have antecedent arthralgias, malaise, fever, sweats, or chills consistent with viral infections (e.g., pharyngitis, tonsillitis, and upper respiratory tract infection) 1 to 2 weeks before onset.
3. The hallmark symptoms are those of **heart failure** (e.g., dyspnea, fatigue, and edema). In many patients who develop heart failure, fatigue and decreased exercise capacity are the initial manifestations. However, diffuse, severe myocarditis can progress rapidly and result in acute myocardial failure and cardiogenic shock. The diagnosis is usually presumptive, based on patient demographics and the clinical course (i.e., spontaneous recovery after supportive care).
4. In some instances, patients may present with **arrhythmia** in the form of syncope, palpitations caused by heart block (i.e., Stokes-Adams attack), ventricular tachyarrhythmia, or even sudden cardiac death. Sinus tachycardia is more frequent than serious atrial or ventricular arrhythmias. Palpitations secondary to premature atrial or ventricular extrasystoles are common.

B. Physical findings.

Patients often present with signs of **acute decompensated heart failure**, including an S_3 (third heart sound) gallop, central and peripheral edema, jugular venous distention, and tachycardia (see Chapter 8). An audible pericardial friction rub may accompany concomitant myopericarditis. Specific findings in special cases are as follows:

1. **Sarcoid myocarditis:** lymphadenopathy, also with arrhythmias, and sarcoid involvement in other organs (up to 70%)
2. **Acute rheumatic fever** (usually affects heart in 50% to 90%)**:** associated signs such as erythema marginatum, polyarthralgia, chorea, and subcutaneous nodules **(i.e., Jones criteria)**
3. **Hypersensitive or eosinophilic myocarditis:** pruritic maculopapular rash and history of onset temporally related to initiation of potential culprit medications
4. **Giant cell myocarditis (GCM):** sustained ventricular tachycardia in rapidly progressive heart failure
5. **Peripartum cardiomyopathy:** heart failure developing in the last month of pregnancy or within 5 months after delivery (see Chapter 38)

III. LABORATORY EVALUATION

A. Inflammatory markers of myocarditis

1. **Complete blood count.** Leukocytosis is common (often lymphocytic), although the presence of eosinophilia may suggest hypersensitive (eosinophilic) myocarditis.
2. **Elevated acute phase reactants** such as erythrocyte sedimentation rates or ultrasensitive C-reactive protein are good monitors of clinical progression or response to therapy, but they have **low specificity** for myocarditis. Novel inflammatory markers under investigation include tumor necrosis factor-α, interleukins, interferon-γ, serum-soluble Fas, and soluble Fas ligand levels. Elevation of these markers portends a worse prognosis.
3. **Serum viral antibody titers** are usually increased fourfold or more acutely and gradually fall during convalescence. However, measurement of viral antibody titers is rarely indicated.
4. **Anticardiac antibody titers.** Because of their low specificity, measurement of anticardiac antibody titers (against sarcolemma, myosin, laminin, ADP/ATP

translocator, or β-adrenergic receptors) is not indicated (only 62% of myocarditis cases have titers ≥1:40).

B. Rheumatologic screening. Screening of antinuclear antibodies and rheumatoid factor is often indicated. Disease-specific testing is indicated if the following conditions are suspected:

1. Systemic lupus erythematosus: anti-dsDNA (reported positive anti-Ro/SSA and anti-La/SSB in lupus carditis in children)
2. Polymyositis: anti-Jo_1
3. Wegener's granulomatosis: c-ANCA (antineutrophil cytoplasmic antibody)
4. Scleroderma: anti-Scl_{70}

C. Serum cardiac enzymes (markers of myonecrosis)**:** creatinine kinase (myoglobin subfraction) is elevated in only 7.5% of patients with biopsy-proven myocarditis, whereas the cardiac **troponin I or T is elevated in at least 50% of patients** with biopsy-proven myocarditis (89% to 94% specificity and 34% to 53% sensitivity).

IV. DIAGNOSTIC TESTING

A. Electrocardiogram. The electrocardiogram often reveals sinus tachycardia, although the presence of nonspecific ST-segment and T-wave abnormalities may represent focal or global ischemia. Occasionally, the changes in electrocardiogram are suggestive of an acute myocardial infarction and may include ST-segment elevation. Pericarditis can accompany myocarditis and is often manifested in pericarditislike changes seen in electrocardiography. The sensitivity of the electrocardiogram for myocarditis is low (47%). In some cases, fascicular block or atrioventricular conduction disturbances and ventricular tachyarrhythmia may be hemodynamically significant.

B. Echocardiogram. A complete echocardiogram is standard procedure for patients with suspected myocarditis to exclude alternative causes of heart failure, detect the presence of intracardiac thrombi and associated valvular disease, and quantify the degree of left ventricular (LV) dysfunction to monitor response to therapy.

1. Occasionally, focal wall motion abnormalities and presence of pericardial fluid may prompt further workup or intervention.
2. Fulminant myocarditis is often characterized by near-normal diastolic dimensions and increased septal wall thickness, whereas acute myocarditis often has increased diastolic dimensions but normal septal wall thickness.
3. In a series of 23 patients with biopsy-proven myocarditis, significant reduction in right ventricular function was a powerful predictor of death or the need for cardiac transplantation.

C. Other imaging modalities

1. **Antimyosin scintigraphy (indium III monoclonal antimyosin antibody)** provides identification of myocardial inflammation, with a high sensitivity (91% to 100%) and negative predictive value (93% to 100%) but low specificity (28% to 33%).
2. **Gallium scanning** identifies severe myocardial cellular infiltration with high specificity (98%) but low sensitivity (36%).
3. **Gadolinium-enhanced magnetic resonance imaging (MRI)** is being used more frequently for diagnosis based on several small observational studies that have found up to 100% sensitivity and specificity depending on the protocol. In one study, MRI was also used for guiding biopsy to areas of focal increased uptake of gadolinium in patients with clinically suspected myocarditis with significantly higher diagnostic yield compared with those who did not have enhancing areas with which to guide the bioptome.

D. Coronary angiography. Cardiac angiography is often indicated to rule out coronary artery disease as the cause of new-onset heart failure, as the clinical presentation of myocarditis may mimic myocardial infarction (i.e., pseudoinfarct pattern), especially if there are focal wall motion abnormalities and localizing electrocardiographic changes.

V. ETIOLOGY. Up to 50% of all cases may not have a clear underlying cause (i.e., idiopathic cases).

A. Infective causes (Table 11.1)

1. Viral myocarditis. Cardiotropic viruses such as enteroviruses (specifically the coxsackie group B and echoviruses) may cause direct cardiotoxic injuries, cytokine activation, cytoskeletal damage, and autoimmune responses. However, data suggest that the incidence of myocarditis after infection is lower than previously projected. Viral myocarditis is often considered when accompanied with a clinical

TABLE 11.1 Causes of Myocarditis

Cause	Examples
Infectious causes	
Viruses	Enteroviruses, coxsackievirus A and B, echovirus, influenza virus, poliovirus, herpesviruses, adenovirus, mumps, rubella, rubeola, hepatitis B or C virus, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B19
Rickettsia	Rocky Mountain spotted fever
Fungi	Cryptococcosis, aspergillosis, coccidioidomycosis, and histoplasmosis
Protozoa	*Trypanosoma cruzi* (Chagas disease) and *Toxoplasmosis gondii*
Helminths	Trichinosis and schistosomiasis
Bacteria	*Legionella*, *Clostridium*, streptococci, staphylococci, *Salmonella*, and *Shigella*
Spirochetes	*Borrelia burgdorferi* (Lyme disease)
Noninfectious causes	
Hypersensitive reaction	Eosinophilic myocarditis
Cardiotoxic drugs	Catecholamines, amphetamines, cocaine, chemotherapeutic drugs (e.g., anthracyclines, fluorouracil, streptomycin, cyclophosphamide, interleukin-2, trastuzumab [Herceptin]), and small pox vaccine
Collagen vascular diseases	Systemic lupus erythematosus (i.e., lupus carditis), Wegener's granulomatosis or Churg-Strauss syndrome, dermatomyositis or polymyositis, and scleroderma
Systemic illnesses	Sarcoidosis, giant cell myocarditis, Kawasaki disease, large-vessel vasculitis (e.g., polyarteritis nodosa and Takayasu arteritis), and inflammatory bowel diseases (e.g., ulcerative colitis and Crohn disease)
Acute rheumatic fever	
Bites and stings	Venoms of scorpions, snakes, wasps, and black widow spiders
Chemicals	Hydrocarbons, carbon monoxide, thallium, lead, arsenic, and cobalt
Physical injury	Irradiation, heatstroke, and hypothermia
Childbirth	Peripartum cardiomyopathy
Alloantigens	Posttransplantation cellular rejection

picture of recent febrile illness, often with prominent myalgias, followed by rapid onset of cardiac symptoms. However, direct proof is lacking (and often unnecessary), and many cases of idiopathic dilated cardiomyopathies have been attributed to antecedent viral myocarditis. Antiviral therapies have not proved to be useful.

2. **Chagas disease.** Cardiomyopathy caused by *Trypanosoma cruzi* in South and Central America, particularly in persons aged 30 to 50 years. It is estimated that 16 to 18 million persons are infected with *T. cruzi* in Latin America. Cardiac involvement usually appears decades after initial treatment and is the leading cause of death of persons aged 30 to 50 years in the endemic areas.
   - **a. Diagnosis**
     - **(1)** Serologic test results should be positive for at least two types of tests (i.e., indirect immunofluorescence, indirect hemagglutination, complement fixation, immunoenzymatic, and radioimmune assays).
     - **(2)** Cardiac lesions diagnosed by in situ polymerase chain reaction methods of analyzing biopsies.
     - **(3)** Typical electrocardiographic changes include right bundle branch block with left anterior hemiblock, premature ventricular complexes, T-wave inversions, abnormal Q waves, variable atrioventricular blocks, low QRS voltage, and sick sinus syndrome.
     - **(4)** Echocardiographic findings include LV aneurysm with or without thrombi, posterior basal akinesis or hypokinesis with preserved septal contraction, and diastolic dysfunction.
   - **b. Clinical presentation**
     - **(1)** The acute and subacute phases (i.e., 4 to 8 weeks of acute inflammation) consist for the most part of local inflammation at the parasite entry site and flulike symptoms. Occasionally hepatosplenomegaly and lymphadenopathy occur, but concomitant meningoencephalitis is rare. These manifestations often result from pathogen-induced cytotoxicity and inflammatory responses. More than 90% of cases resolve in 4 to 8 weeks without therapy.
     - **(2)** The chronic phase (up to 10 to 30 years after acute infection) manifests with symptoms of palpitations, syncope, chest pain, and, subsequently, heart failure. Approximately 5% to 10% of affected patients may develop direct acute-to-chronic progression.
       - **(a)** Heart failure (predominantly right sided in advanced stages) may develop in 25% to 30% of those affected.
       - **(b)** Cerebral or pulmonary thromboembolism may occur in 10% to 15% of those affected.
       - **(c)** Concomitant megaesophagus or megacolon may develop.
       - **(d)** Apical LV aneurysm and apical fibrosis may develop.
     - **(3)** Chagas disease is highly arrhythmogenic.
       - **(a)** Frequent, complex ectopic beats and ventricular tachyarrhythmia occur in 40% to 90% of affected patients, with sudden cardiac death occurring in 55% to 65%.
       - **(b)** Bundle branch block occurs in 50% of affected patients, and bradyarrhythmia with high-grade atrioventricular block occurs in 7% to 8%.
       - **(c)** Atrial fibrillation develops in 7% to 10% of affected patients.
   - **c.** Antibiotic therapy aims to reduce parasitemia and prevent complications.
     - **(1)** Benznidazole (5 to 10 mg/kg/d q12h for 60 days) or
     - **(2)** Nifurtimox (8 to 10 mg/kg po q24h for 90 to 120 days)
3. **Human immunodeficiency virus (HIV)–related cardiomyopathy.** HIV disease has been recognized as an important cause of dilated cardiomyopathy, with an estimated incidence of 1.6%. HIV type 1 (HIV-1) virions appear to infect myocardial cells in patchy distributions, leading to cytokine activation and progressive tissue damage. Cardiac autoimmunity, nutritional deficiencies, and drug

toxicities (i.e., mitochondrial damage from zidovudine and vasculitis or coronary artery disease associated with highly active antiretroviral therapy regimens) are possible contributing causes. In addition, other known viral pathogens, including cytomegalovirus, Epstein-Barr virus, and coxsackievirus B, have been isolated from endomyocardial biopsy (EMB) specimens of HIV-positive patients with myocarditis in conjunction with HIV nucleic acid sequences, suggesting that opportunistic viral infections may play an important role in the pathogenesis of this type of cardiomyopathy.

B. Peripartum cardiomyopathy (see Chapter 38)

C. Giant cell myocarditis (i.e., pernicious myocarditis, Fiedler's myocarditis, granulomatous myocarditis, or idiopathic interstitial myocarditis): This is a rare disorder with an unclear origin. The **hallmark feature is the presence of fused, multinucleated (> 20 nuclei) epithelioid giant cells of histocytic origin within a diffuse, intramyocardial inflammatory infiltrate with lymphocytes**.

1. GCM often presents with an **aggressive clinical course**, with progression over days to weeks. Rapidly progressive heart failure is the presentation in 75% of affected patients. Sustained ventricular tachyarrhythmia occurs in 29% of patients with GCM and atrioventricular block occurs in 50%.
2. The prognosis is **dismal without therapy**, but the disease is often refractory to standard medical therapy, with a 1-year mortality rate of up to 80% (median survival of 3 to 5 months from symptom onset).
3. Small observational series have suggested potential benefits of immunosuppressive therapy, and a randomized, prospective multicenter study is ongoing. Consideration for **early cardiac transplantation** is appropriate (71% 5-year survival after successful transplantation). Often, mechanical support may be required as a temporary bridge to recovery or transplantation. A 20% to 25% rate of histologic recurrence in surveillance EMBs has been observed after transplantation.

D. Hypersensitive reaction (i.e., eosinophilic myocarditis). Eosinophilic endomyocardial disease (i.e., Loeffler's endomyocardial fibrosis, see Chapter 9) occurs as a major complication of idiopathic hypereosinophilic syndrome as a result of direct toxic damage caused by eosinophil granule proteins within the heart. Drug-induced eosinophilic myocarditis is independent of cumulative dose and duration of therapy.

The absence of peripheral eosinophilia does not rule out eosinophilic myocarditis. Although observational series suggest potential clinical benefits of corticosteroid therapy, the best strategy is to remove the causative agent when known.

1. Medications that may cause eosinophilic myocarditis include the following:
   a. Antibiotics (e.g., ampicillin, chloramphenicol, tetracycline, and sulfisoxazole)
   b. Diuretics (e.g., hydrochlorothiazide and spironolactone)
   c. Anticonvulsants (e.g., phenytoin and carbamazepine)
   d. Other drugs (e.g., lithium, clozapine, and indomethacin)
   e. Tetanus toxoid
2. Collagen vascular diseases such as Wegener's granulomatosis or Churg-Strauss syndrome (i.e., allergic granulomatosis and vasculitis) may also lead to eosinophilic myocarditis.
3. Other causes include parasitic infection, drug hypersensitivity, and cellular rejection after cardiac transplantation, as well as postvaccinia myocarditis after small pox vaccination.

E. Systemic autoimmune disorders with myocarditis. Although the histologic appearance of myocarditis occurring as part of sarcoidosis, systemic lupus erythematosus, or polymyositis is similar to that seen in isolated myocarditis, the natural history is different. **Systemic causes of myocarditis often respond poorly to medical therapy and cardiac transplantation**, and their prognoses are often unfavorable. However, small retrospective surveys and case series have identified a significant decrease in mortality and improved clinical course among cardiac sarcoid patients treated with corticosteroids and other immunosuppression strategies.

VI. PROGNOSIS. On the basis of population studies, adults with myocarditis may present with few symptoms or with an acute toxic state of cardiogenic shock or frank heart failure (i.e., fulminant myocarditis). However, adults may present with heart failure years after the initial index event of myocarditis (up to 12.8% of patients with idiopathic dilated cardiomyopathy had presumed prior myocarditis in one case series).

A. Natural history and sequelae of myocarditis. The outlook is poor in the acute phase, regardless of clinicopathologic classification, but those surviving the acute phase have a more favorable prognosis (except for those with chronic active myocarditis).

1. Many patients may have **full spontaneous clinical recovery**, even after weeks of mechanical support (e.g., intra-aortic balloon counterpulsation and mechanical assist devices).
2. In the Myocarditis Treatment Trial, the 1-year mortality rate was 20% and the 4-year mortality rate was 56%.
3. In-hospital case series point to an 11-year survival rate of 93% for patients with fulminant myocarditis and 45% for nonfulminant myocarditis.
4. Evolution to dilated cardiomyopathy
   a. Up to one-half of patients with myocarditis develop subsequent cardiomyopathy over a range of 3 months to 13 years.
   b. Histologic evidence of myocarditis is seen in 4% to 10% of EMBs of patients with idiopathic dilated cardiomyopathy.
5. Severe heart block requiring permanent pacemaker placement occurs in 1% of patients.

B. Predictors for morbidity and mortality

1. Unfavorable factors for survival include extremes of **age** (i.e., very old or very young), **electrocardiographic abnormalities** (e.g., QRS alterations, atrial fibrillation, and low voltages), **syncope**, and **specific diagnoses** (e.g., peripartum cardiomyopathy and GCM).
2. Favorable factors for survival include normal ventricular function, shorter clinical history, and fulminant presentation at onset.

VII. TREATMENT

A. Heart failure management

1. Patients who present with myocarditis with acute dilated cardiomyopathy should be treated according to the current American Heart Association, the American College of Cardiology, the European Society of Cardiology, and the Heart Failure Society of America (HFSA) guidelines. Standard heart failure therapy consists of diuretics, angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists. Studies have not been done to determine when and how to discontinue standard heart failure therapy in patients who recover LV function.
2. Because of its proarrhythmic properties in animal models, digoxin should be avoided.
3. Anticoagulation to prevent thromboembolic events is usually recommended in patients with apical aneurysm with thrombus (e.g., Chagas disease, atrial fibrillation, and prior embolic episodes).
4. Inotropic therapy is reserved for severe hemodynamic compromise, particularly in fulminant myocarditis.
5. Aggressive support with mechanical and surgical intervention is often indicated (see Chapters 8 and 12).
   a. Intra-aortic balloon counterpulsation for hemodynamic support and afterload reduction
   b. Mechanical assistive devices (left ventricular assist device)
   c. Extracorporeal membrane oxygenation

6. Early consideration for cardiac transplantation should be given, especially for patients with progressive, biopsy-proven GCM or peripartum cardiomyopathy. However, patients with myocarditis have increased rates of rejection and reduced survival after heart transplantation compared with those without myocarditis, and recurrent disease may affect the allograft.

B. Exercise restriction

1. There is a theoretical increased risk of myocardial inflammation and necrosis, cardiac remodeling, and death, as shown in animal models.
2. Patients are usually advised to abstain from vigorous exercise for up to 6 months or longer after the onset of symptoms. The length of activity restriction can be based on recovery of LV function.

C. Arrhythmia management

1. Antiarrhythmics provide the first-line treatment using standard therapy such as β-blockers, amiodarone, and sotalol.
2. Implantable cardioverter–defibrillators are used for patients stabilized in the chronic phase with persistently low ejection fraction (EF) and for those with malignant arryhythmias that are refractory to medical therapy.
3. Permanent pacemakers are used for heart block or bradyarrhythmia.

D. Follow-up

1. Clinical follow-up should be close because persistent chronic inflammation may lead to dilated cardiomyopathy. Initially, 1- to 3-month intervals are used for drug and physical activity titration.
2. Serial echocardiographic assessment of ventricular structure and function is often performed, although there is no agreement regarding the frequency of echocardiographic assessment after myocarditis.

E. Immunosuppressive therapy is reserved for refractory disease or biopsy-proven GCM. No benefits have been established for antiviral regimens or nonsteroidal antiinflammatory agents (see Section **VIII.B**). The most recent HFSA guidelines do not recommend routine use of immunosuppressive therapy in patients with myocarditis. More work is needed to identify patient cohorts who will benefit from tailored antiviral and immunosuppressive therapy.

VIII. CONTROVERSIES IN MYOCARDITIS

A. Endomyocardial biopsy

1. **Routine EMB confirmation of myocarditis is unnecessary.**
   a. EMB can be considered in those patients with a **rapid deterioration in cardiac function** of unknown etiology who do not respond to standard medical therapy.
   b. Incidence of biopsy-proven myocarditis in recent-onset, unexplained heart failure can be as low as 8% to 10%. Concerns have emerged that this is caused by low sensitivity of the Dallas criteria, and several recent trials of immunosuppressive therapy have utilized supplemental pathologic criteria to assess myocarditis, including upregulation of human leukocyte antigen, presence of virus, and anticardiac antibodies.
   c. **False-negative rates are high** (50% even in four or five biopsies) because of the small number of lymphocytes and difficulties in distinguishing cell types, with wide interobserver variability.
2. However, EMB may be considered in patients with the following conditions in which a diagnostic biopsy may provide information on prognosis and/or therapeutic possibilities (see Table 11.2):
   a. Rapidly progressive heart failure symptoms despite conventional therapy or new-onset frequent ventricular tachyarrhythmia or conduction disturbances
   b. Suspected specific causes of myocarditis (e.g., GCM, eosinophilic myocarditis, cardiac sarcoidosis, and vaccinia myocarditis)

TABLE 11.2 Relevant ACC/AHA Recommendations for the Role of Endomyocardial Biopsy

Scenario	Class of recommendation
New-onset heart failure of < 2 wk duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I
New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	I
Heart failure of > 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	IIa
Heart failure associated with a dilated cardiomyopathy of any duration associated with suspected allergic reaction and/or eosinophilia	IIa
New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias, or second- or third-degree heart block that responds to usual care within 1–2 weeks	IIb
Heart failure of > 3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias, or second- or third-degree heart block that responds to usual care within 1–2 wk	IIb
Unexplained ventricular arrhythmias	IIb

Adapted from Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease. *Circulation 2007;* 116: 2216–2233.

3. Although specificity is high (98%), sensitivity has been found in some series to be as low as 10% to 22%. It increases with multiple biopsies, but postmortem examinations have found that more than 17 specimens were needed to make the diagnosis with 80% sensitivity in proven myocarditis cases.
4. **Biopsy** for staging of myocarditis:
   a. Cell types include lymphocytic, eosinophilic, neutrophilic, giant cell, granulomatous, and mixed.
   b. Amount of cells: none (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3).
   c. Distribution: focal (i.e., outside of vessel lumen), confluent, diffuse, and reparative (i.e., in fibrotic areas).
5. Other tests:
   a. Immunohistochemical staining to examine upregulation of major histocompatibility complex antigens and quantify inflammation, although rates of correlation with biopsy-proven myocarditis have not been consistent between studies.
   b. Approximately 12% to 50% of patients with acute or chronic myocarditis have persistent viral mRNA detected in biopsy samples.

B. Immunosuppressive therapy in acute myocarditis

1. Routine immunosuppressive therapy is not recommended because of the neutral findings from multiple trials, including the Myocarditis Treatment Trial and the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) study. There is no Food and Drug Administration (FDA)–approved regimen for the treatment of acute or chronic myocarditis.

2. Considerations are reserved for patients with new-onset, rapidly deteriorating, advanced heart failure with suspicion of the following conditions:
   a. GCM is treated with combination therapy (Table 11.3).
   b. Eosinophilic or sarcoid myocarditis is treated with high-dose steroids.
   c. Specific therapy is used for underlying collagen vascular diseases, if present.

TABLE 11.3 Treatment Regimens for Myocarditis in Clinical Trials

Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) study[a]

Intravenous immune globulin (Gamimune N, 10%): 1 g/kg/d IV × 2 d

Giant Cell Myocarditis study[b]

Cyclosporine: 25 mg po bid, increase by 25 mg increments to target level:

Monoclonal whole-blood immunoassay: 200–300 ng/mL

High-performance liquid chromatography assay: 150–250 ng/mL

Fluorescence polarization immunoassay serum-based polyclonal assay: 100–150 ng/mL

Dose reduction if renal dysfunction develops

Muromonab-CD3 (OKT-3): 5 mg IV qd × 10 d

Dose reduction if hypotension develops

Corticosteroid: methylprednisolone, 10 mg/kg IV qd × 3 d, followed by prednisone, 1–1.25 mg/kg with extended taper

Azathioprine: 200 mg po qd

Myocarditis Treatment Trial[c]

Corticosteroid/cyclosporine versus corticosteroid/azathioprine versus placebo (biopsy-proven myocarditis, LVEF < 45%, NYHA ≥ class II)

Oral prednisone: 1.25 mg/kg/d in divided doses × 1 wk; reduce oral dose by 0.08 mg/kg/wk until dose is 0.33 mg/kg/d at week 12; maintain oral dose until week 20 and then reduce dose by 0.08 mg/kg/wk until week 24; then off.

Oral cyclosporine: 5 mg/kg bid to achieve level of 200–300 ng/mL × 1 wk; adjust oral dose to achieve level of 100–200 ng/mL from weeks 2 to 4; adjust oral dose to achieve level of 60–150 ng/mL from weeks 4 to 24.

Immunosuppressive therapy for active lymphocytic myocarditis[d]

Prednisone 1 mg/kg/d for 4 wk; reduced to 0.33 mg/kg/d for 5 mo; azathioprine 2 mg/kg/d for 6 mo

LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association.

[a]McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation.* 2001;103:2254–2259.

[b]Rosenstein ED, Zucker MJ, Kramer N. Giant cell myocarditis: most fatal of autoimmune diseases. *Semin Arthritis Rheum.* 2000;30:1–16.

[c]Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med.* 1995;333:269–275.

[d]Frustaci A, Chimenti C, Calabrese F, et al. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation.* 2003;107:857–863.

3. Studies are ongoing in an attempt to identify markers to predict favorable response to immunosuppressive regimens. A study of 112 patients with histopathologic acute lymphocytic myocarditis who failed to improve with conventional therapy and subsequently received prednisone and azathioprine found that one-half of the treated group improved, with EF rising from 26% to 47% and improvement in biopsy findings. Of those who failed conventional therapy, those patients who responded to immunosuppression were significantly more likely to have positive cardiac antibodies (90% vs. 0%) and less likely to have viral persistence when compared with nonresponders (14% vs. 85%).

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CHAPTER 12

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Nontransplantation Surgical Treatment for Chronic Heart Failure

I. INTRODUCTION. Even with optimal medical therapy, the morbidity and mortality associated with chronic heart failure (CHF) is significant. Fortunately, there are multiple possible surgical interventions available for these patients that may help to avoid or postpone the need for advanced salvage therapies and transplantation. Despite the improvement in surgical techniques and an enhanced understanding of the role of reconstructing structural abnormalities of the failing heart, safety and efficacy data are still limited for many of these procedures. Elective and planned procedures for advanced heart failure (e.g., revascularization, valvular surgery, left ventricular [LV] reconstructive surgery, and cardiomyoplasty) and urgent or bridging procedures (e.g., circulatory support devices and total artificial heart [TAH]) are discussed in this chapter. Surgical approaches to the management of heart failure must be accompanied by continued aggressive pharmacologic therapy.

II. SURGICAL REVASCULARIZATION FOR ISCHEMIC CARDIOMYOPATHY

A. Pathophysiology

1. Loss of coronary flow reserve in severe coronary artery disease leads to reduction in myocardial perfusion, tissue hypoxia, and myocardial dysfunction.
2. Myocardial infarction results in necrosis, scarring, and loss of contractile function. Sites distal to infarction undergo increased mechanical stress and adverse remodeling over time. Progressive ventricular dilation and impairment of systolic and diastolic function occur.
3. Chronic ischemia can decrease perfusion, leading to hibernation, repeated episodes of stunning, and recurrent infarction. The cardiomyocytes may shift metabolic states to hibernation. Thus, revascularization may help retain viability and recover function. Stunning and hibernation may be detected by various imaging modalities (see Chapter 50).
   a. **Stunning** is the loss of contractile function caused by a momentary total occlusion of blood flow with subsequent restoration of flow.
   b. **Hibernation** is the downregulation of myocardial function to match the chronic reduced blood flow. Hibernating cardiomyocytes manifest sustained glucose extraction, decreased glycogen content, and decreased contractile proteins and function.

B. Clinical significance

1. Heart failure, rather than angina or an acute coronary syndrome, is a common presentation of myocardial ischemia in patients with underlying cardiac dysfunction.
2. At least two-thirds of patients with cardiac dysfunction have evidence of epicardial coronary artery disease as the primary etiology. Coronary angiography is indicated when the suspicion of an ischemic cause for cardiomyopathy is high.

3. Some patients may have epicardial coronary artery disease superimposed on an underlying dilated cardiomyopathy. In this scenario, the presence of epicardial coronary artery disease may not necessarily explain the "degree" of depressed myocardial contractility. The role of revascularization remains unclear for these patients.

C. Recommendations

1. Most recently, the Surgical Treatment for Ischemic Heart Failure (STICH) trial reported that in patients with coronary artery disease amenable to coronary artery bypass grafting (CABG) and left ventricular ejection fraction (LVEF) < 35%, there was no difference in the trial's primary end point of all-cause mortality when treated with optimal medical therapy versus CABG. However, benefit was seen in the CABG group with respect to the secondary end point of cardiovascular death at follow-up. There were several limitations to this study: 30-day mortality was high in the CABG group and significant crossover occurred, both of which may have diminished the benefits of CABG in the primary intention to treat analysis.
2. Primary CABG should still be considered for patients with an LVEF > 15%, LV end-diastolic dimensions < 65 mm, distal vessels suitable for grafting, and evidence of a significant amount of ischemic or hibernating myocardium. These guidelines are arbitrary and many centers consider patients with more severe diseases.
3. Patients with hibernating myocardium and severe LV dysfunction who undergo CABG may achieve survival advantage comparable to those receiving cardiac transplantation (about 80% survival in 3 years).
   a. The potential for significant improvement in LV function and symptoms is assumed to be great enough to recommend revascularization when there are four or more viable segments of myocardium, representing approximately 31% of the left ventricle.
   b. Surgical revascularization of the patient with severe heart failure should generally be considered as part of a multifaceted approach, including evaluation for valve repair, ventricular reconstructive surgery, cryoablation for ventricular arrhythmias, and maze procedure or pulmonary vein isolation procedures for atrial dysrhythmias. To maximize the therapeutic benefit from this approach, aggressive complementary pharmacologic approaches are indicated postoperatively.

III. MITRAL VALVE SURGERY

A. Pathophysiology

1. As the ventricle fails, progressive dilation leads to abnormal geometry of the left ventricle, giving rise to mitral regurgitation (MR). MR results in progressive increase in volume overload of the left ventricle, progressive LV dilation, and further worsening of MR.
2. Other alterations of the annular–ventricular apparatus and ventricular geometry contribute to the pathogenesis of MR: papillary muscle ischemia or infarction, myocardial thinning and dilation, blunting of the aortomitral angle, widening of the interpapillary distance, and increased leaflet tethering leading to loss of the zone of coaptation.

B. Clinical significance and recommendations

1. Restoration of zone of coaptation by inserting an "undersized" annuloplasty ring may correct the MR and improve the LV geometry and cardiac output. However, mitral valve repair in ischemic cardiomyopathy ("ischemic MR") is less successful than in degenerative MR.
2. Subvalvular apparatus should be kept intact when possible.

3. In some patients, mitral valve surgery results in improved symptoms and measures of LV function and remodeling but not necessarily in improved survival.
4. In some patients, mitral valve repair with a figure-of-eight stitch (i.e., Alfieri approach) or the "edge-to-edge" technique may be used in addition to annuloplasty to secure the repair.
5. Mitral valve replacement is required in a minority of patients and may be associated with a significantly worse outcome.

IV. LV RECONSTRUCTIVE PROCEDURES

A. Pathophysiology

1. Laplace's law dictates that as the failing heart dilates, the intracavity radius increases and thus wall stress increases. The result is increased myocardial oxygen consumption and stimulation of adverse remodeling.
2. Surgical remodeling helps to decrease ventricular size and wall stress. Endoventricular circular patch plasty (EVCPP, also called the Dor procedure) is performed in patients with ischemic cardiomyopathy and significant areas of LV akinesis or dyskinesis. Partial LV resection, also called the Batista procedure, was performed in the past on patients with dilated, nonischemic cardiomyopathy. This was abandoned because of poor intermediate results and increased mortality, despite promising short-term outcomes.

B. Endoventricular circular patch plasty

1. Acute myocardial infarction leads to tissue necrosis, scar formation, followed by LV remodeling, leading to dilation and heart failure. The Dor procedure is suitable for patients with a left anterior descending artery territory scar or aneurysm with relatively preserved lateral and posterior LV wall function.
   a. It involves opening of the akinetic or dyskinetic scar and placement of a purse-string suture at the neck of the aneurysm. The residual opening may be closed with a Dacron patch, after which the ventriculotomy is closed by running sutures.
   b. This procedure is accompanied by CABG in >90% of cases. Additional valve and ablative surgical procedures are commonly performed.
2. Good candidates for EVCPP include patients with LV aneurysm (or large akinetic area), an increased LV end-systolic index, absence of scar in the circumflex territory, as well as good target tissue and viability for concomitant CABG. Assessment of the severity of MR is needed at the time of surgery, and mitral valve repair is performed in 30% to 50% of patients undergoing EVCPP.
3. EVCPP results in improved LVEF, end-diastolic and end-systolic volume indices for LV volumes, and improvement in New York Heart Association (NYHA) functional class.
   a. In a series of patients with advanced heart failure, the event-free survival rate was 98% at 1 year, 95.8% at 2 years, and 82.1% at 5 years.
   b. Independent predictors of mortality include higher preoperative NYHA class, lower LVEF (< 30%), higher end-systolic volume index, and remote asynergy.
   c. Interestingly, the STICH trial demonstrated that despite the reduced LV volume, there was no difference in symptoms, exercise tolerance, hospitalization, and death in patients who received CABG with surgical ventricular reconstruction versus CABG alone. On the basis of this trial, surgical ventricular reconstruction may not add any benefit to HF patients with documented ischemia who are on optimal medical management.

C. Partial LV resection (i.e., **Batista procedure**) involves the resection of myocardium at the posterolateral wall between the anterolateral and the posteromedial papillary

muscles in nonischemic cardiomyopathy, with or without mitral annuloplasty or mitral valve replacement. For the reasons previously stated, this procedure is no longer performed.

D. Dynamic cardiomyoplasty

1. The procedure involves the mobilization of the entire latissimus dorsi muscle to be used as a pedicle graft. The muscle is passed into the thoracic cavity through a window created by removing the left second rib. The muscle is wrapped around the heart and anchored posteriorly, adjacent to the right atrium and pulmonary artery, and anteriorly around the right ventricle.
   a. Sensing electrodes are placed epicardially on the right ventricle, and intramuscular stimulator electrodes are placed in the latissimus muscle.
   b. The muscle conditioning process takes place 2 weeks after surgery and involves the delivery of a single pulse with every other cardiac cycle for 2 weeks. The signal is then incrementally increased every 1 to 2 weeks for 12 weeks.
2. Cardiomyoplasty is believed to work by systolic augmentation of the failing left ventricle and the girdling effect of the muscle acting as an elastic constraint. This prevents LV dilation and improves symptoms, but has no proven survival advantages. Indeed, early mortality is high, especially in those with NYHA class IV status. This procedure is rarely performed now, and data are lacking on its long-term efficacy.
3. Approximately 80% to 85% of surviving patients show NYHA class improvement (mean 1.4 classes). A phase II multicenter FDA study demonstrated significant improvement in LVEF, LV stroke work, and stroke index.
4. Mortality of surgery for class III patients has been < 10%.
5. Hypertrophic obstructive cardiomyopathy is considered to be a relative contraindication.

V. CIRCULATORY SUPPORT DEVICES (I.E., MECHANICAL ASSIST DEVICES)

A. Background

1. Mechanical circulatory assistance is necessary for patients with hemodynamic compromise that are unlikely to survive without a transplant or advanced salvage therapies. Mechanical circulatory support devices may help bridge the patients to recovery or transplantation.
2. The types of devices include the following: intra-aortic balloon counterpulsation pump (IABP), extracorporeal membrane oxygenation (ECMO), univentricular and biventricular nonpulsatile and pulsatile ventricular assist devices (VADs), and the TAH.
3. The decision about which device to use is based on the predicted duration of use, the reversibility of the underlying condition that caused cardiogenic shock, need for single-chamber versus dual-chamber support, and the patient's size.

B. Patient selection

1. Mechanical support is generally indicated in patients who have an inability to maintain hemodynamic stability despite maximal pharmacologic support and who usually must meet criteria as candidates for cardiac transplantation:
   a. Systolic blood pressure < 75 to 80 mm Hg
   b. Cardiac index of < 1.5 to 1.8 L/min/m^2
   c. Pulmonary venous saturation < 50%
2. Indications for short-term circulatory support devices include the following:
   a. Cardiogenic shock after cardiac surgery
   b. Acute myocardial infarction with cardiogenic shock
   c. Acute (fulminant) myocarditis
   d. Cardiac arrest as a complication of interventional cardiac procedures (associated with high mortality and poor survival rates)

3. The 2006 International Society for Heart and Lung Transplantation (ISHLT) guidelines for cardiac transplant candidates:
   a. The most recent ISHLT recommendations give a class I recommendation to thoroughly evaluate other clinical risk factors prior to device implantation. For instance, an inverse relationship between outcome and age > 60 to 65 years has been reported. However, age by itself should not be a contraindication to implantation.
   b. Patients with serum creatinine > 3.0 mg/dL are at higher risk but may be considered candidates for implantation if renal failure is acute and recovery is likely (class I).
   c. Pulsatile intracorporeal devices should only be implanted in patients with body surface area (BSA) > 1.5 m^2.
   d. In patients with abnormal liver function tests secondary to right ventricular (RV) failure, biventricular support should be considered. In addition, biventricular support should be considered in those with irreversible pulmonary hypertension, RV failure, or multiorgan dysfunction.
   e. Active infection should be identified and treated before implantation.
4. If recovery is anticipated, the best option is to use the least traumatic, least complicated device for the individual patient. If recovery of ventricular function is not expected, patients should be considered for the use of a long-term implantable device.

C. Short-term devices

1. Intra-aortic balloon counterpulsation pump

   a. IABP should be placed percutaneously under fluoroscopy so that the tip is about 2 cm below the left subclavian. Height of the patient will determine the size of the IABP (40 cc balloon for the average-sized male). Swan-Ganz catheter and arterial line are encouraged and typically required for hemodynamic monitoring.
   b. IABP enhances coronary blood flow during inflation and decreases oxygen demand by reducing systolic pressure and LV wall stress during deflation. As a result, myocardial consumption and cardiac work are decreased while cardiac output is increased.
   c. Indications: Cardiogenic shock, severe mitral stenosis, decompensated critical aortic stenosis, ventricular septal defect/rupture, refractory ischemia, ischemia ventricular tachycardia, and bridge to definitive therapy.
   d. Contraindications: Hemodynamically significant aortic insufficiency (≥3+), abdominal or thoracic aortic aneurysm/dissections, severe coagulopathy, and sepsis.

2. Extracorporeal membrane oxygenation

   a. ECMO is an extracorporeal system that uses a centrifugal pump to drive blood from the patient to a membrane oxygenator system for carbon dioxide and oxygen exchange.
   b. The femoral artery and vein are cannulated for peripheral access, but the aorta and right atrium can be used as well. The blood is driven from the venous system to the pump and oxygenator and then back into the arterial system.
   c. The device requires systemic anticoagulation and may cause substantial trauma to blood components.
   d. ECMO has the advantage of providing oxygenation in the presence of severe pulmonary dysfunction resulting in hypoxemia. It can also unload both the right ventricle and left ventricle.
   e. The large number of possible complications makes ECMO suitable only for short-term use. It is generally used as a bridge to transplantation, VAD implantation, or other types of definitive therapy.

3. **Percutaneous LV support devices** (TandemHeart, Reitan Catheter Pump, and Impella Recover) are indicated only for short-term use (up to 5 days) and are similar to an IABP with respect to decreasing afterload and myocardial oxygen consumption. Unlike an IABP, these devices completely unload the ventricle rather than simply augmenting it.
   a. The Impella (LP2.5 and LP5.0) is a catheter-based system inserted through the femoral artery that provides hemodynamic support by an axial pump. Blood is pumped directly from the left ventricle to the ascending aorta.
   b. The Impella LP2.5 and LP5.0 can provide cardiac output support of up to 2.5 and 4.5 L/min, respectively, depending on the maximum speed of the rotor.
   c. The TandemHeart system is an extracorporeal continuous-flow centrifugal assist device that provides hemodynamic support via a left atrial-to-femoral bypass with up to a maximum cardiac output of 5.0 L/min. Oxygenated blood is withdrawn from the left atrium via a transseptal cannula and pumped into the femoral artery.
   d. Both systems require anticoagulation with heparin, prolonged supervision, and bed rest.
   e. Hemodynamic support from the Impella and TandemHeart can be continued for up to 5 days.
   f. These devices can potentially be used to support patients with acute MI with cardiogenic shock, patients with decompensated heart failure with myocarditis, and during high-risk percutaneous coronary intervention or valvuloplasty. The TandemHeart can be used for RV support if the catheters are placed so as to pump from the right atrium to the pulmonary artery.
   g. Recent trials for the Impella 2.5, namely, PROTECT I, ISAR-SHOCK (vs. IABP), AMC-MACH2 (vs. IABP), PROTECT II (vs. IABP), RECOVER II (vs. IABP), and EUROPELLA, demonstrated more favorable hemodynamics, reduction in infarct size, as well as reduction in 30-day major adverse cardiac event.
   h. There is a paucity of data regarding clinical outcomes and safety of patients with TandemHeart despite this being commercially available since 2004.
   i. See Table 12.1 for contraindications and potential adverse events.

TABLE 12.1 Contraindications to and Cautions with Percutaneous Left Ventricular Support Devices

Devices	Contraindications	Potential adverse events
Impella	Mural thrombus in the left ventricle, mechanical aortic valve, constrictive heart device, severe peripheral arterial disease, moderate to severe aortic stenosis (≥2+) and regurgitation (≥2+), severe aortic tortuosity, and calcification	Aortic regurgitation, aortic valve injury, arrhythmias, bleeding, tamponade, infection, stroke/transient ischemic attack, hemolysis, limb ischemia
TandemHeart	Moderate to severe aortic stenosis (≥2+) and regurgitation (≥2+), severe peripheral vascular disease	Bleeding, a femoral arteriovenous fistula, thromboembolic events, atrial septal defect, limb ischemia, wound infection, lymphocele, hypothermia

4. **Centrifugal pumps** such as the BioMedicus Biopump are extracorporeal and are commonly used for biventricular support for small patients (BSA ≤ 1.5 m^2) and also with ECMO.
   a. The nonpulsatile pump uses a spinning chamber to generate blood flow through rotating cones or by an impeller mechanism.
   b. The cannulation site for inflow into the pump is the femoral vein, right atrium, or ventricle, and the outflow cannula is placed in the femoral artery, axillary artery, or aorta. The lines are typically left between an unclosed sternum with only skin closure. This necessitates continuous supervision by trained staff and limits the devices to short-term use only.
   c. Heparin anticoagulation is needed.
5. **Pulsatile pumps** are extracorporeal, asynchronous pumps (e.g., Abiomed BVS5000) that are commonly used for right, left, or biventricular support.
   a. There are atrial and arterial cannulas. The atrial cannula is put into the right or left atrium, and the arterial cannula is in the aorta. The advantage over centrifugal systems is that subcostal lines allow sternal closure.
   b. The pump has an upper chamber and a lower chamber. The upper chamber is filled passively by continuous blood flow from the atrium. The lower chamber has two trileaflet polyurethane valves (i.e., inflow and outflow valves) and is designed to eject a stroke volume of approximately 80 mL.
   c. The pump is pneumatically driven by compressed room air and provides 4 to 5 L/min of pulsatile flow.
   d. Anticoagulation is recommended with heparin or warfarin sodium to lower the rate of thromboembolism.
   e. The disadvantages of this system are the lack of mobility and the lower flow rates achieved compared with the chronically implanted devices. A decision is made after 5 to 7 days of support, and if further mechanical support is needed, the Abiomed is removed and a chronic device is implanted.
   f. In small retrospective studies, outcomes in terms of successful bridge to transplantation, pre- and posttransplant mortality, and hospital discharge have not been shown to be significantly different between pulsatile and nonpulsatile devices.
6. **Axial flow pumps**
   a. Nonpulsatile rotary pumps are similar to centrifugal flow devices, but these generate the energy for acceleration of blood by deflecting the flow in the circumferential direction using impellers.
   b. They are smaller and less noisy than other devices, making them a good option for patients with a smaller BSA, as well as potentially decreasing the risk of infection due to smaller pocket size.
   c. Major complications include an increased tendency for pump thrombus, thus mandating anticoagulation and hemolysis.

D. Longer term implantable devices

1. Pulsatile implantable devices: Thoratec paracorporeal system, the CardioWest TAH, Novacor, and HeartMate XVE are currently used.
   a. Thoratec is a paracorporeal system that can be used for left, right, or biventricular support. Because the system is outside the body, it can be used in patients with BSA ≤ 1.5 m^2. However, this does limit mobility and flow rates (maximum stroke volume is 65 mL and flow rates can reach 7.2 L/min). Systemic anticoagulation is required.
   b. The CardioWest TAH is implanted after removal of the native heart and provides complete support. To accommodate the sizable device, patients must have a BSA > 1.7 m^2 and anteroposterior distance of the chest of > 10 cm. Systemic anticoagulation is required. This device has been approved for use as a bridge to transplantation. Another TAH, the Abiocor, is in the

investigational stages of development. This device is smaller and provides more mobility.

c. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial randomized patients with end-stage heart failure who required ionotropic therapy but were ineligible for cardiac transplantation to a vented electric LVAD or optimal medical therapy. There was a 48% relative reduction in risk of death from any cause in the group that received LVAD compared with the medically treated group. The probability of device failure was 35% at 24 months, and 10 patients had the device replaced. The LVAD group had significant improvement in the quality of life over the trial, but the survival rates with permanent VAD are still far inferior to those for cardiac transplantation. This trial led to the approval of the HeartMate LVAD as a destination therapy in selected patients not eligible for transplant. The follow-up of outcomes in 42 patients who were implanted with destination therapy HeartMate LVAD since the REMATCH trial reveals improved survival rates at 1 month and 1 year and decreased rates of infection and adverse events compared with those found in the trial patients. Occasionally, patients who are implanted with the intent of destination therapy have improvement in conditions such as renal impairment or pulmonary hypertension that had precluded them from eligibility for transplantation earlier in their course and thus are suitable to be reevaluated for transplantation.

2. Axial flow pumps: Jarvik 2000, HeartMate II, and the MicroMed DeBakey.
   a. Produce continuous nonpulsatile blood flow using a small pump with rotor blades. Bearings of the rotor are in direct contact with the blood.
   b. MicroMed and HeartMate II have inflow cannulas that insert in the LV apex. The MicroMed and HeartMate II require a sternotomy and are implanted into a small abdominal pocket. The outflow cannula is attached to the descending aorta.
   c. Jarvik is intraventricular, which eliminates the need for an inlet cannula and eliminates inlet graft kinking, thrombosis, pannus formation in the inlet graft, and inlet obstruction by the septum or lateral wall of the heart. The outflow cannula is attached to the descending aorta. The small size allows the Jarvik to be surgically implanted through a left thoracotomy, with or without cardiopulmonary bypass, and it can be implanted in smaller adults or children.
   d. Axial flow pump is a true LVAD because it augments LV function. Optimal pump speeds are between 8,000 and 12,000 rpm. Native left ventricle is allowed to eject through the aortic valve, giving some pulsatility to the blood flow.
   e. Axial flow pumps can generate flows up to 5 to 7 L/min.
   f. Major complications are thromboembolic events due to inadequate blood flow in the ascending aorta giving rise to thrombus formation and the potential for embolic stroke.
   g. HeartMate II is the best studied LVAD and in turn has become the standard of care in VADs. Miller and colleagues demonstrated the safety and efficacy of the HeartMate II device when used as a bridge to transplantation. Further studies have demonstrated improved quality of life, functional status, and incidence of end-organ failure. Slaughter and colleagues reported a significant improvement in the quality of life and survival free from stroke and device failure with implantation of a continuous-flow LVAD when compared with a pulsatile-flow device for destination therapy.
   h. Data describing experience with the Jarvik 2000 showed that the cardiac index increased by 43%, capillary wedge pressure decreased by 52%, and

80% of the patients improved from NYHA class IV to I. No device thrombosis was reported.

E. Contraindications to VADs

1. Uncontrolled sepsis.
2. Aortic valve incompetence needs to be corrected before implantation of the VAD because it might lead to regurgitation of blood from the outflow cannula back into the left ventricle. Severe mitral stenosis should also be treated to avoid limiting the device output due to decreased native ventricular filling.
3. Preexisting mechanical prosthetic valves may need to be changed to bioprosthetic valves to obviate the need for anticoagulation before implanting the VAD.
4. Hypercoagulable states may preclude the placement of VADs not requiring anticoagulation.
5. Aortic aneurysm or dissection may affect the optimal placement of the outflow cannula in the ascending aorta.
6. Bleeding diathesis.
7. Patent foramen ovale or atrial septal defects need to be closed before implantation of VADs to prevent right to left shunting of blood and paradoxical emboli as the left side of the heart is decompressed.
8. Recent or evolving cerebrovascular accident.
9. Multiorgan failure.
10. Metastatic tumors are an absolute contraindication.

F. Predictors of poor outcomes after implantation of LVADs

1. Age
2. RV failure
3. Urine output < 30 mL/h
4. Central venous pressure > 16 mm Hg
5. Receiving mechanical ventilation
6. Prothrombin time is > 16 seconds; vitamin K is usually given in high doses preoperatively to patients being considered for VAD
7. Reoperation
8. Cachexia syndrome

G. Echo-Doppler assessment of VAD dysfunction. After the implantation of LVAD, intraoperative transesophageal echocardiography is used to assess the following factors:

1. Position of the inflow cannula at the LV apex. If the cannula is angulated toward the interventricular septum, inflow obstruction may result. The velocity of the flow across the inflow cannula is affected by multiple factors, including the flow generated by the device. However, if this velocity is > 2 m/s, then obstruction of the cannula should be considered and thrombus or another mechanical cause of obstruction should be sought.
2. Adequacy of LV decompression.
3. Aortic valve. If the flow rate through the LVAD is adequate, the aortic valve should not open. If there is significant aortic regurgitation, the aortic valve may have to be replaced.
4. Doppler interrogation of the inflow and outflow cannulas is done to exclude inflow and outflow valve dysfunction. Usually, the valves are unable to open, resulting in increased forward flow velocities.
5. Periodic follow-up echocardiographic evaluation is performed to exclude thrombus formation, inflow cannula valve dysfunction, or endocarditis and to evaluate LV systolic function.

H. Right ventricular assist device (RVAD)

1. Decisions for RVAD support (needed by 20% of patients) are based on hemodynamics after LVAD placement. However, implantation of long-term RVAD

devices is more labor intensive and requires long bypass times for placement, which carries higher morbidity.

2. Univariate predictors of RVAD use are small BSAs, female gender, preoperative circulatory support, preoperative mechanical ventilation, and high total bilirubin and aspartate transferase values. Preoperatively, hemodynamic indices of a low mean or diastolic pulmonary artery pressure or a low RV stroke work index (RVSWI < 400 mm Hg · mL/m^2) may indicate the necessity for RVAD after LVAD insertion.
3. Inotropic agents, volume infusions, and vasodilators are used to optimize pulmonary pressures and LVAD flows, with right heart hemodynamic values used as a guide. Aggressive diuresis is often necessary. If VAD flow remains < 2 L/min/m^2, an RVAD system may be placed with the inflow from the right atrium and outflow to the pulmonary artery.
4. Inhaled nitric oxide has gained popularity as a potential alternative to RVAD implantation. In one center, it reduced the need for RVAD support from 7% to 0%.
5. However, the RVAD use is associated with higher incidence of repeat sternotomy for bleeding, and the survival to transplantation is poor at 17%. It may be prudent for patients with risk factors for RV dysfunction to receive a biventricular assist device or a TAH from the start.

I. Complications of VADs

1. **Perioperative bleeding** increases with prolonged cardiopulmonary bypass times and causes excess fibrinolysis and platelet consumption. The degree of bleeding is intimately associated with RV failure and RVAD support. Transfusion is associated with infection and human leukocyte antigen immunization, which can increase the risk of hyperacute humoral rejection for a patient who goes on to transplantation. The use of LVADs increases this risk from 4% to 25% because of the need for perioperative transfusions. Leukocyte-poor blood products should be used to minimize this risk as much as possible.
2. **Gastroinstestinal bleeding** appears to be increased in continuous-flow LVADs in comparison with pulsatile ones, which is thought to be related to decreased levels of large multimers of von Willebrand factor and decreased platelet aggregation. Additional studies have also demonstrated increased incidence of arteriovenous malformations.
3. **Malignant arrhythmias.** There is a high incidence of malignant cardiac arrhythmia after device implantation. Causes include cardiomyopathy, ischemia, chamber dilation, use of inotropic agents, and focal abnormalities at the sewing ring.
4. **Infection.** Antibiotic prophylaxis should be administered to prevent infection. In the long term, there is a 25% to 45% rate of infection, which temporarily removes 20% of patients from the active transplantation list. The most serious infection is VAD endocarditis, which carries a 50% mortality rate and necessitates removal or replacement of the device.
5. **Embolic complications.** Thromboembolism still occurs at a high rate despite appropriate anticoagulation. The Thoratec device carries a 22% risk for cerebrovascular embolic events; the Novacor, 10%; and the HeartMate, 3% to 5% over a 1-year period.
6. **Aortic valve fusion and aortic insufficiency** may develop in patients with continuous-flow LVAD. In a small series of patients who received LVADs for bridge to transplant, examination of the explanted hearts demonstrated some degree of commissural fusion. Echocardiograms of those patients prior to explant demonstrated an increased incidence of aortic insufficiency during LVAD therapy. It is thought that the combination of valve fusion and continuous high pressure on the valve may contribute to the development of aortic insufficiency.

7. **RV failure** is responsible for significant morbidity and mortality after the institution of LVAD therapy. The complex pathophysiology resulting in RV failure includes RV myocardial dysfunction, changes in RV afterload, and interventricular dependence. Risks for the development include biochemical signs of congestions (elevated total bilirubin and aspartate aminotransferase/alanine aminotransferase), decreased RVSWI, increased pulmonary vascular resistance, female gender, smaller patients, and pre-LVAD support. Therapies include inotropic support as well as right-sided mechanical support.

J. Bridging to transplantation. Patients presenting with severe, refractory low cardiac output states need mechanical support as a bridge to transplantation. However, it has been recognized that major end-organ dysfunction affects the survival after transplantation. Mechanical support of the failing heart using short-term circulatory support devices can permit time to assess the reversibility of major organ dysfunction and allow a full workup for the suitability of cardiac transplantation. If the patient meets the selection criteria found in Table 12.2, full LVAD support can be implemented, and if the major organ dysfunction normalizes, a successful bridge to transplantation can be expected. It is expected that 70% to 80% of patients with an LVAD can be successfully bridged to transplantation, compared with 36% of patients managed on inotropic agents with or without an IABP, and 80% of these transplant patients will survive to be discharged from hospital. The percentage of transplant patients requiring mechanical support has increased steadily from 3% in 1990 to > 28% in 2004. Most LVAD implantations (75%) are performed with the strategy of bridge to transplantation. For those with biventricular failure that necessitates mechanical support, the options are combined RVAD and LVAD therapy or support with a TAH. The CardioWest TAH has been approved as a bridge to transplantation therapy.

TABLE 12.2 Patient Selection Criteria for Ventricular Assist Device Support as a Bridge to Cardiac Transplantation

1. Upper age consistent with successful cardiac transplantation, usually about age 70 y
2. Lower age limit determined by patient size large enough to accommodate a device
3. Suitable candidate for cardiac transplantation
4. Imminent risk of death before donor heart availability, usually with evidence of deterioration on maximal appropriate inotropic support and/or intra-aortic balloon support
5. General hemodynamic guidelines:
   - **a.** Cardiac index < 1.8 L/min/m^2
   - **b.** Systolic arterial blood pressure < 90 mm Hg
   - **c.** Pulmonary arterial capillary wedge pressure > 20 mm Hg despite appropriate pharmacologic management
6. Adequate psychological criteria and external psychosocial support for transplantation and potentially prolonged LVAD support
7. Informed consent of patient or family
8. Absence of fixed pulmonary hypertension (pulmonary vascular resistance > 6 Wood units)
9. Absence of irreversible renal or hepatic failure (LVAD support not expected to reverse existing renal or hepatic dysfunction)

LVAD, left ventricular assist device.

Adapted from Kirklin JK, McGriffin D, Young JB. *Heart Transplantation.* New York, NY: Churchill Livingstone; 2002.

K. Bridging to recovery. Clinical recovery sufficient to allow mechanical support device removal has been reported in small numbers at a few institutions. In theory, chronic mechanical unloading may permit reverse remodeling with downregulation of collagen production and hypertrophy and decrease in circulating inflammatory cytokines. Likelihood of successful recovery is greater in those with acute nonischemic cardiomyopathy and much less likely in those with chronic dilated cardiomyopathy. Currently, approximately 5% of LVAD implantations are performed with the strategy of bridge to recovery.

ACKNOWLEDGMENTS: *The authors thank Drs. Bethany Austin, Kenneth Ng, and James O'Neill for their contributions to earlier editions of this chapter.*

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CHAPTER 13

Peter Zimbwa

Cardiac Transplantation

I. INTRODUCTION. Christiaan Barnard performed the first cardiac transplant in Cape Town in 1967. Since then, cardiac transplantation has become a well-established therapeutic option for a select group of patients with end-stage heart disease. It offers these patients, who have no other alternatives, a chance for extended survival and improved quality of life. Cardiac transplantation, however, should not be perceived as a curative procedure. Although the patient's primary problem of heart failure is alleviated by a successful transplantation, a new set of potential long-term complications arises primarily owing to the secondary effects of chronic immunosuppression.

Almost 89,000 heart transplants have been reported worldwide to the International Society for Heart and Lung Transplantation (ISHLT) registry since 1983 (1). As reporting to the ISHLT is voluntary, this number underestimates the actual number of cardiac transplants. There has, however, been a reduction in the number of annual heart transplants from a peak of > 4,000 in the mid-1990s to > 3,000 now. With an estimated additional 2,000 heart transplants per year not reported to the ISHLT, the total number of cardiac transplants likely exceeds 5,000 per year worldwide.

In the United States, the United Network for Organ Sharing (UNOS) reports a 10% reduction in cardiac transplantations over the same time period. UNOS is a national organization which, along with local organ procurement agencies, maintains organ transplantation waiting lists, initiates the evaluation of potential organ donors, allocates organs when a donor is identified, and compiles statistics annually on all aspects of the transplant process, including survival. Since 1990, the number of patients listed and waiting for a cardiac transplant in the United States has more than doubled. There is a shortage of donors, and each year 1.5 to 3 times as many patients are listed for cardiac transplantation as there are donors, so this problem is only going to escalate as the population gets older unless there is a significant increase in organ donation. The annual mortality rate while on the waiting list in 2001 was 15%, which has declined continually over the last decade, probably because of improved medical therapy for end-stage congestive heart failure and increased use of implantable cardioverter–defibrillator. As the annual number of cardiac transplantations has declined, wait times have continued to lengthen. The national median waiting time by UNOS status at listing from 2003 to 2004 data is as follows: 49 days for status 1A, 77 days for status 1B, and 308 days for status 2 patients. However, this can be misleading, as patients with different blood types such as blood type O wait significantly longer than other blood types such as blood type AB on average. A blood type O, status 2 patient could easily wait for > 2 years for a cardiac transplantation.

In the last 5 years (January 2005 to June 2009), the primary indication for adult cardiac transplantation has been nonischemic cardiomyopathies (53%), followed by ischemic cardiomyopathies (38%). Valvular heart disease (3%), adult congenital disease (3%), and retransplantation (3%) and miscellaneous causes (< 1%) account for the remainder (1). The average cardiac transplant recipient is male (77.1%), with an average age of 54 years, which reflects the demographics of the patients on the waiting list. The average donor age is 33 years, and donors > 50 years of age, which were rarely reported before 1986, now account for > 12% of all donors. Outcomes of transplantation continue to improve despite transplants performed on older, sicker patients. Recent data show that 44.5% of recipients were on intravenous inotropic support compared with 34% of recipients 10 years ago. Mechanical circulatory support is also more common, with > 31% of patients on some form of mechanical circulatory support at the time of transplantation, including 20.1% with a left ventricular assist device (LVAD) compared with only 15% on mechanical circulatory support (11% with an LVAD) 10 years ago (1). Survival rates post cardiac transplantation have improved from a median of 8.3 years in the 1980s to 13 years for those surviving to 1 year (1). The risk of death is highest in the first 6 months posttransplantation. Pretransplant factors associated with higher risk of mortality in the first posttransplant year include requiring mechanical circulatory support bridging to transplantation, congenital heart disease, and ischemic cardiomyopathy. Other risk factors include hemodialysis, mechanical ventilation, prior blood transfusion, and infection (1).

Because of the scarcity of donor organs and growing transplant waiting lists, it is crucial that cardiac transplant programs adequately screen and properly select potential transplant recipients. Effective use of this limited resource is essential to avoid "wasting" organs that become available for suboptimal recipients.

II. INDICATIONS FOR CARDIAC TRANSPLANTATION

A. Patients should be on optimal medical therapy for congestive heart failure, as recommended by the American College of Cardiology/American Heart Association guidelines, including angiotensin-converting enzyme (ACE) inhibitor, digoxin, diuretic, β-blocker, and spironolactone. If a patient is intolerant to an ACE inhibitor, she or he should be on an angiotensin receptor blocker.

B. Medically reversible causes of decompensated congestive heart failure should be excluded, including hypothyroidism, tachycardia-mediated cardiomyopathy, alcohol abuse, obstructive sleep apnea, hypertension, and medical noncompliance.

C. Surgically reversible causes of decompensated congestive heart failure should be excluded, including valvular heart disease, unrevascularized coronary artery disease with large territories of ischemia or viability, hypertrophic obstructive cardiomyopathy, and LV (left ventricular) aneurysm for which resection would improve overall cardiac hemodynamics.

D. Patients should be too ill or not candidates for cardiac resynchronization therapy. Alternatively, cardiac resynchronization therapy might have failed to improve symptoms or to halt progression of the underlying pathology.

E. If the previous criteria are met, indications for a cardiac transplant evaluation are as follows:

1. Cardiogenic shock requiring mechanical support (i.e., LVAD or intraaortic balloon pump counterpulsation)
2. Cardiogenic shock requiring continuous intravenous inotropic therapy for hemodynamic stabilization
3. New York Heart Association (NYHA) class III or IV congestive heart failure symptoms, particularly if progressively worsening
4. Recurrent life-threatening LV arrhythmias despite an implantable cardiac defibrillator, antiarrhythmic drug therapy (usually amiodarone), or attempted catheter-based ablation, if appropriate
5. End-stage complex congenital heart disease without pulmonary hypertension
6. Refractory angina without potential medical or surgical therapeutic options

III. COMPONENTS OF A CARDIAC TRANSPLANT EVALUATION AND CONTRAINDICATIONS.

The purpose of a cardiac transplant evaluation is to exclude patients with medical and psychosocial comorbidities and to quantify the severity of a patient's cardiac functional impairment. Recommended investigations prior to a transplantation are summarized in Table 13.1 and exclusion criteria for cardiac transplantation are summarized in Table 13.2.

A. **Blood work.** A standard blood work includes a complete blood cell count; a complete metabolic panel, including hepatic enzymes and thyroid function tests; and blood typing and antibody screening. A serologic assessment should also be performed to determine a potential recipient's presensitization to cytomegalovirus (CMV), toxoplasmosis, hepatitis B and C viruses, and human immunodeficiency virus (HIV).

1. Patients who are anemic should have a thorough evaluation, including iron studies and a colon examination. Esophagogastroduodenoscopy and a hematologic evaluation, including a bone marrow biopsy, may also be necessary. Some patients may benefit from erythropoietin treatment to increase red blood cell counts without the need for transfusions that may expose the patient to further antigens.
2. Patients found to have an elevated serum creatinine level should undergo further evaluation to determine its relationship with low renal perfusion. A normal urinalysis result suggests the absence of renal parenchymal disease. This should include an assessment of cardiac hemodynamics and a renal ultrasound to assess renal parenchymal size and the presence of two kidneys without evidence of obstruction.
3. Patients found to have elevated hepatic enzymes should undergo further evaluation to determine the right-sided filling pressures and they should undergo a hepatic ultrasound scan. All patients should have their hepatitis B and C viral serologies assessed.
4. The patient's serum should be screened for antibodies against human leukocyte antigen (HLA) of B and T lymphocytes, drawn from community volunteers representative of the major HLA allotypes. These antibodies are collectively referred to as panel reactive antibodies (PRAs) and are often elevated in multiparous women and patients with multiple transfusions (often perioperatively in the past). Elevated PRA levels (> 10%) necessitate a pretransplant donor HLA crossmatch

TABLE 13.1 Recommended Evaluation prior to Transplantation

Complete history and physical examination
Laboratory investigations:
- Complete blood count with differential and complete metabolic panel
- Thyroid function studies (thyroid-stimulating hormone)
- Liver function panel, creatinine clearance
- Lipid profile, hemoglobin A1c, and urinalysis

Immunologic data:
- Blood type and antibody screen
- Human leukocyte antigen typing
- Panel reactive antibodies' screen

Serology for infectious diseases:
- Hepatitis (HBsAg, HBsAb, HBcAb, and HepCAb)
- Herpes group virus
- Human immunodeficiency virus
- Cytomegalovirus IgG antibody
- Toxoplasmosis
- Varicella and rubella titers
- Epstein-Barr virus IgG and IgM antibodies
- Venereal Disease Research Laboratory or Rapid Plasma Reagin

Cardiovascular investigations:
- Electrocardiogram, chest X-ray, and echocardiogram
- Exercise test with oxygen consumption
- Right and left heart catheterization
- Myocardial biopsy (if indicated, e.g., to rule out infiltrative process such as amyloidosis)

Vascular assessment:
- Carotid Doppler
- Peripheral vascular assessment (ankle–brachial index and/or duplex ultrasound)
- Abdominal ultrasound
- Ophthalmology examination (if indicated, e.g., to rule out diabetic retinopathy)

Cancer screening:
- Prostate-specific antigen (in men if indicated)
- Papanicolaou smear and mammography (in women if indicated)
- Colonoscopy (if indicated)

Psychosocial evaluation:
- Support system
- Substance abuse history (alcohol, tobacco, and drug use)
- Psychiatric history

Baseline investigations:
- Dental examination
- Bone density scan
- Pulmonary function tests

TABLE 13.2 Exclusion Criteria for Cardiac Transplantation

Irreversible pulmonary parenchymal disease
Renal dysfunction with Cr > 2.0–2.5 or CrCl < 30–50 mL/min (unless for combined heart-kidney transplant)
Irreversible hepatic dysfunction (unless for combined heart–liver transplant)
Severe peripheral and cerebrovascular obstructive diseases
Insulin-dependent diabetes with end-organ damage
Acute pulmonary embolism
Irreversible pulmonary hypertension (PVR > 4.0 Wood units after vasodilators)
Psychosocial instability or substance abuse
History of malignancy with probability of recurrence
Advanced age (> 70 y)
Severe obesity
Active infection
Severe osteoporosis

PVR, pulmonary vascular resistance.

and increase the likelihood of it being positive, making waiting times longer and transplantation more difficult. If a patient has elevated PRA levels, an attempt to reduce them before transplantation with intravenous immunoglobulin, plasmapheresis, mycophenolate mofetil (MMF), or cyclophosphamide, alone or in combination, may be considered. Traditionally, each potential recipient would undergo a thorough HLA tissue typing analysis, including a cytotoxicity assay for assistance in matching donor hearts. In this assay, random donor lymphocytes are incubated with recipient sera. Complement-dependent antibody-mediated cytolysis identifies potential donor-specific antibodies present in that recipient. Currently, most programs use flow cytometry to assess preformed antibodies, rather than cytotoxic assays. This allows for the detection of weaker interactions and provides a wider, more efficient screening process.

B. Imaging

1. All patients should undergo coronary angiography or a functional assessment for ischemia and viability. If ischemia or viability can be demonstrated, consideration should be given to percutaneous or surgical revascularization.
2. Bilateral carotid ultrasound scans should be performed in patients with risk factors for atherosclerosis. Select patients with carotid stenoses, who would otherwise be cardiac transplant candidates, may undergo pretransplantation percutaneous or surgical intervention, thereby eliminating this contraindication.
3. Occasionally, an abdominal aortic ultrasound is obtained to rule out an aneurysm, particularly in patients being considered for mechanical support.

C. Functional assessment

1. Metabolic stress testing is performed to assess the severity of cardiac functional impairment. Patients with compensated congestive heart failure and a peak oxygen consumption of < 14 mL/kg/min or < 50% predicted are considered sufficiently impaired for transplantation (2). Adequate patient effort during the stress test can be assessed by the respiratory exchange ratio, which should be > 1.1, indicating the onset of anaerobic metabolism.

2. Generally, a right heart catheterization is performed to assess cardiac hemodynamics and to optimize a patient's medical therapy. Fixed, severe pulmonary hypertension, defined as a pulmonary vascular resistance (PVR) > 4 Wood units, is a contraindication to cardiac transplantation. In this setting, the donor right ventricle will likely immediately fail after implantation because it is not accustomed to high pulmonary pressures. An attempt should be made to medically decrease the pulmonary hypertension with inotropic agents, nitrates, or nitroprusside. Sometimes an LVAD is required to sufficiently decompress the left ventricle to reverse the pulmonary hypertension. Rarely, endomyocardial biopsy (EMB) is performed, except when an infiltrative cardiomyopathy is suspected.
3. Pulmonary function tests are performed to exclude patients with significant chronic obstructive or restrictive pulmonary disease.
4. Peripheral vascular studies may be obtained to exclude patients with significant peripheral arteriosclerosis obliterans.

D. Comorbidities and implications of heart transplant listing. Advanced age, cancer, and obesity are the three common comorbidities that remain somewhat controversial with respect to their impact on whether an individual program will list a patient for heart transplantation.

1. Age criteria for eligibility were initially quite rigorous; however, it has become apparent that **chronologic and physiologic age are often discrepant**. Most centers do not have a fixed upper age limit, but generally patients > 65 years of age are very carefully screened to rule out comorbidities. ISHLT recommends considering patients for cardiac transplantation if they are ≤70 years of age (3). Patients > 70 years of age may be considered for cardiac transplantation at the discretion of the transplant program and should theoretically be in excellent health except for heart disease. An alternate type of program has been proposed for these patients, whereby older donor hearts would be utilized in this population (3).
2. Active **malignancy** other than skin cancer is an absolute contraindication to cardiac transplantation due to limited survival rates. Chronic immunosuppression is associated with a higher than average incidence of malignancy and is associated with increased recurrence of prior malignancy. Patients with cancers that have been in remission for ≥5 years and patients with low-grade cancers such as prostate cancer are generally accepted for transplant evaluation. Preexisting malignancies are heterogeneous in nature and some are readily treatable with chemotherapy. Thus an individualized approach to these patients is required, and consultation with an oncologist regarding prognosis is often very helpful.
3. Traditionally, centers have been cautious when considering **obese** patients for transplantation. Most currently available data indicate that patients with a pretransplant body mass index (BMI) > 30 kg/m^2 have poor outcomes following cardiac transplantation, with increased rates of infection and higher mortality rates. However, this area remains controversial and some recent data presented in abstract form only demonstrate no significant mortality differences between obese (BMI, 30 to 34.99) transplant recipients and overweight (BMI, 25 to 29.99) transplant recipients. Despite this controversy, the current ISHLT recommendations are that patients achieve a BMI < 30 kg/m^2 or a percent ideal body weight < 140% prior to being listed for cardiac transplantation (3). This cutoff will vary from center to center, but generally a BMI > 35 kg/m^2 will preclude listing for cardiac transplantation.

E. Consultations

1. A **psychosocial assessment** is a crucial component of every cardiac transplant evaluation. Accepted psychosocial contraindications for cardiac transplantations include active smoking; active substance abuse, including alcohol; medical noncompliance; and significant untreated psychologic or psychiatric diagnoses.

Relative psychosocial contraindications to cardiac transplantation include posttraumatic stress disorder and lack of an adequate support structure.

2. For **diabetic patients, an ophthalmology consultation** is obtained for an assessment of retinal end-organ damage related to the diabetes.

IV. UNOS AND THE RECIPIENT LIST. After a patient is accepted as a potential cardiac transplant recipient by a UNOS-certified transplant program, the patient's name is entered on a national list compiled by UNOS. The patient is given a status level based on predefined clinical criteria (Table 13.3), which can be adjusted as the patient's clinical situation evolves. A patient's priority on the UNOS list depends on his or her status level and the duration of time on the list. **Highest priority is given to patients with status 1A and those who have been waiting the longest**. A critical patient initially listed as status 1A immediately has a higher priority than a patient with a status 1B, regardless of the duration of time spent as status 1B. Whether a patient is hospitalized or not does not affect priority on the list, other than the fact that hospitalized patients are more likely to be receiving hemodynamic support (mechanical or inotropic) and are

TABLE 13.3 Description of Status Levels in the United Network of Organ Sharing List

Status	Description
1A	Must be an inpatient
	Life expectancy < 7 d
	LVAD and/or RVAD (maximum 30 d)
	VAD-related thromboembolism
	VAD-related infection (including the pocket and the driveline)
	Mechanical failure of VAD
	Total artificial heart
	Extracorporeal membrane oxygenation
	Intraaortic balloon pump with inotropic criteria
	Life-threatening refractory arrhythmias with or without a VAD
	Mechanical ventilation
	High-dose single intravenous inotrope (see doses below) or multiple intravenous inotropes, in addition to Swan-Ganz catheter
1B	Inotrope-dependent
	VAD not meeting criteria for 1A status
2	Not inotrope-dependent
7	Inactive on list because of improved clinical status or short-term contraindications to cardiac transplantation (e.g., active infection)
Inotrope criteria for status 1a	
1.	Two or more inotropes, regardless of dose
2.	Intravenous milrinone, at least 0.5 μg/kg/min by continuous infusion
3.	Intravenous dobutamine, at least 7.5 μg/kg/min by continuous infusion

LVAD, left ventricular assist device; RVAD, right ventricular assist device; VAD, ventricular assist device.

at a higher status level. A hospitalized patient on continuous inotropic therapy has the same status as a similar patient on home continuous inotropic therapy. Patients on home continuous inotropic therapy awaiting cardiac transplantation are generally thought to have an increased mortality related to the proarrhythmic effect of inotropic therapy, and most programs require implantation of an intracardiac defibrillator as a prerequisite for discharge.

V. WORKUP OF A POTENTIAL CARDIAC DONOR. Potential cardiac donors are patients who are declared brain dead but otherwise have viable internal organs. Generally, these are patients with lethal head injuries or catastrophic central nervous system events (i.e., intracranial hemorrhage, stroke, or cerebral anoxia).

A. Declaration of brain death. A neurologist or a neurosurgeon usually declares the brain death of a potential organ donor. Usually, this declaration is made after a period of observation (about 12 hours) during which no neurologic improvement is seen. Physicians involved in the care of potential transplant recipients are not involved in this decision to avoid conflicts of interest. Criteria for the determination of brain death are very specific. Absence of any one of the following criteria makes the patient ineligible for organ donation.

(1) A known cause of death
(2) Absence of hypotension, hypothermia, hypoxemia, and metabolic perturbations
(3) Absence of medical or recreational drugs known to depress the central nervous system
(4) Absence of cerebral cortical function
(5) No response to painful stimuli
(6) Absence of brainstem reflexes
  (a) Pupillary constriction to light
  (b) Corneal reflex
  (c) Vestibular ocular reflexes (i.e., doll's eyes or cold caloric testing)
  (d) Gag reflex
  (e) Cough reflex
(7) Positive apnea test: no spontaneous respiration despite arterial $P_{CO_2} > 60$ mm Hg for at least 10 minutes after disconnection from the ventilator
(8) An electroencephalogram (EEG) is not required but may be performed at the discretion of the examining physician. The EEG should demonstrate electrical silence.

B. Potential donor screening. After a patient is declared brain dead, a local organ procurement organization (OPO), under the auspices of UNOS, performs the initial evaluation of a potential donor. This evaluation includes a thorough patient and family history, focusing specifically on cardiac risk factors and potentially transmittable diseases (i.e., malignancy and infection). Preliminary blood tests are done, including determinations of cardiac enzymes; serologies for hepatitis B and C viruses, HIV, toxoplasmosis, and CMV; ABO blood group typing; and HLA antigen typing. An echocardiogram is routinely performed to assess the cardiac function and to rule out congenital anomalies and valvular disease. At the request of the potential recipient's physician, a coronary angiogram may be obtained if a donor has significant cardiac risk factors, has positive cardiac enzymes, or is relatively advanced in age. Cardiac donor selection criteria are summarized in Table 13.4.

If the potential recipient also has elevated PRA levels, a prospective complement-dependent antibody-mediated lymphocytotoxic crossmatch is usually performed, in which the recipient's serum is incubated with donor lymphocytes to identify potential donor–recipient HLA incompatibility. Many centers today perform a "virtual crossmatch" for patients with elevated PRA levels to improve donor availability. With the HLA technologies available today, the exact antigen specificity of the recipients' anti-HLA antibodies is known. If the HLA tissue typing of the potential donor

TABLE 13.4 Cardiac Donor Selection Criteria

Must meet legal requirements for brain death
No history of chest trauma or cardiac disease
No prolonged hypotension or hypoxemia
Normal ECG
Normal cardiac angiogram, performed if indicated by donor age (male > 45 y or female > 50 y) and history
Negative HBsAg, hepatitis C virus, and human immunodeficiency virus serologies
Systolic blood pressure > 100 mm Hg or mean arterial pressure > 60 mm Hg
Central venous pressure 8–12 mm Hg
Inotropic support < 10 μg/kg/min dopamine or dobutamine
Age < 55 y preferred

ECG, electrocardiogram.

does not include the antigens against which the recipient is sensitized, it is assumed that the actual crossmatch will be negative (i.e., a "virtual" negative crossmatch). If a prospective crossmatch is not performed, a retrospective crossmatch (by lymphocytotoxic assay or by flow cytometry) is performed using donor lymphocytes obtained from donor aortic lymph nodes retrieved at the time of harvest.

C. Donor–recipient matching. UNOS maintains a computerized list of all patients listed and waiting for cardiac transplantation. A list of potential recipients with compatible blood types is generated for each potential donor organ and is made available to the OPO. In this list, priority is given to local patients (defined as within the OPO's territory) with the highest status level who have been waiting the longest. Recent changes to the UNOS donor net criteria mean that a local status 2 patient is no longer higher on the list than a status 1A patient from outside the OPO's territory.

Transplant physicians of the potential recipient may also reject a potential organ because of a positive prospective crossmatch, donor–recipient size mismatch, or a prolonged projected ischemic time (usually related to long-distance travel). Matching donor and recipient size is important, because an oversized donor organ may not allow closure of the chest without compression of the organ and an undersized donor organ may not be able to pump a sufficient quantity of blood. **Current guidelines suggest that the recipient's weight should range between 70% and 130% of a potential donor's weight** (4).

VI. SURGICAL ISSUES RELATED TO CARDIAC TRANSPLANTATION. Most surgical issues related to cardiac transplantation are beyond the scope of this chapter and are mainly of interest to the cardiac surgeon. The main surgical issue of interest to the transplant cardiologist is related to the anastomosis of the right atrium. The surgeon may suture the donor atrium to the recipient atrium (i.e., **biatrial anastomosis**) or suture the donor superior vena cava to the recipient superior vena cava and the donor inferior vena cava to the recipient inferior vena cava (i.e., **bicaval anastomosis**). The bicaval anastomosis approach is more time consuming but reduces the incidence of atrial arrhythmias (including sinus

node dysfunction), reduces the incidence of posttransplant tricuspid regurgitation, and improves right atrial hemodynamics. The bicaval anastomosis approach does, however, provide some potential difficulties to the cardiologist trying to perform surveillance EMBs, because these anastomoses have a tendency to scar and narrow the central lumen over time. Currently, most centers employ the bicaval anastomosis approach, although no survival advantage has been conclusively demonstrated with this approach.

VII. POSTOPERATIVE COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

A. Surgical complications. The most common surgical complication is the development of a **pericardial effusion** with or without tamponade. Pericardial effusions are very common because of the large potential space left behind as the dilated and dysfunctional recipient left ventricle is replaced with a more appropriately sized donor left ventricle. Rarely, pericardial tamponade develops, necessitating percutaneous or surgical evacuation of the pericardium. Other surgical complications are much less common but can be catastrophic and usually result from a problem either at a site of anastomosis or at a site of cannulation.

B. Early graft dysfunction

1. **LV systolic dysfunction.** It is common for transplant recipients to require inotropic support as they come off cardiopulmonary bypass. The most commonly used inotropic agents in this setting are dobutamine, milrinone, and isoproterenol, used alone or in combination. It is also common for transplant recipients to require peripheral vasoconstrictors such as epinephrine, norepinephrine, and dopamine in the early postoperative period, because most are on large quantities of oral or intravenous vasodilators before transplantation. Most patients can be weaned off inotropic therapy and peripheral vasoconstrictors within the first 48 hours.
2. **LV diastolic dysfunction** is very common soon after cardiac transplantation. It usually results from reversible ischemia or reperfusion injury to the donor organ and normally resolves over a period of days to weeks. If the ischemia or reperfusion injury is sufficiently severe to induce significant contraction band necrosis or myocardial fibrosis, as seen on EMB, chronic diastolic dysfunction can ensue. Another potential cause of diastolic dysfunction is donor–recipient mismatch, particularly with a small donor organ or acute rejection.
3. **Right ventricular dysfunction** is much more common than LV dysfunction after cardiac transplantation, especially in patients with preexisting pulmonary hypertension. The right ventricle is subjected to similar ischemic or reperfusion injury risks as the left ventricle. Right ventricular dysfunction is usually accompanied by right ventricular dilation and the failure of coaptation of the tricuspid valve leaflets, leading to severe tricuspid regurgitation. The treatment for perioperative right ventricular dysfunction is usually intravenous milrinone and nitrates to increase cardiac output and lower the PVR. In patients with refractory pulmonary hypertension, other agents to be considered include nitroprusside, nesiritide, isoproterenol, or rarely, inhaled nitric oxide. Usually, the pulmonary hypertension and right ventricular dysfunction improve over a period of days to weeks.

C. Cardiac arrhythmias. Most transplant recipients require perioperative temporary atrioventricular pacing. Sinus node dysfunction is very common, probably because of a combination of surgical trauma, ischemia or reperfusion injury, and denervation. The incidence of sinus node dysfunction is believed to be reduced by the bicaval anastomosis technique compared with the biatrial anastomosis technique. With time, the sinus node usually recovers, and a permanent pacemaker is unnecessary. Preoperative use of amiodarone increases the likelihood of bradycardia after transplantation. Other cardiac arrhythmias are rare, especially off inotropic therapy, and may signify acute rejection.

D. Renal dysfunction. Preoperatively, many transplant recipients have some degree of impaired renal function. There is a risk of worsening renal function perioperatively.

This risk is compounded by the fact that the major immunosuppressive agents (i.e., cyclosporine and tacrolimus) are nephrotoxic. If renal function does worsen postoperatively, induction therapy is begun to delay initiation of cyclosporine or tacrolimus. Most centers no longer use OKT3 for induction therapy but rather use interleukin-2 (IL-2) receptor blockers or thymoglobulin for induction therapy.

VIII. SYSTEMIC IMMUNOSUPPRESSION. Much of the success in cardiac transplantation today is attributed to advances in immunosuppression. However, balancing the risk of allograft rejection against the inherent risk of immunosuppression remains a challenge in transplant medicine. Immunosuppressant protocols during and after cardiac transplantation vary greatly from program to program and even from patient to patient within a program. Triple therapy, which constitutes the cornerstone of modern immunosuppressive regimens in cardiac transplantation, including a calcineurin inhibitor (such as cyclosporine or tacrolimus), a cell cycle–modulating or antiproliferative agent (such as MMF or azathioprine), and a corticosteroid (4), is increasingly being challenged. Recently, the Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) trial prospectively randomized 150 cardiac transplant patients in an open fashion to receive either tacrolimus monotherapy or tacrolimus and MMF. Corticosteroids were used in all patients but were successfully discontinued over 8 to 9 weeks. The addition of MMF to tacrolimus did not provide an advantage over tacrolimus alone in terms of primary end point of rejection over the first 6 months, the secondary end points of allograft vasculopathy, and 3-year survival (5). The trial has, however, been criticized for being underpowered to demonstrate true differences in the primary and secondary end points, its use of an unvalidated biopsy grading scale, inconsistent timing of intravascular ultrasound (IVUS), use of higher and potentially nephrotoxic levels of tacrolimus, and the lack of a control arm of routine triple drug immunosuppression for comparison with the two study arms (6). Controversy remains about the advisability of using cytolytic or induction therapy in the nonpresensitized recipient without renal failure (Table 13.5).

A. Steroids. The mechanism by which steroids serve as immunosuppressants is complex and incompletely understood. Steroids bind to nuclear receptors, thereby preventing gene expression of various cytokines important for B-cell and T-cell activation and proliferation, the most important of which is IL-2. Steroids also have important anti-inflammatory properties and suppress macrophage activity. Important side effects of steroids include diabetes, hypertension, weight gain, osteoporosis, and avascular necrosis of the femoral head.

Steroid-dosing protocols vary tremendously from one institution to another. A dose of 500 to 1,000 mg of intravenous Solu-Medrol is usually given to the patient before being brought to the operating room and then 125 to 150 mg is usually repeated every 8 hours for a total of three more doses. At that point, if the patient is extubated, oral prednisone is begun. Some centers start at a divided dose of 1 mg/kg/d and wean by 5 mg daily, whereas others start immediately at only 20 mg daily. The dose of steroid is slowly tapered, provided the patient continues to have a clean biopsy record. The trend in clinical practice is to wean most patients completely off steroids. Some centers continue to advocate the indefinite use of low-dose prednisone (2.5 to 5 mg daily). If a decision is made to withdraw steroids completely, it should be done approximately 1 month before the next scheduled biopsy to ensure continued lack of acute cellular rejection.

Steroids are also given in "pulses" to treat episodes of acute cellular rejection. If a patient has acute cellular rejection associated with hemodynamic compromise, she or he is admitted for 1 g of intravenous Solu-Medrol daily for 3 days and may be given cytolytic therapy or plasmapheresis, or both. If no hemodynamic compromise is associated with the episode of rejection, a daily dose of 100 mg oral prednisone for 3 days is usually sufficient, followed by repeat biopsy, at most 2 weeks later to ensure resolution.

TABLE 13.5 Common Immunosuppressants

	Steroids	Calcineurin inhibitors	MMF	AZA	TOR inhibitors	OKT3	Polyclonal antilymphocyte antibodies	IL-2 receptor blockers
Drugs	Prednisone (P) (po) Solu-Medrol (S) (IV)	Neoral (N) Tacrolimus (T)	—	—	Rapamycin (R) Everolimus (E)	—	Atgam (A) Thymoglobulin (T)	Basiliximab (B) Daclizumab (T)
Indication	Chronic IM, acute rejection	Chronic IM	Chronic IM, skin cancer with AZA	Chronic IM	Chronic IM, vasculopathy	Induction, acute rejection	Induction, acute rejection	Induction
Dosing								
Initial	IV 125–150 mg q8h	N: 100 mg bid T: 2 mg bid	1.5 g bid	1–2 mg/kg/d	R: 2–5 mg qd E: 1.5–3 mg qd	—	—	—
Induction	—	—	—	—	—	5 mg qd × 5–15 d	A: 15 mg/kg/d T: 1.5 mg/kg/d × 5–15 d	B: 20 mg on days 1 and 4 D: 1 mg/kg q1-2wk × 5 doses
Maintenance	Weaned off	Adjusted to levels	1.5 g bid	1–2 mg/kg/d	Adjusted to levels	—	—	—
Acute rejection	P: 100 mg qd × 3 S: 1g IV qd × 3	Consider change from CsA to tacrolimus	—	—	—	As above	As above	—

Target levels	—	See Tables 12.3 and 12.4	2–4 ng/mL, 12-h trough, WBC > 3.0	WBC > 3.0	R: 4–12 ng/mL, 18-h trough	CD3 count < 20 cells/mL	CD3 count < 20 cells/mL	—
Common side effects	Diabetes, osteoporosis, weight gain, hypertension, and adrenal insufficiency	Nephrotoxicity, hypertension, tremors, and gingival hyperplasia	Diarrhea, nausea, and myelosuppression	Myelosuppression, skin cancer	Hypertriglyceridemia and thrombocytopenia	Cytokine release, hypotension, capillary leak syndrome, PTLD, and CMV superinfection	Thrombocytopenia, fevers, chills, PTLD, and CMV superinfection	—
Common drug interactions	—	Erythromycin, diltiazem, verapamil, rapamycin, anticonvulsants, rifampin, and statins	Cholestyramine and probenecid	Allopurinol	Cyclosporine	—	—	—

AZA, azathioprine; CMV, cytomegalovirus; CsA, cyclosporin A; IL, interleukin; IM, immunosuppression; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; TOR, target of rapamycin.

B. Calcineurin inhibitors. Calcineurin is a phosphatase enzyme that triggers transcription of new messenger RNA after activation of the T-cell receptor by an appropriate antigen, leading to increased gene expression of IL-2 and other important cytokines. Calcineurin antagonists inhibit this phosphatase activity, thereby preventing the synthesis of these cytokines, which prevent B-cell and T-cell proliferation.

1. **Cyclosporine** (Neoral, Gengraf, and Sandimmune) is a calcineurin antagonist with a highly variable pattern of bioavailability, depending on the oral formulation taken. Bioavailability of the original soft gelatin capsule (Sandimmune) was low and depended on emulsification by bile salts. The newer microemulsion formulation (Neoral) does not depend on bile salts for emulsification and has a more consistent bioavailability. Nevertheless, there remain tremendous interpatient differences in bioavailability, and dosing of Neoral is primarily based on serum drug trough levels. Because of the narrow therapeutic range of cyclosporine, drug trough levels are also important to prevent toxicity. Nephrotoxicity is the most important side effect of cyclosporine therapy and is related to renal afferent arteriolar vasoconstriction and the resultant reduced renal perfusion. Other side effects include systemic hypertension, gingival hyperplasia, and tremors. Calcium channel blockers, particularly diltiazem, reduce hepatic metabolism of cyclosporine, thereby increasing serum drug levels. This drug interaction is frequently used clinically to reduce the oral dose of cyclosporine required to achieve a given serum drug concentration, thereby minimizing the cost of immunosuppression.

   Postoperatively, once the patient is hemodynamically stable with good urine output, cyclosporine is initiated via continuous infusion at 1 mg/h. When the patient is able to take oral medicines, Neoral is begun at a dose of 100 mg twice daily, with adjustments in the dose based on serum trough levels (Table 13.6). The dose of Neoral is gradually reduced over a period of 1 year if the patient has a clean biopsy record.

2. **Tacrolimus** (Prograf), previously known as FK506, is another calcineurin inhibitor that has low oral bioavailability. Tacrolimus has never been prospectively shown to be superior to cyclosporine in the prevention of acute cellular rejection. However, it has become a standard practice to change cyclosporine in a patient's immunosuppressive regimen to tacrolimus in the setting of recurrent or persistent acute cellular rejection with adequate cyclosporine levels. Some programs empirically use tacrolimus for all female patients because a common side effect of cyclosporine is hirsutism. The major side effects of tacrolimus are nephrotoxicity and neurotoxicity (most commonly tremor).

   Like cyclosporine, tacrolimus is initiated postoperatively once the patient is hemodynamically and renally stable. A dose of 0.01 mg/kg/d of tacrolimus is administered by continuous infusion. Unfortunately, intravenous tacrolimus is seemingly more nephrotoxic than cyclosporine. Tacrolimus can be given sublingually using an oral to sublingual dose ratio of 1:1. After the patient starts taking

TABLE 13.6 Target Serum Cyclosporin A Levels

Time	Target level (12-h trough)
0–3 mo	250–350 ng/mL
3–12 mo	200–250 ng/mL
>12 mo	150–175 ng/mL

TABLE 13.7 Target Serum Tacrolimus (FK506) Levels

Time	Target level (12-h trough)
0–30 d	12–20 ng/mL
1–6 mo	8–15 ng/mL
6–18 mo	5–15 ng/mL
>18 mo	5–10 ng/mL

medicines orally, the dosage of tacrolimus is changed to 0.5 to 2 mg twice daily, with dose adjustment based on serum FK506 levels (Table 13.7).

C. Mycophenolate mofetil (CellCept). MMF inhibits DNA synthesis by inhibiting de novo purine synthesis. Because human lymphocytes depend on the de novo synthesis of purines for DNA replication, MMF has the unique ability to inhibit B-lymphocyte and T-lymphocyte proliferation without affecting DNA synthesis in other cell lines, which can obtain purines through the parallel and unaffected purine salvage pathway. MMF has become the preferred immunosuppressant over azathioprine at most transplant centers because of a reduced mortality rate at 1 year (6.2% vs. 11.4%; $p = 0.03$), especially among patients with treated biopsy-proven rejection and severe hemodynamic compromise (32% vs. 0%). Although there is a trend toward a reduced incidence of grade 3A (now 2R) rejection in MMF-treated patients compared with azathioprine-treated patients, it did not reach statistical significance (45% vs. 52.9%; $p = 0.055$). The main disadvantage of MMF over azathioprine is the increased cost (almost 10-fold) and the potential increased risk of opportunistic viral infections. Toxicities of MMF include gastrointestinal symptoms (nausea, vomiting, and diarrhea) and myelosuppression. Some patients on MMF develop clinically significant leukopenia, necessitating dose reduction or discontinuation of the drug. The incidence of these adverse events is higher in patients receiving > 3 g/d of MMF. Most symptoms will resolve with the reduction of dose.

MMF is given intravenously or orally. Because of the high bioavailability (> 90%), the initial dose of MMF is 1 g taken twice daily, regardless of the route of administration. The initial dose is given within the first 12 hours after transplantation. Few centers monitor the serum levels of mycophenolic acid (MPA), the active metabolite of MMF. The serum levels of MPA are higher when MMF is administered with tacrolimus compared with cyclosporine; therefore, it may be advisable to empirically reduce the dosage of MMF when switching from cyclosporine to tacrolimus. Although there is no consensus on dose adjustment of MMF, at the Cleveland Clinic, the dose is adjusted to maintain MPA 12-hour trough concentrations in the range of 2 to 4 μg/mL.

D. Azathioprine (Imuran) is a purine analog that impairs DNA synthesis, thereby preventing B-lymphocyte and T-lymphocyte proliferation in response to antigen stimulation. Azathioprine has largely been replaced by MMF as the antiproliferative agent of choice in the triple immunosuppressant cocktails of today. Because there is no drug level assay available, azathioprine dosing is usually fixed between 1 and 2 mg/kg/d. The major side effect of azathioprine is myelosuppression, and the dose of azathioprine is usually adjusted to maintain a white blood cell count of > 3,000/mL. Azathioprine is metabolized by xanthine oxidase, and xanthine oxidase inhibitors such as allopurinol can lead to the accumulation of toxic levels of azathioprine and profound and prolonged myelosuppression.

E. Inhibitors of the target of rapamycin (TOR) enzyme: sirolimus (Rapamune) and everolimus (Certican, previously known as RAD). Immunosuppressants have been developed that inhibit the enzyme TOR. TOR is activated after IL-2 stimulation of the T-cell IL-2 receptor and is critical for lymphocyte growth and proliferation. In contrast to calcineurin inhibitors, inhibitors of TOR do not block cytokine production (e.g., IL-2) but rather block the cellular response to these cytokines. TOR inhibitors also inhibit vascular smooth muscle cell growth and proliferation in response to various growth factors. It is hoped that this property of TOR inhibitors will help reduce the rate of progression of chronic transplant coronary vasculopathy. Unlike calcineurin inhibitors, TOR inhibitors are not nephrotoxic. When used in combination with cyclosporine, TOR inhibitors appear to act synergistically with regard to immunosuppression. However, worsening of renal function is common but can be prevented by lowering the cyclosporine dose without worsening of immunosuppression. The main side effects of this class of compounds are significant hypertriglyceridemia and thrombocytopenia.

Sirolimus and everolimus are both TOR inhibitors. They are structurally similar, but everolimus has a much higher bioavailability than sirolimus. The appropriate dosing of these agents remains unclear, but for sirolimus, it is probably 1 to 5 mg/d, and for everolimus, it is probably 1.5 to 3 mg/d. Sirolimus appears to lower the incidence of acute cellular rejection in humans (7) and to slow the progression of transplant vasculopathy (8). Preliminary human studies using intravascular coronary ultrasonography have also shown a reduction in neointimal proliferation with both sirolimus and everolimus.

It remains unclear where TOR inhibitors will fit in with current immunosuppressive protocols. The most likely scenario is their use in combination with a calcineurin inhibitor and prednisone, in place of MMF or azathioprine. Alternatively, they could be used in place of calcineurin inhibitors and in combination with MMF or azathioprine and prednisone, particularly in patients with either preexisting or worsening renal dysfunction.

F. Induction therapy and therapy for steroid-resistant acute rejection. The purpose of induction therapy is to deplete T lymphocytes or to prevent lymphocyte proliferation during the most immunoreactive phase, which occurs immediately after transplantation. Induction therapy has continued to be a subject of controversy in heart transplantation for more than 20 years. Induction therapy is not routinely used in posttransplant patients because of a lack of evidence of improved survival or less acute rejection. The two clear indications to use induction therapy are as follows: (1) in patients who have severe renal dysfunction, which precludes the introduction of calcineurin inhibitors within the first 2 days following transplantation and (2) in patients who have acute graft failure secondary to an immune mechanism such as with hyperacute rejection or humoral rejection. The two scenarios in which induction therapy is often used are in patients with preexisting significant renal dysfunction and in significantly presensitized patients.

The principle behind the treatment of steroid-resistant acute rejection is similar, in that the depletion of activated T lymphocytes presumably prevents further clonal expansion of the antigen-activated offending lymphocyte population.

1. **OKT3** (Muromonab-CD3) is a murine-based monoclonal anti-CD3 antibody. The CD3 antigen is part of the T-cell receptor complex present on activated, circulating T lymphocytes. OKT3 binds to the CD3 antigen and produces cell death by multiple mechanisms or T-cell receptor internalization, thereby inactivating the lymphocyte.

   The dose of OKT3 is 5 mg/d, for a total of 5 to 10 days. After a course of OKT3, there is an immediate and well-recognized rebound in CD3-positive (activated) T-lymphocyte counts that can lead to acute cellular or humoral rejection. Cytokine release syndrome frequently occurs and typically begins 30 to 60 minutes after administration of a dose of OKT3 and may persist for

several hours. Premedication with acetaminophen, steroids, and antihistamines may help minimize symptoms. CD3+ T cells are generally undetectable during OKT3 therapy; however, within 12 to 24 hours after cessation of OKT3, CD3+ T cells reappear in circulation, unlike after treatment with antithymocyte globulin (ATG) preparations, with which the lymphocyte depletion is present for weeks. Therefore, many programs prophylactically increase the steroid dose during withdrawal from OKT3. Since OKT3 is a murine-based monoclonal antibody, patients may develop antibodies toward the mouse component of the antibody that may limit the effectiveness of future courses of OKT3. Patients treated with OKT3 have had an increased incidence of posttransplant lymphoproliferative disorder (PTLD) and lymphoma with a cumulative dose of > 75 mg. Opportunistic viral infections are also more common after OKT3 therapy.

2. **Polyclonal antilymphocyte antibodies** are produced by injecting animals with human lymphocytes or thymocytes and then collecting the animal's serum. Two commercially available formulations are antithymocyte globulin (Atgam), which is horse-based, and Thymoglobulin, which is rabbit-based. The antibodies produced in this manner are directed against a variety of targets on the surface of B and T cells and induce complement-mediated lymphocytolysis. The recommended doses of Atgam and Thymoglobulin are 15 mg/kg/d and 1.5 mg/kg/d, respectively, for a total of 7 to 10 days. Adequate lymphocyte depletion can be ensured by quantifying the CD2-positive lymphocytes, a marker present on all lymphocytes. Similar to OKT3, immunity may develop to the animal component of these antibodies, rendering them ineffective if further courses of therapy are necessary. An increased incidence of PTLD, lymphoma, and opportunistic viral infections has also been observed. Patients receiving either formulation are often prophylactically treated with ganciclovir to prevent CMV infection.
3. **IL-2 receptor blockers** are competitive fully humanized monoclonal anti-CD25 antibodies. CD25 antigen is the IL-2 receptor and is only present on the cell surface of activated T lymphocytes. In contrast to OKT3, there is no initial receptor agonist phase and no cytokine release syndrome.

   For the two commercially available IL-2 receptor blockers, basiliximab (Simulect) and daclizumab (Zenapax), there are data to support the use of daclizumab only for induction therapy after cardiac transplantation, particularly in patients with preexisting renal dysfunction in whom calcineurin inhibitor avoidance is preferable in the early postoperative period. Fewer patients treated with daclizumab, in addition to standard triple immunosuppressant therapy, developed acute rejection compared with controls (9). Patients treated with daclizumab also had a lower severity and frequency of acute rejection during the first 3 months and had a longer time to the first episode of rejection. In contrast to other agents used for induction therapy, daclizumab does not appear to increase the risk of lymphoma, PTLD, or opportunistic viral infections. The serum half-life of daclizumab is 21 days, and dosing strategies call for a dose of 1 mg/kg every 1 to 2 weeks after transplantation, for a total of five doses (including the initial dose). There is no indication for either basiliximab or daclizumab as therapy for steroid-resistant persistent acute rejection. Given the virtual absence of side effects from IL-2 receptor blockade, the critical issue that needs to be addressed for these agents to become widely used clinically is whether the reduction in early acute rejection episodes translates into improved long-term survival and a reduction in transplant coronary vasculopathy.

IX. REJECTION. In the ISHLT registry, 30% of the cardiac allograft recipients between January 2003 and June 2008 experienced rejection during the first year. Females and young patients were at higher risk than males and older patients, respectively. Allograft rejection involves both the cellular and humoral arms of the adaptive response. An ideal immune monitoring strategy has been described as the one that would be noninvasive,

TABLE 13.8 Grading Scale (2004) for Endomyocardial Biopsies

Grade	Severity of cellular rejection	Histologic findings
1R[a]	Mild	Interstitial and/or perivascular infiltrate with up to 1 focus of necrosis
2R	Moderate	≥2 foci of infiltrate with associated necrosis
3R	Severe	Diffuse infiltrate with multifocal necrosis ± edema ± hemorrhage ± vasculitis

[a]R = revised.

would reliably distinguish between the presence and absence of rejection, and would detect overimmunosuppression (10). Such a strategy does not, however, exist. The immunologic status of a transplant recipient is currently monitored by immunosuppressant drug levels, echocardiographic assessment of allograft function, and EMB. Noninvasive monitoring therapies have been tested in the hope of overcoming these limitations. Gene expression profiling (GEP) test, which is also known as the AlloMap test, and cardiac magnetic resonance (CMR) imaging are examples of promising alternatives that are being evaluated.

A. Endomyocardial biopsy. The current gold standard of rejection surveillance after cardiac transplantation is EMB. However, EMB is invasive, inconvenient, expensive, and subject to sampling error and interobserver variability. Rejection of the cardiac allograft is usually clinically silent unless it is accompanied by significant hemodynamic compromise (i.e., congestive heart failure). As a result, EMBs are routinely performed for rejection surveillance (see Chapter 63). To mitigate the interobserver variability, the ISHLT revised and simplified the grading criteria for acute cellular rejection (Table 13.8) (11). Because the likelihood of acute rejection is highest early after transplantation, the frequency of biopsies is high during this period and then gradually tapers off, depending on the results (Table 13.9).

B. Surrogate markers of rejection

1. **Peripheral biomarkers.** While high levels of circulating pretransplant, donor-specific antibodies to HLAs have been demonstrated to predict greater risk of severe

TABLE 13.9 Endomyocardial Biopsy Schedule

Weeks after transplantation	Biopsy frequency
1–4	Weekly
5–12	Every 2 wk
13–24	Monthly
25–52	Every 2 mo
Year 2	Every 3–4 mo
Years 3–4	Every 6 mo
>4 y	Only if clinically indicated
After biopsy with acute rejection	2 wk after initial biopsy

rejection, no peripheral markers have been shown to reliably correlate with allograft rejection posttransplantation among those evaluated, including cytokine levels, markers of myocardial necrosis (CK-MB and troponin), complement fragments, prothrombin, P-selectin fragments, CD69 membrane protein, soluble CD30, endothelin, serum nitrate, thromboxane A_2, matrix metalloproteinase-1 in brain, vascular endothelial growth factor, natriuretic peptide, and C-reactive protein (12).

2. **Echocardiography.** Echocardiography is ubiquitous in cardiac transplant centers, drawing investigative attention to it as a noninvasive surveillance alternative to EMB for cardiac allograft rejection. For it to be a useful screening tool, however, echocardiography must identify graft rejection before global LV systolic dysfunction ensues. The challenge has been to identify such sentinel markers. Myocardial performance index, pressure halftime, intraventricular relaxation time, and acoustic quantification of cardiac filling volumes have not shown consistency. Changes > 10% in serial measurements of pulsed wave tissue Doppler measurements of early diastolic basal posterior wall motion velocity were able to exclude clinically relevant rejection with positive predictive value and negative predictive value of 92% and 95%, respectively. Technical limitations with this technique in the cardiac transplant population together with inconsistent observer interpretation have meant that echocardiography is neither sufficiently sensitive nor specific to supplant routine EMB (12).
3. **Gene expression profiling.** GEP is a new modality for surveillance of cardiac allograft rejection. **This test uses microarray and quantitative polymerase chain reaction (PCR) of peripheral blood mononuclear cells to measure the expression of 20 genes** (11 informative, 9 control and normalization) (13). A score ranging from 0 to 40 is generated by a multigene algorithm. It has been shown to correlate strongly with histologically diagnosed cellular allograft rejection. In the Cardiac Allograft Rejection Gene Expression Observational (CARGO) study, scores of < 34 were associated with a negative predictive value of > 99% for grade ≥3A/2R rejection. Several factors influence AlloMap score, including time posttransplantation, peripheral alloimmune activity, corticosteroid dose, and CMV. Transplant vasculopathy has been shown to be associated with increased AlloMap GEP score. GEP testing can be used in clinically stable cardiac transplant recipients who are > 15 years of age and 6 months or more posttransplantation. It is used to identify patients at low risk for moderate/severe (≥3A original ISHLT grade or ≥2R revised ISHLT grade) cellular rejection (8). In the Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial, 602 patients who had undergone cardiac transplantation at least 6 months previously were randomly assigned to the AlloMap test or EMB. The composite primary outcome of the study was allograft dysfunction, death, or retransplantation. At 2 years, the cumulative rate of this composite end point was 14.5% with GEP and 15.3% with EMB. The AlloMap test was thus not inferior to EMB in detecting allograft rejection. However, wholesale embrace of the IMAGE trial is tempered by the limitations of the trial, including the enrolment of only 20% of potentially eligible patients and of patients at lower risk for rejection. The noninferiority margin chosen was wide and included events that would not be associated with rejection since not all cases of graft dysfunction, death, or retransplantation are due to rejection (14).

   The frequency of rejection surveillance using the GEP or AlloMap testing should be individualized to the patient's rejection history, immunosuppression regimen, time posttransplantation, and transplant center protocol. GEP is a cost-effective and less expensive alternative to EMB for monitoring allograft rejection in cardiac transplant patients. It has demonstrated great clinical promise in these early studies and may one day surpass EMB as the gold standard for rejection surveillance after cardiac transplantation.

4. **Cardiac magnetic resonance.** CMR is able to evaluate both the myocardial tissue composition, including edema and necrosis, and the allograft function, which makes it an attractive modality for assessing cardiac allograft rejection. Studies to date have, however, not demonstrated consistent results in human populations (15). Marie et al. (16) demonstrated a 97% negative predictive value and a 35% positive predictive value of elevated T2 relaxation times in a series of 123 scans in 68 heart transplant recipients, 82% of whom were within 1 year of transplantation. Relaxation time of at least 56 milliseconds measured with a black-blood sequence predicted moderate or greater biopsy-proven rejection with 89% sensitivity and 70% specificity, and treatment of rejection episodes resulted in normalized relaxation times. Subgroup analysis showed a correlation between positive results in conjunction with a negative biopsy and subsequent rejection episodes in the following 3 months (16). In another study, Taylor et al. (17) compared the performance of CMR with EMB in assessing acute cardiac allograft rejection in 50 patients, 802 ± 224 days posttransplantation. Acute rejection was confirmed by EMB in 11 cases and presumed in 8 cases with a recent fall in left ventricular ejection fraction (LVEF) not attributable to coronary allograft vasculopathy. CMR evaluated myocardial function, edema, and early and late post-gadolinium-DTPA contrast enhancement. With rejection defined as increased early contrast enhancement or myocardial edema, the sensitivity and specificity of CMR compared with EMB were 100% and 73%, respectively. Eight patients with presumed rejection had significantly elevated early myocardial contrast enhancement compared with controls, which reduced along with improvement in LVEF following increased immunosuppression. The drawback of CMR, however, is that it is expensive, time consuming, nonspecific, and not universally available. Moreover, it cannot be used in claustrophobic patients or those with significantly reduced renal function (i.e., those with acute kidney injury or chronic kidney disease with a glomerular filtration rate < 30 mL/min/1.73m^2) in whom the use of gadolinium has the attendant risk of nephrogenic systemic fibrosis.

A. Types of rejection

1. **Hyperacute rejection** is usually fatal and is the result of allograft rejection by preformed antibodies. It can occur immediately on surgical reperfusion. The incidence of hyperacute rejection is thankfully rare in the era of PRAs and prospective crossmatches.
2. **Cell-mediated rejection** is characterized by infiltration of mononuclear inflammatory cells that are predominantly T cells directed against the allograft. Variability in the interpretation of histologic grading of cellular rejection of EMB by pathologists led to the revision of the grading system in 2004 (11). Biopsy grades of ≥2R warrant accentuation of immunosuppression. If there is no hemodynamic compromise, then patients are routinely treated as outpatients with 100 mg of prednisone taken orally for 3 days. If there is a hemodynamic compromise or persistent or recurrent severe rejection (at least grade 2R), then many therapeutic options are available, including 1 g of intravenous Solu-Medrol for 3 days, conversion from cyclosporine to tacrolimus, OKT3, Atgam, Thymoglobulin, plasmapheresis, photopheresis, and total lymphoid irradiation (4).

Grade 0R: no acute cellular rejection.
Grade 1R: mild, low-grade, acute cellular rejection.
Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage.
Grade 2R: Moderate, intermediate-grade, acute cellular rejection.
Two or more foci of infiltrate with associated myocyte damage.
Grade 3R: Severe, high-grade, acute cellular rejection.

Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis.

3. **Antibody-mediated rejection (AMR)** occurs due to preformed or de novo alloantibody (immunoglobulin G or M) against donor antigens. Such antibodies and complements are deposited in the donor coronary microvasculature and are demonstrable by immunofluorescence or by immunohistochemistry staining against CD68, C4d, or C3d complement fragments that mediate vascular injury and, ultimately, allograft failure. There has, however, been no consensus on its diagnosis. The ISHLT has recently proposed a framework for reporting AMR (18):

pAMR 0: negative for pathologic AMR.
Both histologic and immunopathologic studies are negative.
pAMR 1 (H+): histopathologic AMR alone.
Histologic findings are present and immunopathologic findings are negative.
pAMR1 (I+): immunopathologic AMR alone.
Histologic findings are negative and immunopathologic findings are positive.
pAMR 2: pathologic AMR.
Both histologic and immunopathologic findings are present.
pAMR 3: severe pathologic AMR.

This category recognizes the rare cases of severe AMR with histopathologic findings of interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis and/or karyorrhexis, and marked edema. The reported experience of the group was that these cases are associated with profound allograft dysfunction and poor clinical outcomes.

AMR is not routinely screened for in EMBs unless suspected clinically because of allograft dysfunction or hemodynamic compromise. Treatment options for patients with vascular rejection include intravenous or oral steroids, plasmapheresis, or immunoadsorption (4).

X. INFECTIOUS DISEASE AFTER TRANSPLANTATION. The risk of infection is highest in the first year post cardiac transplantation, accounting for 29% of deaths. Thereafter, the risk falls but remains > 10%. In the first month post transplantation, nosocomial infections predominate. The therapeutic immunosuppression consequent upon transplantation leaves cardiac allograft recipients vulnerable to opportunistic infections or reactivation of latent infection, particularly between 1 and 6 months. Infections after 6 months are usually community-acquired. An infectious disease specialist with an interest in transplantation is an invaluable resource to any transplant program. The two pathogens of particular interest in the transplant patient are CMV and pneumocystis jiroveci pneumonia (PJP), formerly called pneumocystis carinii pneumonia, but there are several potential pathogens including *Mycobacterium*, *Nocardia*, *Listeria*, *Candida*, *Aspergillus*, and *Strongyloides* (1,4).

A. Cytomegalovirus. Primary CMV infection occurs when a CMV-negative recipient receives a CMV-positive donor organ or is infected de novo from another source. Secondary CMV infection occurs when a CMV-positive recipient has reactivation of quiescent CMV infection with viremia after immunosuppression, particularly with induction therapy or bolus immunosuppression prescribed for a rejection episode. Active CMV disease may manifest as fevers, myalgias, gastritis, colitis, pneumonitis, retinitis, or leukopenia and thrombocytopenia. The most sensitive and specific test for diagnosing CMV is quantitative PCR. PCR detects CMV DNA in plasma and quantifies the CMV viral load. Although CMV DNA replication may be detected by PCR, most patients do not have the clinical syndrome of CMV disease. The issues of whether a detectable CMV viral load will progress to the clinical syndrome and whether to treat patients with CMV detection in the absence of symptoms remain controversial.

Prophylaxis against CMV disease is considered to be the standard of care for CMV-positive recipients (regardless of the CMV status of the donor) and CMV-negative patients with a CMV-positive donor. There is no consensus on the duration

of ganciclovir therapy in these patients. Most patients are initially treated with intravenous ganciclovir, followed by a variable course of oral valganciclovir or acyclovir. Periodic monitoring of the CMV viral load may assist in guiding the duration of therapy in these patients.

Passive immunization with CMV immunoglobulin (CytoGam) may be considered in patients deemed at risk for CMV disease, particularly if they have low levels of serum immunoglobulins (< 500 mg/dL). Patients undergoing induction therapy, polyclonal or monoclonal antibody therapy for steroid-resistant rejection, or increased immunosuppressive therapy for acute rejection should be deemed at risk for reactivation of CMV disease.

The duration of therapy with valganciclovir for active CMV disease is usually 3 to 6 weeks. An undetectable CMV viral load should be demonstrated in such patients before consideration is given for antiviral therapy discontinuation (4).

B. *Pneumocystis jiroveci* pneumonia. Transplant recipients are at increased risk for the development of PJP because of their immunocompromised state. PJP is rare if appropriate prophylaxis with trimethoprim–sulfamethoxazole (TMP–SMX) is provided. Patients intolerant to TMP–SMX may be treated with inhaled pentamidine or dapsone. PJP is rarely seen at maintenance immunosuppressant doses in transplant patients. TMP–SMX may be discontinued at 6 to 12 months after transplantation in most patients (4).

XI. CARDIAC ALLOGRAFT VASCULOPATHY (CAV).

CAV is a progressive, neointimal proliferative process in the epicardial coronary vasculature and in the microcirculation. It is common, with an incidence of 20%, 30%, and > 50% at 3, 5, and 10 years after transplantation. CAV is a significant cause of mortality beyond the first year after transplantation, accounting for 30% to 50% of deaths at 5 years. The pathophysiology of CAV is not completely understood. **Initially CAV was thought to be an accelerated form of atherosclerosis; however, it is now clear that both immunologic and nonimmunologic factors are involved in the process**. Chronic, subclinical, and immune-mediated injury at the level of the donor coronary endothelium creates a chronic inflammatory milieu. The exact mediator of the endothelial injury remains controversial, but it is probably multifactorial, including chronic humoral and cellular rejection, ischemic and reperfusion injury at the time of transplantation, and chronic CMV infection of endothelial cells. Table 13.10 lists risk factors for the development of CAV, of which older donor age and hyperlipidemia are well-established risk factors, whereas the others are potential risk factors.

Because donor hearts are denervated at explantation, **the transplant recipient typically will not experience cardiac angina from advanced CAV.** The clinical presentation of CAV previously unrecognized in a patient may include symptomatic or asymptomatic LV dysfunction, myocardial infarction, or cardiac arrhythmia, including ventricular arrhythmias, heart block, syncope, or sudden cardiac death. Owing to the usually asymptomatic nature of CAV, transplant recipients require frequent surveillance studies to detect significant vasculopathy, including coronary angiography with or without IVUS, cardiac perfusion magnetic resonance imaging, and dobutamine echocardiography. The frequency and method of surveillance are center-specific. Although coronary angiography is useful for the diagnosis of nontransplant coronary artery disease, its sensitivity is considerably less in CAV because of the diffuse nature of this disease. Coronary IVUS imaging provides useful tomographic perspective to study the development and progression of CAV and is now considered by many to be the gold standard modality for diagnosing CAV. However, not all centers have access to routine IVUS imaging and thus its use will vary greatly from center to center. The nomenclature of CAV has not been standardized until recently (19). The recommended nomenclature for CAV is as follows:

CAV0 (not significant): no detectable angiographic lesion.

ISHLT CAV1 (mild): angiographic left main (LM) < 50%, primary vessel with maximum lesion of < 70%, or any branch stenosis < 70% (including diffuse narrowing) without allograft dysfunction.

TABLE 13.10 Risk Factors for the Development of Cardiac Allograft Vasculopathy

Older donor age
Hyperlipidemia
Donor brain death secondary to spontaneous intracranial hemorrhage
Cytomegalovirus infection
Increased C-reactive protein levels (> 1.66 mg/L)
Recurrent cellular rejection
Humoral (vascular) rejection
HLA antigen mismatch
Donor hepatitis B and C
Female donor
Peritransplant myocardial ischemia
Pretransplant coronary atherosclerotic disease
Conventional atherosclerosis risk factors (diabetes, hypertension, and smoking)

HLA, human leukocyte antigen.

ISHLT CAV2 (moderate): angiographic LM < 50%, a single primary vessel ≥ 70%, or isolated branch stenosis ≥ 70% in branches of two systems, without allograft dysfunction.

ISHLT CAV3 (severe): angiographic LM ≥ 50%, two or more primary vessels ≥ 70% stenosis, or isolated branch stenosis ≥ 70% in all three systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤ 45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific).

Definitions

(a) A "primary vessel" denotes the proximal and middle 33% of the left anterior descending artery, the left circumflex, the ramus, and the dominant or codominant right coronary artery with the posterior descending and posterolateral branches.

(b) A "secondary branch vessel" includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches, or any portion of a nondominant right coronary artery.

(c) Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio > 2 (> 1.5 in children), shortened isovolumetric relaxation time (< 60 milliseconds), shortened deceleration time (< 150 milliseconds), or restrictive hemodynamic values (right atrial pressure > 12 mm Hg, pulmonary capillary wedge pressure > 25 mm Hg, and cardiac index < 2 L/min/m^2).

The detection of significant CAV should prompt aggressive percutaneous or more rarely surgical revascularization. Because of its relationship with chronic rejection, advancement of the immunosuppressant regimen has also been advocated. Statins have been shown prospectively to decrease the incidence of transplant vasculopathy and improve survival, regardless of the patient's lipid profile (20). Preliminary studies investigating the antiproliferative effects of TOR inhibitors (sirolimus and everolimus) suggest a significant reduction in coronary neointimal proliferation and, therefore, transplant coronary vasculopathy. In the future, the development of transplant vasculopathy may prompt a switch to a TOR inhibitor–based immunosuppressant regimen if the initial suggestion of attenuation of progression, and perhaps regression, of transplant vasculopathy is confirmed in larger, prospective clinical trials. In severe, advanced CAV, frequently the only viable option is repeat transplantation (1,4).

XII. MALIGNANCY

A. Malignancy is a common and devastating complication of cardiac transplantation. In immunocompetent people, the cellular arm of the immune system actively defends against a variety of neoplastic processes. With the initiation of immunosuppression after transplantation, this defense mechanism is rendered feeble and previously undeclared neoplastic foci may proliferate. Because up to 38% of patients undergo cardiac transplantation for ischemic cardiomyopathy, a significant proportion of which is smoking-related, lung cancers can occur. Other common tumors include lymphomas, skin cancers, colon cancers, and breast cancers. Skin cancers are particularly common in patients on azathioprine, and they usually prompt a substitution of MMF for azathioprine. Posttransplantation malignancies are particularly common in patients who have received cytolytic or induction therapy with OKT3, Atgam, or Thymoglobulin, and the risk correlates with cumulative dosing of immunosuppression. The risk of developing a malignancy as a result of immunosuppression is enhanced by the inability to adequately assess for overimmunosuppression. Underimmunosuppression is readily detected because of the development of acute rejection, whereas there is no clinical finding to suggest overimmunosuppression.

PTLD is an Epstein-Barr virus–related clonal expansion of B lymphocytes. PTLD may develop in any location but most commonly affects the gastrointestinal tract, lungs, and central nervous system. The primary treatment for PTLD is a reduction in immunosuppression (by about 50%), which can frequently be curative. Surgical debulking, systemic chemotherapy, and antiviral therapy may also be indicated in selected patients (1,4).

XIII. HYPERTENSION

Arterial hypertension commonly develops after cardiac transplantation secondary to the untoward effects of immunosuppression. **Hypertension developing after cardiac transplantation occurs in most cyclosporine-treated and tacrolimus-treated patients**. Three mechanisms proposed are as follows:

(1) direct sympathetic activation,
(2) increased responsiveness to direct circulating neurohormones, and
(3) direct vascular effects.

A common end point of these proposed mechanisms is vasoconstriction of the renal vasculature, leading to sodium retention and an elevated plasma volume. Corticosteroids play a minor role in the pathogenesis of cardiac transplant hypertension, which is described as a salt-sensitive type. Abnormal cardiorenal reflexes secondary to cardiac denervation may also contribute to salt-sensitive hypertension and fluid retention.

Patients with blood pressure consistently > 140/90 mm Hg should be treated. Titrated monotherapy with either ACE inhibitors or calcium channel blockers is usually effective in about 50% of the patients. Some patients will be prone to hyperkalemia secondary to the combined effect of cyclosporine and ACE inhibition on the kidney. The use of diltiazem, verapamil, or amlodipine necessitates the use of lower doses of cyclosporine and initially more frequent cyclosporine level monitoring because these drugs are competitive antagonists of cyclosporine at the cytochrome P450 level. Combination therapy with both an ACE inhibitor and a calcium channel blocker is a commonly employed strategy. Problematic hypertensives requiring multiple agents often require diuretics as part of their regimen. Hypertension in some patients is inadequately controlled despite maximally tolerated doses of both calcium channel blockers and ACE inhibitors. The final tier of management would be to add a β-blocker such as clonidine or doxazosin in refractory cases. β-Blockers traditionally have been avoided due to their known tendency to reduce exercise performance and because of concerns about excessive bradycardia. Some transplant cardiologists, however, routinely use β-blockers to manage hypertension in their transplant patients. Thus, β-blockers are not contraindicated but rather may be used with due caution (1,4).

XIV. OUTCOMES AFTER CARDIAC TRANSPLANTATION. Survival outcomes after cardiac transplantation continue to improve on a yearly basis despite what is generally accepted as a population of transplant recipients at greater risk, primarily because of advancing recipient age and increasing severity of heart failure. The 1-year survival rate after cardiac transplantation is 84% nationwide, but it is frequently > 90% at large transplant centers. The mortality in the first year after transplantation primarily results from postoperative complications, including multiorgan failure, primary graft failure, and systemic infection. Those surviving the first year posttransplantation have a median survival of 13 years. It is unlikely that any major improvements in early posttransplant survival will occur in light of these excellent results. However, a 10-year survival rate after cardiac transplantation is only 50%. Mortality in the long term primarily results from transplant coronary vasculopathy, malignancy, and renal failure. It is hoped that a major impact can be made on long-term survival with newer immunosuppressive drug regimens that may be less nephrotoxic and more effective at preventing transplant coronary vasculopathy (1).

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RELEVANT WEB SITES

International Society for Heart and Lung Transplantation (ISHLT) (www.ishlt.org).
Scientific registry of solid-organ transplant recipients in the United States (www.ustransplants.org).

CHAPTER 14

Praneet Kumar
W.H. Wilson Tang

Pulmonary Hypertension

I. INTRODUCTION. Pulmonary hypertension (PH) is a routinely made diagnosis in contemporary cardiology and pulmonary clinics. It is essential for the specialist as well as the internist to have a high index of clinical suspicion for this devastating disease, as early diagnosis and referral may affect the survival. Substantial advances are being made in the management of pulmonary arterial hypertension (PAH), which is more rapidly available at centers specializing in PH.

A. Terminology/definitions. PH is defined as mean pulmonary artery pressure (mPAP) > 25 mm Hg. PH encompasses a heterogeneous group of diseases with a common clinical manifestation. The terms PH, which is a hemodynamic and pathophysiologic condition, and PAH, a clinical condition, are different terminologies that should not be used interchangeably. The clinical classification of PH is based on hemodynamic data derived from right heart catheterization (RHC). Some terminologies that are commonly employed in PH include the following:

1. **Trans-pulmonary gradient (TPG)** is defined as the pressure difference between mean left atrial pressure (LAP) (more commonly pulmonary capillary wedge pressure [PCWP] is used as a surrogate) and mPAP.
2. **Pulmonary vascular resistance (PVR)** is defined as TPG divided by the cardiac output (PVR = TPG/CO in Wood units).
3. **PAH** is hemodynamically defined as PH (i.e., mPAP ≥ 25 mm Hg) with increased PVR (more than 3 Wood units) and normal wedge pressure (< 15 mm Hg). It is a clinical condition characterized by precapillary PH and pathologic changes in the lung microcirculation.
4. **Pulmonary venous hypertension is characterized by mPAP ≥ 25 mm Hg, PVR > 3** Wood unit**, and elevated wedge pressure (PCWP ≥ 15 mm Hg).**

B. Classification. The World Health Organization has endorsed the clinical classification of PH based upon pathologic, pathophysiologic, and therapeutic characteristics. The most recent classification derived from the world symposium on PH held in Dana Point, California, in 2008 is listed in Table 14.1.

C. Epidemiology. The total PH burden of the disease is substantial as it represents an end stage of multiple disease processes such as left-sided heart disease, chronic lung diseases, as well as PAH which is very rare. Most of the patients who are diagnosed with PH on routine testing (echocardiogram with pulmonary arterial systolic pressure [PASP] > 40 mm Hg) will end up having left heart disease (nearly 80%), some with lung disease and hypoxia (10%), and only a small minority (4%) will have PAH.

Data from registries estimate the prevalence at around 15 to 50 cases/million adults and its incidence at around 2.4 cases/million adults/year. Idiopathic PAH (IPAH) and familial PAH (previously known as "primary PH") are rare diseases with a prevalence of around 6 cases/million**. Familial cases account for 5% to 10% of all PAH cases. Mutations in the *bone morphogenetic protein receptor-II* (BMPR2)**

TABLE 14.1 Dana Point Classification of Pulmonary Hypertension (Simplified)

	Type	Subtype
1	Pulmonary arterial hypertension	Idiopathic Heritable Drugs and toxins induced Associated with CTD, HIV, portal hypertension, congenital heart disease, schistosomiasis, and chronic hemolytic anemia Persistent PH of newborn
1′	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis	
2	PH due to left heart disease	Systolic Diastolic Valvular
3	PH due to lung disease and/or hypoxia	COPD ILD Mixed obstructive and restrictive lung disease Sleep-disordered breathing Alveolar hypoventilation syndromes, etc.
4	Chronic thromboembolic PH	
5	PH with unclear and/or multifactorial mechanisms	Hematologic Systemic such as sarcoid and vasculitis

PH, pulmonary hypertension; CTD, connective tissue disease; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

gene have been identified in about 70% of patients with familial PAH and 10% to 40% of patients with sporadic IPAH. Hence, relatives of patients with familial IPAH should be advised about the availability of genetic testing and counseling in addition to echocardiographic screening.

PAH has been associated with environmental factors such as the use of drugs and toxins. **Anorexigens** (appetite suppressant drugs that increase serotonin release and block serotonin reuptake) have been associated with PAH, with agents such as aminorex fumarate and (dex) fenfluramine. Select patient populations at an increased risk of developing PAH are discussed below.

1. **Patients with connective tissue diseases** (CTDs), especially the **limited cutaneous form of systemic sclerosis (formerly referred to as the CREST syndrome)**. The prevalence of hemodynamically proven PAH in systemic sclerosis is around 10%. In other CTDs, such as systemic lupus erythematosus, mixed CTD, rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome, PAH is observed less frequently.
2. **Human immunodeficiency virus (HIV) infection** is associated with approximately 0.5% incidence of PAH. However, because of this low incidence, routine screening is not recommended.
3. Patients with **cirrhosis and portal hypertension** are at an increased incidence of PH (5% of patients were referred for liver transplantation).

4. **Congenital heart disease** may lead to PAH when the underlying systemic-to-pulmonary shunt is not corrected. Most commonly, it occurs with conditions where blood flow is high and the pulmonary vasculature is exposed to systemic level pressures (e.g., ventricular septal defect and patent ductus arteriosus). However, high blood flow alone, as in atrial septal defect, may be sufficient. Once PVR approaches or exceeds the systemic vascular resistance, the shunt is reversed, leading to desaturation and cyanosis (Eisenmenger syndrome).

II. SIGNS AND SYMPTOMS

A. Symptoms. The symptoms of PH are nonspecific and are gradual in onset; therefore, there is a lag time of about 2 years (from symptom onset to diagnosis) in 90% of patients with PAH. These symptoms may include dyspnea on exertion, fatigue, weakness, chest pain, palpitations, syncope, abdominal distention, and pedal edema. Symptoms at rest occur only at late stages of the disease and portend poor prognosis.

Some patient populations are at an increased risk for developing PH and should be carefully screened by clinicians by careful history taking, examination, and laboratory tests. These populations include patients with known, or relatives of those with, BMPR2 mutations, CTD, HIV infection, portal hypertension, prior appetite suppressant use, congenital heart disease with shunt, recent acute pulmonary embolism, left heart disease, chronic obstructive pulmonary disease, interstitial lung disease, or sleep apnea.

It is advisable to perform annual screening with echocardiography in select high-risk groups, such as

(1) those with known BMPR2 mutation;
(2) first-degree relative of the patient with BMPR2 mutation or within pedigree of two or more patients with PAH;
(3) those with systemic sclerosis; and
(4) those with sickle cell disease.

B. Physical examination. Physical examination may provide clues as to the cause of PH. Findings of telangiectasia, digital ulceration, and sclerodactyly suggest scleroderma, while inspiratory crackles may point toward interstitial lung disease. Patients should be carefully screened for the presence of stigmata of liver disease, such as spider naevi, testicular atrophy, and palmar erythema. The presence of clubbing suggests congenital heart disease or pulmonary veno-occlusive disease. Cardiovascular examination of patients with PH may reveal a left parasternal lift, a loud P_2 at the apex, a pansystolic murmur of tricuspid regurgitation that increases with inspiration, a diastolic murmur of pulmonary insufficiency, and a right ventricular (RV) S_3. Lung sounds are usually normal (except for those with class 3 PH). Jugular vein distension, hepatomegaly with a pulsatile liver, peripheral edema, and ascites are ominous signs suggestive of advanced stages with right-sided heart failure.

III. LABORATORY EVALUATION

A. Blood work

1. Routine biochemistry, hematology, and thyroid function tests.
2. **Serologic testing** is important to detect the underlying CTDs, HIV (mandatory screening), thrombophilia (in chronic thromboembolic pulmonary hypertension [CTEPH]), and hepatitis (in patients with suspected liver disease). More than a third of patients with IPAH have low-titer elevation in antinuclear antibodies. Systemic sclerosis is the most important CTD to exclude because of high prevalence of PAH in this syndrome. Anti-centromere antibodies are usually positive in limited scleroderma as are other antinuclear antibodies, including dsDNA, anti-Ro, U3-RNP, B23, Th/To, and U1-RNP. In the diffuse variety of scleroderma, U3-RNP is positive. In patients with systemic lupus erythematosus, anticardiolipin antibodies may be found.

3. **Biomarkers.** Several circulating biomarkers have prognostic implications in patients with PAH, but their value in everyday clinical practice is still not established. Uric acid levels are shown to be increased in patients with IPAH, and elevated plasma troponin T levels (> 150 pg/mg) have been associated with worse outcomes in patients with CTEPH and PAH. BNP levels have also been used to monitor response to therapy or clinical course, as those with persistently elevated levels have worse outcomes. Similarly, NT-proBNP below cutoff levels < 1,400 pg/mL has been associated with better outcomes. BNP/NT-proBNP plasma levels should be checked for the initial risk stratification and may be considered for monitoring the effects of treatment, in view of their prognostic implications. Low and stable or decreasing BNP/NT-proBNP may be a marker of successful disease control in PAH.

B. The electrocardiogram (ECG). In typical cases of PH, the ECG shows right atrial (RA) dilatation, RV hypertrophy with strain, and a right axis deviation. In advanced stages of the disease, atrial flutter or atrial fibrillation often occurs, leading to further clinical deterioration.

C. Chest radiograph. Initial chest x-rays are abnormal in majority (90%) of patients with IPAH at the time of diagnosis. There is often central pulmonary arterial (PA) dilatation with "pruning" (loss) of the peripheral blood vessels, clear lung fields, and a prominent RV border. The chest x-ray may also point to lung abnormalities and show features suggestive of left heart disease.

D. Echocardiography. If PH is suspected based on history, risk factor assessment, and physical examination, an echocardiogram is the next appropriate study. By using the Doppler technique, peak velocity of the tricuspid regurgitation jet can be measured. From this measured velocity, the pressure difference between right ventricle and right atrium can be estimated by employing the simplified Bernoulli equation ($\Delta P = 4v^2$). On condition that there is no pulmonic valve stenosis, PASP = 4 × (tricuspid regurgitant jet velocity)^2 + right atrial pressure (RAP). RAP can be estimated on the basis of inferior vena cava (IVC) characteristics. If the IVC is plethoric and there is clinical evidence of Jugular venous distension (JVD), RAP is presumed to be 10 to15 mm Hg, whereas if findings are normal, it is usually calculated as 5 mm Hg.

Other echocardiographic characteristics may raise the suspicion of PH, such as RA or RV dilatation, flattening of the interventricular septum with D-shaped left ventricle, increased RV wall thickness, dilatation of the pulmonary artery, and the presence of pericardial effusion. These features tend to occur later in the course of the disease.

Although echocardiography is a useful screening tool, Doppler-derived pressure estimation can both underestimate PASP in patients with severe tricuspid regurgitation and overestimate PASP in non-PH patients. Ultimate confirmation requires RHC.

E. Right heart catheterization. RHC is required to ***confirm the diagnosis of PH, to assess the etiology and severity, and to test for vasoreactivity of the pulmonary circulation***. At experienced centers, morbidity (1.1%) and mortality (0.055%) rates are low. Consecutively, RAP, right ventricular pressure (RVP), PAP, and PCWP are recorded using a balloon-tipped fluid-filled catheter (Table 14.2). Cardiac output can be determined using the thermodilution method and/or the Fick method (measurement of mixed venous saturation SvO_2 needed). The PCWP is taken as a surrogate measure of LAP and, in the absence of mitral stenosis, left ventricular end-diastolic pressure (LVEDP). This measurement is very important because it helps differentiate PH associated with left heart disease from other conditions. However, it is subject to error in measurement and interpretation. Occasionally, it may be necessary to perform a left heart catheterization for direct measurement of LVEDP.

TABLE 14.2 Normal Values of Pressures and Measurements Derived from a Right Heart Catheterization

Measured characteristic	Normal value
Right atrial pressure	Mean 1–10 mm Hg
RVSP/RVDP	15–30/1–10 mm Hg
PASP/PADP	15–30/5–10 mm Hg (mean < 20 mm Hg)
PCWP	Mean 5–12 mm Hg
LVEDP	5–12 mm Hg
Cardiac output Cardiac index	5–7.5 L/min 2.5–4.0 L/min/m^2
PVR	0.25–1.6 Wood units
TPG	4–6 mm Hg

RVSP/RVDP, right ventricular systolic and diastolic pressures; PASP/PADP, pulmonary artery systolic and diastolic pressures; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient.

Temporal evolution of the hemodynamic variables with progression of PAH is depicted in Figure 14.1. As the disease progresses, the right ventricle starts to fail, leading to reduction in CO. As a result, PAP may decrease again. This decrease may give a false impression of hemodynamic improvement or suggest that there is mild to moderate disease. Therefore, it is imperative to measure PVR, which will be high in this situation. Usually, the RAP and PCWP also increase, implying RV failure and left ventricular (LV) diastolic dysfunction, respectively. The latter is the consequence of ventricular interdependence and abnormal compliance of the left ventricle produced by an enlarged right ventricle.

Vasoreactivity testing in PAH: In PAH, vasoreactivity testing should be performed to identify patients who may benefit from long-term therapy with calcium channel blockers

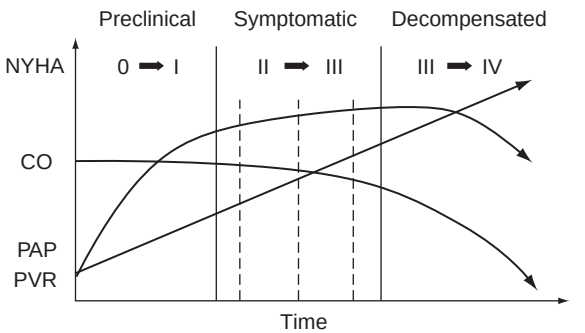

FIGURE 14.1 Evolution of hemodynamic variables in function of disease severity. CO, cardiac output; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance. (From Galie N, Manes A, Palazzi M, et al. Pharmacological impact on right ventricular remodelling in pulmonary arterial hypertension. *Eur Heart J.* 2007; 9:H68-H74, with permission.)

(CCBs). The agent most often used to test this is inhaled NO, with (i.v.) epoprostenol and (i.v.) adenosine as alternatives.

A positive acute response is defined as a > 10 mm Hg decrease in mPAP to reach an absolute value of mPAP < 40 mm Hg with an increased or unchanged CO and without significant drop in systemic blood pressure.

In patients with IPAH, about 10% to15% are acute responders and nearly half of these will prove to be long-term responders with a more favorable prognosis. This concept is less clear in other forms of PAH, although vasoreactivity testing is still recommended but controversial in congenital heart disease. It is not useful in other forms of PH (groups 1', 2, 3, 4, and 5). In veno-occlusive disease and left heart disease, it can even provoke pulmonary edema. However, in patients considered for heart transplantation, pulmonary vasoreactivity testing may be used to assess reversibility and operability.

It is important to understand the difference between PAH vasoreactivity testing and the assessment of PH reversibility in left-sided heart failure. In PAH, vasodilator response testing is performed to select patients who may respond favorably to CCBs as the first agent versus those who will likely not. In left-sided heart failure and PH, vasodilatory drugs that affect the LV afterload, such as sodium nitroprusside, are given with an intention to reduce LV filling pressure and, evaluate for reversible pulmonary hypertension. Those who have persistent elevation in TPG and PVR to high levels (such as when TPG remains elevated to > 15 mm Hg and/or PVR is > 3 Wood units despite the reduction of PCWP to < 15 mm Hg) are at high risk for transplant failure, as the transplanted heart may not withstand persistently elevated PAPs , which results in right heart failure.

F. Pulmonary testing and arterial blood gas (ABG). Pulmonary function tests and ABGs are used to identify underlying airway or parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (typically in the range of 40% to 80% predicted) and mild to moderate reduction in lung volumes. Arterial oxygen partial pressure is normal or only slightly lower than normal at rest and arterial carbon dioxide partial pressure is decreased because of alveolar hyperventilation. The severity of emphysema and of interstitial lung disease can be diagnosed using high-resolution computed tomography (CT). If clinically suspected, screening overnight polysomnography may diagnose significant obstructive sleep apnea.

G. Six-minute walk distance. The 6-minute walk test (6MWT) is the most commonly employed measure of exercise capacity in patients with PH, both in clinical assessment and in research settings. In addition to the distance walked, the degree of dyspnea (Borg score) and oxygen saturation are also measured. **A 6-minute walk distance of < 332 m and a drop in oxygen saturation by > 10% are suggestive of poor prognosis**. It is also measured on routine follow-ups and can be indicative of clinical deterioration. It may also be used to assess the response to therapy.

H. Other tests. Chest CT and ventilation–perfusion (V/Q) scans are indicated to exclude primary parenchymal or thromboembolic diseases as a cause of PH. For excluding thromboembolic disease, V/Q scan is the preferred screening test. A normal or low-probability V/Q scan effectively excludes CTEPH with a sensitivity of 90% to 100% and a specificity of 94% to 100%, while a high-probability scan warrants further evaluation with a pulmonary angiogram. Pulmonary angioscopy may be considered at specialized centers in cases of CTEPH to determine surgical candidacy.

IV. PATHOGENESIS

A. Hemodynamically, PH is a disease state with increased pulmonary pressures. Applying Ohm's law to the pulmonary circulation

TPG or pressure difference (mPAP – PCWP) = flow (CO) × resistance (PVR).

Thus, elevated mPAP may be a consequence of ***elevation in PCWP, increase in flow, or increase in PVR***. However, pulmonary vessels are highly compliant and capable of recruitment with progressive reduction in PVR for the increment in flow. These low-pressure, low-resistance, and high-compliance characteristics of the pulmonary vascular bed are regulated by a balance between vasodilators and vasoconstrictors and between cell proliferation and apoptosis. Genetic and environmental factors may disturb this balance, resulting in excessive vasoconstriction, vascular remodeling, and micro-thrombosis, which leads to pulmonary (arterial) hypertension. This leads to elevated PVR and an increase in RV afterload, ultimately resulting in RV dilatation and hypertrophy. This may progress to RV failure with further dilatation, thinning of the wall and tricuspid regurgitation, and worsening outcome.

B. Histologically, PAH is a panvasculopathy predominantly affecting the small pulmonary arteries. The initial lesions seem to be intimal hyperplasia and medial hypertrophy followed by more irreversible lesions such as intimal fibrosis, thrombosis in situ, inflammation, and plexiform arteriopathy. These lesions may be present in various distributions, local or diffuse, in a patient.

C. Molecular and endothelial abnormalities. Various vasoactive molecules play an important role in the pathologic evolution of PAH. Our understanding of these factors and various pathologic forces is limited, but some pathways have been elucidated mainly due to their therapeutic potential (Fig. 14.2).

1. **Prostacyclin/thromboxane A_2:** Prostacyclin and thromboxane A_2 are arachidonic acid metabolites in vascular cells. Prostacyclin has potent vasodilating, antiproliferative, and platelet-inhibiting properties, whereas thromboxane A_2 has the opposite effect. In PAH, the balance is shifted toward thromboxane A_2 in small and medium-sized pulmonary arteries.
2. **Endothelin-1 (ET-1):** ET-1 is produced by endothelial cells and exerts its effect on the smooth muscle cells through two receptors: endothelin receptor A (ET_A), expressed on vascular smooth muscle cells, and endothelin receptor B (ET_B), expressed on both vascular endothelial cells and smooth muscle cells. Stimulation of both receptors on the vascular smooth muscle cells causes vasoconstriction and has a mitogenic effect, whereas stimulation of ET_B on the endothelial cells causes vasodilatation via increased production of prostacyclin and nitric oxide (NO). In patients with PH, ET-1 levels are increased and ET-A receptors are abundant.
3. **Nitric Oxide:** NO is produced in endothelial and epithelial cells in the lung from L-arginine by three isoforms of NO synthases (NOSs). It is a potent vasodilator and an inhibitor of platelet activation and of vascular smooth muscle cell proliferation. Once formed, the effects of NO are mediated by cyclic guanosine monophosphate (cGMP), which is rapidly inactivated by the phosphodiesterase enzymes, especially type 5 (PDE-5). Decreased endothelial NOS (NOS 3) has been observed in patients with PAH.
4. **Others:** Various molecules such as serotonin, vasoactive intestinal peptide, and angiopoietin-1, and various inflammatory cells have been associated with PAH.

V. TREATMENT. The treatment of group 1 PH (or PAH) is primarily in the form of pulmonary-specific vasodilator therapy, whereas treatment in groups 2, 3, and 4 PH is mainly oriented toward treating the underlying condition (such as left heart disease and chronic lung disease).

A. General measures. A few general measures apply to all the PH groups:

(1) Mild physical activity, possibly via exercise rehabilitation, is beneficial.

(2) Routine influenza and pneumococcal vaccinations are recommended.

(3) Contraception should be discussed with females of child-bearing age, as pregnancy carries a 30% to 50% mortality risk and is contraindicated.

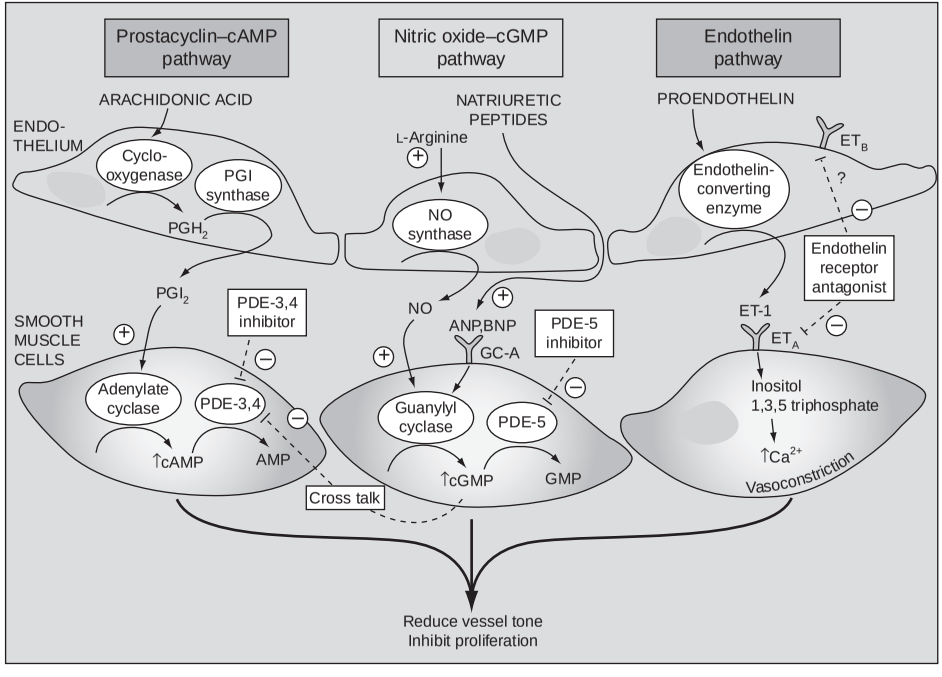

FIGURE 14.2 Therapeutic targets in pulmonary hypertension. cAMP, cyclin adenosine monophosphate; cGMP, cyclin guanosine monophosphate; PGI_2, prostacyclin; PGH_2, prostaglandin H_2; PDE, phosphodiesterase; NO, nitric oxide; ET, endothelin. (Reprinted from Benza RL, Park MH, Keogh A, et al. Management of pulmonary arterial hypertension with a focus on combination therapies. *J Heart Lung Transplant*. 2007;26(5):437–446, with permission from Elsevier.)

(4) Oxygen supplementation is advised to maintain saturation above 90%.
(5) Exposure to high altitude should be avoided. If flying, supplemental oxygen should be used if the patient's preflight saturation is less than 92%.
(6) Diuretic therapy is indicated to manage RV failure with volume overload.
(7) Digoxin may be considered in the case of atrial tachyarrhythmias.
(8) Oral anticoagulation is recommended in CTEPH, in IPAH, and in advanced diseases (e.g., continuous i.v. therapy). In PAH, a low therapeutic value of international normalized ratio (between 1.5 and 2) is generally targeted; however, this has not been evaluated in a randomized controlled trial (RCT).

B. Pulmonary vasodilators. The initial treatment choice in PAH is guided by vasoreactivity testing. For the responders (about 10% to 15% of the IPAH population), CCBs are the first line of treatment. Careful reassessment for safety and efficacy is mandatory, because only half of these patients will prove to be long-term responders and many will need additional vasodilators. The current treatment algorithm for PAH as suggested by the 2009 ACCF/AHA expert consensus document is shown in Figure 14.3.

1. **Prostacyclin analogs:** Prostacyclin is a potent endogenous vasodilator and an inhibitor of platelet aggregation and also appears to have antiproliferative activity. This may explain why *epoprostenol* (Flolan) can be used to acutely lower PAPs (as used in vasoreactivity testing) as well as to achieve long-term hemodynamic improvement in patients with PH who are nonresponders. In RCTs, epoprostenol has been shown to improve the functional class, exercise tolerance, hemodynamics, and survival in patients with IPAH. Epoprostenol has to be administered in a continuous i.v. infusion, and early titration often results in unbearable side effects of nausea, headache, flushing, jaw and leg pain, and diarrhea. Adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis. *Treprostinil* (Remodulin) is another prostacyclin analog that can be administered by inhalation, orally, or via continuous subcutaneous pump. It has been shown to improve the exercise

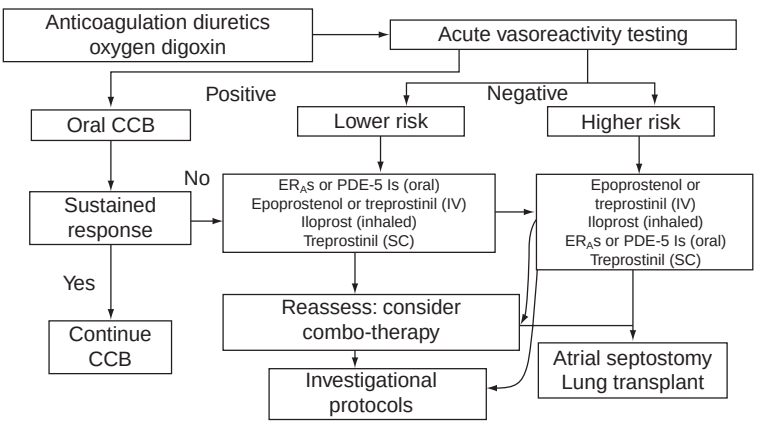

FIGURE 14.3 PAH treatment algorithm. CCB, calcium channel blocker; ERA, endothelin receptor antagonist; PDE-5 Is, phosphodiesterase type 5 inhibitors. (Reprinted from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. *J Am Coll Cardiol*. 2009;53(17):1573–619, with permission from Elsevier.)

capacity, hemodynamics, and symptoms. Infusion site pain is the most common side effect. *Iloprost* (Ventavis) is available as an aerosol administration and has a proven beneficial effect in patients with PAH and CTEPH.

2. **Endothelin receptor antagonists (ERAs):** *Bosentan* (Tracleer) is an oral active dual ET_A/ET_B receptor antagonist that has been shown to improve the exercise capacity, functional class, hemodynamics, and cardiac performance as measured by echocardiography and clinical outcomes. *Sitaxsentan* and *ambrisentan* are more selective ET_A receptor antagonists with similar benefits as bosentan. Liver injury and teratogenicity are major concerns and require monthly monitoring.
3. **PDE-5 inhibitors:** Orally active PDE-5 inhibitors prevent the degradation of cGMP, causing vasorelaxation. *Sildenafil* (Revatio) has favorable effects on exercise capacity, symptoms, and hemodynamics. Tadalafil (Adcirca) has the same effects, although it also delays the time to clinical worsening. Headache, flushing, dyspepsia, and epistaxis are the usual side effects.

In low-risk patients, oral therapy with ET receptor antagonists or PDE-5 inhibitors is the first choice, whereas i.v. epoprostenol is reserved for the high-risk population. Combination therapy is being routinely employed if treatment goals are not achieved with one compound ("goal-directed therapy"). The rationale is based on attacking different pathologic processes with different agents.

C. Treatment of non-group 1 PAH. Many pulmonary vasodilators have been evaluated for various non-PAH groups such as left-sided heart disease and lung disease. The following recommendations are based on current evidence:

1. **Group 2 PH (left-sided heart disease):** prostanoids and ERAs are associated with an increased event rate in patients with LV dysfunction and are contraindicated. There is some evidence of improvement in the quality of life, exercise performance, and hemodynamics with sildenafil in patients with left heart disease and in patients bridged to transplantation with a left ventricular assist device.
2. **Group 3 PH (lung disease of hypoxia):** pulmonary vasodilators are not recommended.
3. **Group 4 PH (CTEPH):** prostanoids, ERAs, or PDE-5 inhibitors may be used prior to surgery to improve hemodynamics. It may be used in patients with predominant peripheral disease or in those with persistent PH after surgery.

D. Surgical therapies. In CTEPH, surgery (pulmonary endarterectomy) is potentially curative in patients with accessible (proximal) disease. It is recommended that surgical evaluation and procedure be performed at high volume centers. Balloon atrial septostomy is rarely performed for palliation in patients with advanced PAH with recurrent syncope and/or right heart failure who have failed all available medical treatments. RV assist devices have emerged as a therapy in postoperative RV failure in the presence of PH. Heart–lung transplantation should be considered in a subset of eligible patients who remain in New York Heart Association functional class III or IV or in those who cannot achieve a significant exercise and hemodynamic improvement after 3 months of epoprostenol therapy.

VI. CONTROVERSIES.

Several controversies exist in the clinical and research arenas regarding PH, leading to frequent difference of opinions among referring internists, pulmonologists, and cardiologists. It is therefore important to identify such areas of concern. This may help target future research and identify these patients who would benefit from management at a specialized center where a multidisciplinary approach may be provided.

A. Most therapies (except epoprostenol) in PAH have not shown mortality benefits. Most therapeutic trials are small randomized clinical trials with soft end points such as 6MWT, exercise tolerance, and improvement in dyspnea scoring. While this raises

valid concerns regarding the long-term benefit of many expensive drugs, it is interesting that the overall survival in this patient population is improving.

B. Pulmonary vasodilators have generally been ineffective or harmful in patients with left-sided heart failure. However, PDE-5 inhibitors are an exception, as there have been multiple small studies that suggest improvement in exercise parameters and hemodynamics. One study, PhosphodiesteRasE-5 Inhibition to Improve CLinical Status And EXercise Capacity in Diastolic Heart Failure Study (RELAX), is currently enrolling participants to study the effect of sildenafil in patients with diastolic heart failure.

C. In "out-of-proportion" PH, many patients with left-sided heart failure may have only modest increase in PCWP (< 22 to 25 mm Hg) but very high PAP (systolic PAP > 60 mm Hg) with high TPG (> 18 mm Hg). This usually happens in patients who have developed a "fixed" PH, as opposed to a very few who have both left-sided heart failure and PAH.

D. Pulmonary vasoreactivity is often used in heart transplant candidates with "out-of-proportion" PH by administering sodium nitroprusside or nitroglycerin in the cardiac catheterization laboratory and assessing hemodynamics with reduction in PCWP. Those who have reduction in PAP and TPG may be able to undergo transplantation without right heart failure.

E. The treatment for "out-of-proportion" PH is primarily focused on treating the underlying left-sided failure.

VII. PROGNOSIS AND FOLLOW-UP

A. Prognosis. Survival in patients with PH differs between PH groups and also within each group depending on the etiology. For example, the prognosis in patients with severe aortic stenosis with PH will be different from that of patients with diastolic heart failure and PH. Similarly, it is quite different between idiopathic and scleroderma-related PH. Evaluating disease severity and predicting survival is important because it may guide clinical management. Best data regarding prognosis are available for the IPAH subset population. The natural history of this group shows survival rates of 68%, 48%, and 34% after 1, 3, and 5 years, respectively. There is registry level evidence that prognosis has improved with pulmonary vasodilator therapies. Table 14.3 outlines clinical, echocardiographic, and hemodynamic features that may

TABLE 14.3 Prognostic Variables in Pulmonary Hypertension

Lower	Determinants of risk	Higher
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO class	IV
Longer (> 400 m)	6-Min walk distance	Shorter (< 300 m)
Minimally elevated	BNP	Very elevated
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion Significant RV dysfunction
Normal/near-normal RAP and CI	Hemodynamics	High RAP, low CI

RV, right ventricular; BNP, brain natriuretic peptide; RAP, right atrial pressure; CI, cardiac index.

Adapted from McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension*: ACCP evidence-based clinical practice guidelines *Chest*. 2004;126:78s–92s.

predict the prognosis in patients with PAH. Again, these data are mainly derived from the IPAH population, and it is unknown whether these data are transferable to other P(A)H populations.

B. Follow-up

1. **Frequency**: Longitudinal follow-up of patients with PAH should be done at a center that specializes in PAH management with a sizeable patient population. Such centers have nurses, physicians, and ancillary support who are experienced in managing the disease and its complications. The frequency of follow-up depends on the clinical course. Those who have stable clinical course (i.e., with no evidence of heart failure, normal RV size/function, functional class I–II, 6MWT > 400 m, normal/near-normal hemodynamics, and stable BNP levels, and those maintained on oral therapy) should have clinical visits every 3 to 6 months. Unstable patients—those with sign of right heart failure, 6MWT < 300 m, abnormal hemodynamics, increasing BNP, and on i.v. therapy or combination therapy—should be evaluated every 1 to 3 months.
2. **Routine evaluation:** Assessment at each visit should include physical examination, assessment of functional class, 6MWT at each visit, and echocardiogram at 6 to 12 months, and blood work including biomarkers are usually performed at each visit or with change in clinical status or therapy; RHC is performed every 6 to 12 months in unstable patients and in stable patients it is performed when there is clinical deterioration or change in therapy.

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