Heart failure (HF) is a debilitating cardiac syndrome characterized by dyspnea, poor exercise tolerance, and chronic fatigue along with high morbidity and mortality. Heart failure may be defined as the pathophysiologic state in which the heart is incapable of pumping a sufficient supply of blood to meet the metabolic requirements of the body or requires elevated ventricular filling pressures to accomplish this goal. The caveat about high filling pressures acknowledges that a failing heart may continue to maintain systemic perfusion via the compensatory Frank-Starling mechanism, resulting in the maintenance of normal stroke volume (SV) despite reduced ejection fraction (EF). Conversely, low filling pressure with hypoperfusion indicates a pump-priming problem distinct from cardiac disease. The American Heart Association (AHA) and American College of Cardiology (ACC) guidelines define HF related to systolic dysfunction as a left ventricular (LV) ejection fraction (LVEF) less than 40%. Diastolic dysfunction, a pathologic condition involving failure of ventricular relaxation with consequent high filling pressures, may exist in up to half of older individuals with HF.

HF is a progressive and multifaceted disease that begins long before symptoms and signs are evident. A complex neurohormonal regulatory relationship exists between the heart and multiple organ systems. Feedback loops mediated through a variety of vasoactive substances secreted by the heart, autonomic nervous system, kidneys, adrenals, lungs, and vascular endothelium are most important. Perturbations of function in any of these organs affect the others (Fig. 81-1). Accordingly, the cardiovascular system should be viewed as a dynamic one, continually adapting to optimize organ perfusion. Dysfunction of the heart or any component of the cardiopulmonary system initiates adaptive neurohormonal activation of the sympathethic nervous system, renin-angiotensin-aldosterone system (RAAS), natriuretic peptides, endothelin (ET), vasopressin, and other regulatory mechanisms. Neurohormonal activation initially compensates for circulatory system dysfunction. These mechanisms eventually lead to increased mechanical stress on the failing heart, however, causing maladaptive electrical and structural events, progressive cardiac fibrosis and apoptosis, and further impairment of systolic and diastolic function. This creates a vicious cycle of increasing myocardial dysfunction causing further neurohormonal modulation, leading to a progressive downward spiral. The degree of myocardial dysfunction depends on both the amount of primary myocardial disease and other pathologic conditions, particularly in the pulmonary, renal, and peripheral vascular systems. Understanding these underlying compensatory mechanisms is leading to progressive improvement in the management of HF, with a shift from a hemodynamic to a neurohormonal model.

**Epidemiology**

HF represents the only significant cardiovascular disease that is increasing in prevalence in our society. It is a common cause of poor quality of life and premature death. About 5,800,000 individuals (approximately 2% of the population) in the United States in 2009 had HF, and almost 550,000 new cases are diagnosed annually. The incidence approaches 10 per 1000 in people older than 65 years. Decompensated HF is the most common reason for hospital admission in this age group and also for readmission within 60 days of discharge. The ED is the main portal of entry for acute HF patients, with admission rate approximately 80%. HF results in an annual estimated health care cost of about $40 billion. It is also responsible for high rates of outpatient visits, hospitalizations, and readmissions. The aging population, coupled with improvements in the medical therapy of HF, will result in increased prevalence of this disease.

HF carries approximately a 50% mortality at 5 years after symptom onset, and one third of patients with the most severe disease die within the first year after diagnosis. Females have a survival advantage over males. Progressive hemodynamic deterioration accounts for approximately 50% of deaths, but sudden death resulting from malignant ventricular dysrhythmias occurs in up to half. Multiple medical therapies decrease the death rate by improving functional status and slowing progression of pump dysfunction.

The prognosis in HF is related to a number of factors, including age, LV EF, exercise tolerance, plasma norepinephrine and B-type natriuretic peptide (BNP) levels, cardiothoracic ratio on chest radiograph, resting heart rate (HR),  electrocardiogram (ECG) evidence of left ventricular hypertrophy, atrial fibrillation (AF), or presence of ventricular dysrhythmias, hemoglobin A 1c level, and renal function. One third to one half of patients with HF have some degree of renal insufficiency, which is one of the strongest predictors of mortality in patients with HF. HF disproportionately affects black compared with white Americans, and they have a higher mortality.

**Cellular Mechanisms**

The heart is composed of a mass of individual striated muscle cells (myocytes) that form a branching syncytium. Each myocyte contains an intracellular tubular system termed the sarcoplasmic reticulum, and numerous cross-banded strands termed myofibrils that traverse the length of the myocyte. Myofibrils, in turn, contain multiple subunits called sarcomeres, which form the basic functional unit of myocardial contraction. Sarcomeres occupy...
CARDIAC PHYSIOLOGY

The normal cardiac index is 2.5 to 4.0 L/min/m² at rest. It is determined by contractility, preload, afterload, and HR. In normal hearts, the collective force of contraction of the cardiac chamber is the sum of forces generated by individual myocytes. Myocyte force is in turn a function of the ability of contractile proteins to generate power (inotropic state or contractility) as well as degree of sarcomere stretch at the start of contraction (preload). Stretching the sarcomere progressively toward its optimal length of 2.2 µm increases the force of contraction by allowing the maximum number of actin-myosin myofilament interactions. This forms the basis of the Frank-Starling relation, which states that within physiologic limits, force of ventricular contraction is directly related to end-diastolic length of the myofibril. Contractility may be affected by a host of factors. Multiple physiologic depressants (e.g., hypoxia, hypercarbia, acidosis, ischemia) and pharmacologic depressants (e.g., antidysrhythmic agents, calcium channel blockers, beta-blockers, alcohol) decrease myocardial contractility. Correcting physiologic myocardial depressant factors and discontinuing unnecessary medications with negative inotropic properties are important first steps in managing HF. Inotropic agents enhance contractility and may improve hemodynamics both acutely, such as with catecholamines, and chronically, as with cardiac glycosides.

**Preload** is the amount of force stretching the myofibril before contraction. In the intact ventricle, preload is produced by venous return.
return into the chamber, resulting in stretch of the myofibrils constituting the chamber walls. The volume filling the chamber also results in development of pressure that can be measured in either ventricle. The pressure measured within a chamber is determined by both the volume stretching the chamber wall and compliance characteristics of the muscle. For this reason, ventricular pressure is only an indirect reflection of preload. Changes in compliance may occur acutely with ischemia or chronically with hypertension and may substantially alter the relationship between chamber volume, pressure, and preload (Fig. 81-2).

Optimal preload is the filling pressure that stretches ventricular myofibrils maximally and leads to greatest stroke output per contraction. The actual optimal preload is unique for each patient because it is affected by LV loading conditions and compliance characteristics. For example, patients with acute myocardial infarction (AMI) tend to have a stiffer, less compliant left ventricle. In these patients, optimal LV pressure ranges are higher. Despite the inotropic state of the ventricle, optimizing preload results in the maximum stroke output for that ventricle (Fig. 81-3). Ventricles with normal compliance accommodate larger volumes before the chamber pressure rises. Accordingly, if pressure is used to estimate preload, the normal ventricle has more dramatic increases in stroke output for similar increases in filling pressure (steeper Starling curve). The risk of pulmonary edema increases when LV end-diastolic pressure rises significantly above normal ranges (6-12 mm Hg). In patients with low colloid osmotic pressures secondary to hypoalbuminemia, pulmonary edema may occur at even lower filling pressures.

Afterload, for clinical purposes, can be thought of as the pressure against which the heart must pump to eject blood. Blood pressure (BP) is determined by the product of cardiac output (CO) and systemic vascular resistance (SVR) (BP = CO × SVR). Hypertension is a major contributor to HF in about 75% of cases. Patients with HF and low CO tend to maintain BP through peripheral vasoconstriction mediated mainly by endogenous catecholamines and the RAAS. Afterload represents the mural tension on myocardial cells during contraction and is determined by the total peripheral vascular resistance and the cardiac chamber size. The peripheral resistance is affected by the total cross-sectional area of the circulation, the blood viscosity, and other factors. The arterioles are the major resistance vessels in the circulation. Flow is directly proportional to the fourth power of the vessel radius (Poiseuille’s law). The larger the ventricular cavity, the more mural tension and thus myocardial work is required during contraction (law of Laplace).

Failing ventricles have difficulty overcoming increases in peripheral resistance, instead dilating further, increasing end-diastolic volume to maintain SV, even with decreasing EF (preload reserve). Failing hearts are therefore extremely afterload sensitive, and modest vasodilation can dramatically increase CO, particularly in those most compromised (Fig. 81-4). Afterload reduction may be beneficial because it allows conversion of pressure work into flow work. When BP is decreased, CO increases as long as preload is maintained. Because flow work is proportionally less oxygen demanding, afterload reduction therapy has the additional benefit of decreasing myocardial oxygen demand.

HR and rhythmic contraction are important determinants of optimal CO (CO = HR × SV). As HR increases to the range of 150 to 160 beats/min in the adult, CO increases progressively. Tachycardia above this level compromises diastolic filling time and may lead to decreased CO. Coronary perfusion, which occurs only during diastole, also becomes impaired by severe tachycardia. SV is maximized when atrial contraction “primes” the ventricular pumps before they contract. Therefore any derangement of intracardiac conduction or dysrhythmia can reduce SV. Loss of atrial priming (e.g., in AF) can lead to marked deterioration in CO,
especially in diseased, stiffer hearts that require high filling pressures to optimize preload. Synchronized contraction of myocardial tissue and chambers is now a focus of therapeutic intervention.

**PRIMARY DISEASE PROCESSES RESULTING IN HEART FAILURE**

HF can result from primary disease of coronary arteries, myocardium, cardiac valves, pericardium, peripheral vessels, or lungs. Frequently the cause is multifactorial. Often, determination of the causes of HF is simpler early in its course than during later stages.

**Coronary Artery Disease**

In developed countries, atherosclerotic coronary artery disease remains the leading cause of HF, present in almost 70% of patients in multicenter HF trials. Acute coronary thrombosis leads to focal myocardial necrosis, with resultant fibrosis and scarring. This process leads to areas of dyskinesis that result in decreased EF. Aneurysmal dilation of infarcted areas with paradoxical motion during systole may disproportionately decrease EF. When approximately 40% of the LV muscle mass is acutely infarcted, cardiogenic shock ensues. Transient loss of contractile function may result from episodes of myocardial ischemia that do not cause frank necrosis, or from an ischemic zone surrounding the infarct. This “myocardial stunning” may persist for several days. Owing to improved treatment of acute coronary syndromes, the rates of secondary death and HF are decreasing.

Chronic coronary insufficiency leads to a more diffuse myocardial fibrosis termed ischemic cardiomyopathy. Revascularization of ischemic but not infarcted myocardial tissue provides a survival benefit in patients with HF related to ischemic LV systolic dysfunction. Diseases affecting the coronary microcirculation, such as vaso-occlusive sickle cell anemia and diabetes mellitus, result in similar pathology. Compensatory mechanisms may occur after large MI and progressive cardiac disease, which are collectively termed ventricular remodeling. They include cardiac dilation, reactive hypertrophy, progressive fibrosis, and changes in wall conformation. These may result from elevated chamber filling pressures as well as neurohumoral adaptive responses.

**Cardiomyopathy and Myocarditis**

Cardiomyopathies are a group of disease processes that primarily affect myocardium. Myocardial diseases resulting from coronary, valvular, and pericardial pathologies are excluded. Cardiomyopathy is categorized as primary if cause is unknown, or secondary if some cause is identified. Clinically, patients with cardiomyopathy tend to have three forms—dilated, hypertrophic, or restrictive—each associated with HF. Dilated cardiomyopathy is much more common than the other two and is the second most common cause of HF. The specific cardiomyopathies and myocarditis, which may also cause HF, are discussed in Chapter 82.

**Valvular Heart Disease**

Cardiac valvular disease is the third leading cause of HF, after ischemic heart disease and dilated cardiomyopathy. Most acute valvular dysfunction involves either the mitral or the aortic valve, and usually results in severe regurgitation. Acutely stenotic lesions are predominantly restricted to mechanical catastrophes of prosthetic valves. These patients may be in extremis with fulminant pulmonary edema. Valvular disease is discussed in Chapter 83.

Mitrval insufficiency and aortic stenosis are most commonly associated with chronic HF. Knowledge of the precise valvular pathology may have important implications for emergent HF therapy. For example, patients with decompensated aortic stenosis should generally not receive vasodilator agents, as flow cannot increase across a fixed obstruction. These patients may become hypotensive owing to reduced preload, with resultant decreased systemic and coronary perfusion. On the other hand, patients with mitral regurgitation benefit greatly from vasodilators, which improve antegrade flow by reducing afterload.

**Pericardial Diseases**

Pericardial diseases may significantly affect ventricular function, decreasing CO and increasing intracardiac pressures. In particular, cardiac tamponade may cause dyspnea and hypoperfusion not easily clinically distinguished from HF. ED use of bedside ultrasound has great usefulness in rapidly identifying this problem. Pericardial diseases are fully discussed in Chapter 82.

**Pulmonary Disease**

Chronic obstructive pulmonary disease (COPD), which has a prevalence of 20 to 30% in HF, may obscure recognition of HF. Pulmonary dysfunction reduces myocardial oxygen supply while CO must be increased because tissue is being perfused with suboptimally oxygenated blood. Hypoxia leads to pulmonary arteriolar vasoconstriction, reducing lung vascular bed area and elevating pulmonary artery pressures. Chronic increases in pulmonary arterial pressure lead to right ventricular (RV) hypertrophy and dilation. When compensatory mechanisms fail, the patient develops right-sided HF (cor pulmonale), usually with LV output preserved, at least at rest. Causes of acute cor pulmonale, such as a large pulmonary embolus, may precipitate sudden systemic hypotension and death, partly because of decreased LV priming.

Distinguishing primary pulmonary disease causing predominantly right-sided HF from LV failure with secondary right-sided dysfunction is clinically challenging. Wheezing or rhonchi may be seen in both entities. The chest radiograph may be difficult to interpret because both presentations cause interstitial changes. Hyperinflation depresses the diaphragm, which elongates the cardiac silhouette and may mask cardiomegaly. Competition for intrathoracic space reduces lung capacity in patients with chronic HF. Natriuretic peptide levels are only slightly elevated in primary pulmonary disease compared with much higher levels in LV failure.

**COMPENSATORY MECHANISMS IN HEART FAILURE**

**Physiologic Mechanisms**

**Increase in Stroke Volume**

Increased SV occurs in response to increase in preload (Frank-Starling mechanism). This compensatory mechanism is immediate and effective in improving CO in response to acute systemic demands. It is a limited response, however, because myofibril stretch to a sarcomere length beyond 2.2 µm does not further increase and may actually reduce stroke output. Also, this mechanism greatly increases myocardial oxygen demand, which may lead to dysfunction in the setting of significant coronary artery disease.

**Increased Systemic Vascular Resistance**

Increased SVR results in redistribution of a subnormal CO away from skin, skeletal muscles, and kidneys to maintain normal
and oxygen consumption of the failing ventricle and are counter-rodohormonal mechanisms also increase the hemodynamic burden greatly increases myocardial work. 

Elevated vasopressin levels in HF increase volume overload while from the pituitary gland in response to decreases in perfusion. Metabolic receptors in muscles also exert changes in perfusion. Metabolic receptors also exist on endothelial cells, vascular smooth muscle cells, and renal epithelial cells and in the myocardium. Natriuretic peptides promote water and sodium excretion, increase peripheral vasodilation, and inhibit the RAAS. In early HF they play a key role in compensation for LV dysfunction. Attenuation of renal response to natriuretic peptides occurs as HF progresses.

Neurohormonal Modulation

Neurohormonal mechanisms maintain BP and vital organ perfusion and are activated by LV dysfunction. Regrettably, these neurohormonal mechanisms also increase the hemodynamic burden and oxygen consumption of the failing ventricle and are counter-productive on a chronic basis.

Cardiac Neurohormonal Response

Increases in myocardial wall stretch activate release of cardiac natriuretic peptides, which are structurally related proteins important in volume and sodium homeostasis. They include atrial, brain (BNP), and C-type natriuretic peptide. All are elevated in patients with LV dysfunction and HF. A variety of natriuretic peptide receptors exist on endothelial cells, vascular smooth muscle cells, and renal epithelial cells and in the myocardium. Natriuretic peptides promote water and sodium excretion, increase peripheral vasodilation, and inhibit the RAAS. In early HF they play a key role in compensation for LV dysfunction. Attenuation of renal response to natriuretic peptides occurs as HF progresses.

Central and Autonomic Nervous System Neurohormonal Response

The heart and great vessels contain sensory receptors that detect changes in perfusion. Metabolic receptors in muscles also exert inhibitory and excitatory influences on brainstem vasomotor neurons. Arginine vasopressin (antidiuretic hormone) is released from the pituitary gland in response to decreases in perfusion. Elevated vasopressin levels in HF increase volume overload while decreasing osmolality. This adversely affects hemodynamics and cardiac remodeling while potentiating effects of angiotensin II and norepinephrine. HF results in a generalized stimulation of sympathetic activity and inhibition of parasympathetic tone. Increased sympathetic outflow results in release of epinephrine and norepinephrine from the adrenal glands and norepinephrine at peripheral sympathetic nerve endings. These elevated catecholamine levels stimulate surface receptors in the heart and blood vessels, increasing cardiac contractility, HR, and vascular tone. The resulting increased vascular tone augments preload through venous contraction as well as afterload by arterial vasoconstriction. Acutely, arterial BP is improved and CO increased by catecholamines. Chronically, a decrease in the number and affinity of surface catecholamine receptors occurs in myocardial tissue, reducing responsiveness to epinephrine and norepinephrine. Elevated catecholamines adversely affect myocardial perfusion, leading to progressive apoposis and cardiac fibrosis.

Renal Neurohormonal Response

Decreased glomerular perfusion results in reduced renal excretion of sodium. Renal arteriolar and adrenergic receptors stimulate renin release by the juxtaglomerular apparatus. Renin facilitates the conversion of angiotensinogen to angiotensin I, which is further converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor and an important stimulus for aldosterone release by the adrenal cortex. Aldosterone increases renal sodium retention and potassium excretion. Renal adaptation to hypoperfusion occurs mainly through production of vasodilatory hormones such as prostacyclin, along with prostaglandins PGI2 and PGE2. Aspirin and other nonsteroidal anti-inflammatorv drugs (NSAIDs) interfere with prostaglandin synthesis by inhibiting cyclooxygenase. Therefore, except for the useful antiplatelet effect of aspirin, NSAIDs optimally should be avoided in patients with chronic HF because they may contribute to acute renal insufficiency with concomitant salt and water retention.

Vascular Endothelial Neurohormonal Response

Endothelial function locally regulates vasomotor tone. A family of ETs is produced by endothelial and smooth muscle cells as well as neural, renal, pulmonary, and inflammatory cells. This occurs in response to hemodynamic stress, hypoxia, catecholamines, angiotensin II, and many inflammatory cytokines. ET-1 is the most important ET and the most potent vasoconstrictor known. It exerts its main vascular effects, vasoconstriction and cell proliferation, through specific ETα and ETβ receptors on vascular smooth muscle cells. ETα receptor activation causes vasoconstriction, whereas ETβ receptor stimulation increases prostacyclin and nitric oxide (NO) release, causing vasodilatation. ET-1 plasma levels are elevated in HF, correlate with symptoms as well as hemodynamic stress, and are associated with adverse prognosis.

NO is produced in almost all tissues and plays a critical role in the homeostasis of cardiac function. NO exerts its biologic signaling through production of cyclic guanosine monophosphate (cGMP), which is broken down by cyclic nucleotide phosphodiesterases (PDEs). Reduced synthesis or increased degradation of NO at the endothelial level is detrimental in HF. NO-mediated endothelial dysfunction may represent the earliest stage of target organ damage, which ultimately leads to hypertensive heart disease and HF.

CLASSIFICATION OF HEART FAILURE

Many different methods of classifying HF exist, including acute versus chronic, systolic versus diastolic, right sided versus left sided, and high output versus low output. Early in HF, these may be useful clinical descriptors suggesting particular causes and treatment strategies. Late in the disease process, these distinctions blur.
Acute versus Chronic Heart Failure

The prototypical case of acute HF involves a healthy person who develops a large myocardial infarction (MI) or acute valvular dysfunction. Chronic HF is best characterized by a disease state such as dilated cardiomyopathy, with gradual deterioration of cardiac function. In acute HF, early presentation may be a result of systolic dysfunction and hypoperfusion, often with acute pulmonary edema (APE) resulting from sudden reduction in chamber compliance. Chronic HF usually arises with symptoms related to fluid retention, with compensatory mechanisms adjusted so that normal perfusion exists, at least in the resting state. In clinical practice, approximately 80% of HF cases seen the ED involve acute decompensation of chronic heart disease.42

Systolic versus Diastolic Dysfunction

Systolic dysfunction refers to impairment of contractility, with stroke output reduced and forward flow compromised. Systolic dysfunction is typically caused by myocyte damage such as in MI or myocarditis. Asymptomatic LV systolic dysfunction in patients 45 years of age or older has an estimated prevalence of 6% and is much more common than symptomatic systolic HF.43,44 Most cases of systolic dysfunction also involve some degree of diastolic dysfunction.

Diastolic dysfunction indicates a primary problem with ability of the ventricles to relax and fill normally.45 In many cases, normal or even supernormal systolic function is preserved. Echocardiographic and nuclear imaging techniques demonstrate that 40 to 50% of patients with congestive symptoms have normal EFs and experience diastolic dysfunction, also termed heart failure with normal ejection fraction.46 The proportion of HF that is primarily diastolic increases with age, from about 45% in patients younger than 45 years to almost 60% in patients older than 85 years. Asymptomatic diastolic dysfunction is much more common than asymptomatic systolic dysfunction. Diastolic dysfunction is the predominant pathophysiology in hypertrophic and restrictive cardiomyopathies, valvular aortic stenosis, and, most important, hypertension.

Diastolic dysfunction occurs predominantly as a result of one of three mechanisms: impaired ventricular relaxation, increased ventricular wall thickness, or accumulation of myocardial interstitial collagen. Impaired lusitropic capacity of the myocardium leads to higher ventricular filling pressure, resulting in congestive symptoms. Myocardial relaxation is an active, energy-requiring process. Failure of myocytes to relax may be secondary to low intracellular energy stores. Physiologic stresses causing increased cardiac demands can precipitate lusitropic abnormalities. In chronic renal disease, mortality is higher in diastolic than systolic HF.47 In addition, systolic contractile dyssynchrony occurs in one third of diastolic HF patients, whereas diastolic dysynchrony is present in more than half, with therapeutic implications.48,49

As with the other classification schemes, most patients with HF have components of both systolic and diastolic dysfunction, with the predominant type allowing specific treatment strategies. For example, patients with predominantly diastolic dysfunction have the advantage of intact myocardial contractile function. Stiffer hearts, however, have steep pressure-volume curves. Therefore small reductions in diastolic filling volume, as may occur with aggressive vasodilator or diuretic therapy, may markedly decrease ventricular filling and compromise stroke output (see Fig. 81-3).

Right-Sided versus Left-Sided Heart Failure

The notion that one cardiac chamber can fail independently of the others is somewhat artificial. The right and left circulations are connected and, over time, output from the two sides must be equal. Furthermore, the right and left ventricles share an interventricular septum, and dysfunction in one chamber may have an immediate impact on the other. For example, acute right-sided HF from pulmonary hypertension secondary to acute respiratory failure causes bulging of the interventricular septum into the LV chamber. This so-called “septal shift” results in decreased LV preload and low CO that is volume responsive. Chronic left-sided HF leads to pulmonary hypertension with resultant right-sided HF. In addition, cardiac biochemical changes such as an abnormal catecholamine response affect all chambers.

Nonetheless, the terms have usefulness in identifying the predominant clinical presentation. Fluid accumulation “behind” the involved ventricle is responsible for many of the clinical manifestations of HF. For example, LV failure leads primarily to pulmonary congestion with symptoms mostly of dyspnea and orthopnea. Patients with right-sided HF have symptoms of systemic venous congestion, such as pedal edema and hepatomegaly.

When previously healthy patients have acute pathology, the concept of left- versus right-sided HF may be clinically useful. Patients with acute MI may have APE; yet unlike patients with chronic HF, they may not have jugular venous distention or pedal edema because central venous pressure may remain within normal limits. A chest radiograph reveals evidence of pulmonary venous congestion, interstitial edema, and, in fulminant cases, alveolar edema. Because there has not yet been time for cardiac dilation, the cardiac shadow is often of normal size.

Acute RV infarction is an important cause of hypoperfusion with jugular venous distention and absent pulmonary congestion. There is often evidence of ST segment elevation or depression in the V1 lead, and right-sided leads may provide further evidence of RV infarction. Approximately one third of patients with acute inferior infarction have significant RV involvement, leading to inadequate pulmonary perfusion and low LV priming (decreased preload). These patients have right-sided HF with hypotension that is often symptomatic. Aggressive crystalloid resuscitation, followed by inotropic support with norepinephrine, may be required for adequate LV preload and restoration of BP.

High-Output versus Low-Output Failure

High-output failure refers to a hyperdynamic state with supranormal CO and low arteriovenous oxygen difference (decreased oxygen extraction ratio). The hyperdynamic state may result from increased preload (e.g., renal retention of salt and water, or excess mineralocorticoids), decreased SVR (e.g., arteriovenous fistulas, pregnancy, cirrhosis, severe anemia, beriberi, thyrotoxicosis, Paget’s disease, or vasodilator medications), increased beta-sympathetic activity, or persistent tachycardia. A persistent hyperdynamic state results in myocardial damage over time. Early recognition of the hyperdynamic state may allow effective therapy of the underlying condition, thus avoiding development of HF. As the condition progresses, myocardial dysfunction with circulatory overload is superimposed on this background, and symptoms progress. At some point, CO becomes normal or even low, indistinguishable from classic HF.

Low-output failure is the more typical variety of HF and occurs as a result of entities such as ischemic heart disease, dilated cardiomyopathy, valvular disease, and chronic hypertension. Low CO (systolic dysfunction), high filling pressures (diastolic dysfunction), and an increased systemic oxygen extraction ratio (widened arteriovenous oxygen difference) characterize this more commonly encountered form of HF.
CLINICAL EVALUATION OF PATIENTS WITH SUSPECTED HEART FAILURE

Precipitating Causes of Heart Failure and Exacerbating Factors

When cardiac decompensation occurs because of an acute precipitating cause, intervention can focus on the precipitating factor(s), and the prognosis is much better than when there is simply progression of intrinsic cardiac failure. Causes of acute cardiac decompensation are provided in Box 81-1.

Iatrogenic causes of HF should also be considered, especially in patients who have recently received intravenous fluids. Patients with known renal insufficiency most often experience pulmonary edema as a consequence of salt and fluid overload, as well as missed dialysis. In chronic HF, the most common cause of decompensation is inappropriate decrease in intensity of treatment, including drug therapy, dietary sodium restriction, limited physical activity, or a combination of these measures.

Sodium and Volume Excesses

Increased sodium ingestion, most often a result of dietary noncompliance, or plasma volume expansion by excessive crystalloid infusion or transfusion, may prompt cardiac decompensation. Noncompliance with renal dialysis, in particular, is a very common cause of HF in patients who come to the ED.

Systemic Hypertension

Sudden elevation of arterial pressure acutely increases afterload, which may precipitate rapid onset of HF. This is particularly common when antihypertensive therapy is abruptly discontinued. Pheochromocytoma and other states associated with high sympathetic outflow may be implicated. Cocaine and other sympathomimetic drugs of abuse frequently precipitate HF. Emotional upset can dramatically increase afterload as well as precipitate coronary vasospasm, with the extreme example being acute stress cardiomyopathy (Takotsubo syndrome; see Chapter 78).

Myocardial Infarction and Ischemia

A new ischemic event may precipitate HF by impairing contractility and decreasing LV compliance. Pulmonary edema may occur rapidly in this setting, especially when large areas of myocardium are involved. In the compromised heart, even local ischemia may precipitate HF. Occult acute coronary syndrome is common, particularly in the elderly, and should be considered in any HF exacerbation. The presence of HF on admission in patients with acute coronary syndromes is associated with increased short- and long-term rates of death and MI.52-54

Systemic Infection

Infection results in increased systemic metabolic demands. The sepsis syndrome is associated with a reversible form of myocardial depression, mediated by various cytokines, including interleukin (IL)-1, IL-2, and IL-6, as well as tumor necrosis factor.55 Proinflammatory cytokines such as tumor necrosis factor alpha and IL-6 also play an important pathogenic role in chronic HF.56

Dysrhythmia

Both tachydysrhythmias and bradydysrhythmias can severely affect CO, especially when acute. Tachydysrhythmias compromise diastolic filling time, reduce CO, and impair coronary perfusion as well as myocardial oxygen delivery. The tachycardia also results in increased myocardial oxygen demand. These factors may precipitate ischemia, which may further impair contractility and exacerbate HF.

The prevalence of AF in patients with HF increases from less than 10% in New York Heart Association (NYHA) functional class I to approximately 50% in NYHA functional class IV.57 Neurohumoral alterations, electrophysiologic changes, and mechanical factors create an environment in which HF predisposes to AF and AF exacerbates HF. New-onset AF or other dysrhythmias that affect coordinated atrial priming of the ventricular pump may seriously reduce preload, especially in disease states with reduced ventricular compliance. Significant bradydysrhythmias may also reduce CO simply by reducing the number of systolic ejections per minute (CO = SV × HR).

Acute Hypoxia and Respiratory Problems

Both COPD exacerbations and respiratory tract infections are very important precipitating factors for HF exacerbation.58 Pulmonary infection, which is more common in patients with pulmonary vascular congestion, may add hypoxia to the metabolic stressors of fever, tachycardia, and increased tissue perfusion requirements.

Anemia

With chronic anemia, oxygen delivery to tissues is maintained by increased CO (isovolumic hemodilution). Anemia increases in prevalence with increasing severity of HF, especially with declining renal function and increasing age. Anemia is associated with poorer survival in HF59-61 with greater disease severity, greater LV mass index, and higher hospitalization rates. Abrupt exacerbations of anemia increase systemic perfusion demands and, especially if coupled with reduced coronary oxygen delivery, may prompt onset or exacerbation of HF.

Pregnancy

CO is normally increased significantly during pregnancy, which may lead to decompensation with underlying valvular disease or other cardiac pathology. Peripartum cardiomyopathy is a type of dilated cardiomyopathy that may occur late in pregnancy or more commonly in the early postpartum period.

Box 81-1 Common Precipitating Causes of Acute Heart Failure

- Sodium and volume excess
- Systemic hypertension
- Myocardial infarction or ischemia
- Systemic infection
- Dysrhythmias
- Acute hypoxia or respiratory problems
- Anemia
- Pregnancy
- Thyroid disorders
- Acute myocarditis
- Acute valvular dysfunction
- Pulmonary embolus
- Excess exertion or trauma
- Pharmacologic complications
Thyroid Disorders

HF may be a clinical manifestation in patients with previously compensated cardiac disease who develop hyperthyroidism. Hypothyroidism also adversely affects myocardial pump function. Restoration of normal thyroid function usually reverses the abnormal cardiovascular hemodynamics.\(^{62}\)

Acute Myocarditis

A variety of infectious and inflammatory diseases, including viral agents and acute rheumatic fever, may precipitiously impair myocardial contractility.

Acute Valvular Dysfunction

Almost all causes of acute HF resulting from cardiac valve dysfunction are secondary to aortic or mitral insufficiency. Mitral valve papillary muscle dysfunction or rupture may result from acute MI, whereas acute aortic insufficiency is more commonly precipitated by acute bacterial endocarditis or aortic dissection. Occasionally, acute valvular stenosis may occur, usually as a consequence of acute dysfunction of a prosthetic valve.

Pulmonary Embolus

The pulmonary hypertension and hypoxia that accompany pulmonary embolus may cause acute HF. Accordingly, this diagnosis should be entertained in patients who have unexplained HF and risk factors for pulmonary embolism.

Excessive Exertion or Trauma

Increased physical activity may lead to decompensation, particularly in patients with significant HF. Trauma and injury also increase demand on the heart.

Pharmacologic Complications

Beta-blocking and calcium channel blocking agents have negative inotropic effects and may precipitate overt HF with excessive administration. Many antidyshrhythmic agents have similar effects. Glucocorticoids, NSAIDs, vasodilator medications, and others may result in sodium retention with substantial increases in plasma volume that may precipitate HF.\(^{63}\) NSAIDs in particular interfere with prostaglandin synthesis through cyclooxygenase inhibition, thereby impairing renal homeostasis in patients with HF. They also interfere with the effects of diuretics and ACE inhibitors. Nonadherence to medication regimens for hypertension, HF, or ischemia is the most common pharmacologic cause of HF decompensation.

Evaluation of Heart Failure

The NYHA classification system is a time-honored categorization for patients with chronic HF based on degree of activity causing symptoms (Box 81-2).\(^{64}\) Careful consideration of the differential diagnosis of HF is symptom based. The most common manifestation of acute HF is respiratory distress caused by pulmonary edema. Therefore the differential diagnosis includes exacerbation of COPD or asthma, pulmonary embolus, pneumonia, anaphylaxis, and other causes of acute respiratory distress. Hypoperfusion may be caused by some of these as well as by sepsis syndrome, hypovolemia, hemorrhage, cardiac tamponade, and tension pneumothorax.

History

The presence and character of dyspnea, chest pain, previous heart disease, cardiac catheterization, surgery, current medications (and adherence), and possible intercurrent illness should be explored.

Paroxysmal nocturnal dyspnea results from pulmonary congestion precipitated by plasma volume expansion that occurs during recumbency as interstitial edema is reabsorbed into the circulation. Orthopnea occurs through the same mechanism, with the supine position causing rapid increases in diastolic filling pressure. Symptoms abate after the patient stands or props up the trunk and venous return decreases. Nocturia results from the same pathophyslogic process. Many historical features increase the likelihood of HF. Most predictive is a past history of HF or paroxysmal nocturnal dyspnea, and the absence of dyspnea on exertion reduces the likelihood of chronic HF.\(^{65}\)

Physical Examination

Most HF patients are hypertensive, which is prognostically preferable to normal or low BP. Clammy, vasoconstricted patients with a thready pulse and delayed capillary refill may have systemic hypoperfusion despite adequate BP, which is maintained by intense vasoconstriction. Noninvasive assessment of BP in the vasoconstricted patient with low CO can be inaccurate.\(^{66}\) If available, intra-arterial pressure monitoring may more accurately reflect the systemic hemodynamic state and guide the choice of inotropic or vasoconstrictor therapy in hypotensive HF patients.

Most patients with APE are diaphoretic because of intense sympathetic activation. Patients with pulmonary congestion secondary to HF develop interstitial and alveolar pulmonary edema, causing reduced pulmonary compliance and decreased functional residual capacity. Clinical findings include diffuse moist rales, which may be absent with decreased ventilation in more agonal patients. Peribronchial edema may cause wheezing or rhonchi, which can mimic bronchospastic disease (“cardiac asthma”). A positive response to bronchodilator therapy does not exclude HF. Jugular venous distention is present in approximately 50% of cases, and one third of these patients have peripheral edema. An S\(_3\) gallop may be present in up to 25% but is often difficult to hear.

These common clinical findings of chronic HF are prevalent among patients with APE because most patients have acute exacerbations superimposed on chronic underlying disease. Jugular venous distention, pedal edema, and cardiomegaly may be absent in previously healthy individuals with pulmonary edema resulting from an initial episode of acute HF. The presence of a third heart sound significantly increases the likelihood of HF, whereas absence of rales decreases the likelihood.\(^{67}\) Physical examination of patients with APE resulting from acute MI may identify surgically correctable lesions such as acute mitral regurgitation or ventricular septal defect.

Diagnostic Testing in Heart Failure

An upright chest radiograph helps distinguish cardiogenic pulmonary edema from other causes of dyspnea. An enlarged cardiac silhouette is seen in 70% of cases. A normal heart size suggests acute cardiogenic pulmonary edema in a patient without prior HF,

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**Box 81-2**  
**Classification System for Chronic Heart Failure:**  
**New York Heart Association Functional Classes**

I. Asymptomatic on ordinary physical activity  
II. Symptomatic on ordinary physical activity  
III. Symptomatic on less than ordinary physical activity  
IV. Symptomatic at rest
diastolic dysfunction, COPD, or noncardiogenic pulmonary edema. An early ECG for arrhythmia recognition and management is important, as well as for identification of acute coronary syndrome. Absence of cardiomegaly on chest radiography and a normal ECG greatly decrease the likelihood that HF is causing the presentation. Obtaining a complete blood count (CBC) to evaluate for anemia and a basic metabolic panel to determine electrolyte status as well as renal function is generally useful. Cardiac biomarkers help evaluate for ongoing myocardial injury, which may be clinically silent.

In most cases, and particularly when the diagnosis of HF is unclear, natriuretic peptide levels should be obtained. Pre-proBNP is synthesized in the ventricles in response to myocyte stretch, then released and enzymatically cleaved to NH₂-terminal–proBNP (NT-proBNP) and BNP. NT-proBNP and BNP levels help identify patients with HF and may improve management of patients in the ED with dyspnea. The “breathing not properly” BNP Multinational Study was a prospective evaluation of patients who came to the ED with acute dyspnea. BNP levels above 500 pg/mL were highly associated with HF (likelihood ratio [LR] 8.1), and levels of 100 to 500 pg/mL were generally indeterminate (LR = 1.8). A low BNP level (<100 pg/mL) indicated that HF was highly unlikely (LR = 0.13). ED use of BNP and NT-proBNP assays aids diagnosis of HF and can reduce admission rates and length of hospitalization in acute dyspnea.

Natriuretic peptide levels correlate with ventricular function, NYHA classification, and prognosis. Results of large clinical trials confirm that BNP levels are the strongest predictor of outcome in HF compared with other neurohormones and clinical markers. There is often a disconnect between the perceived severity of HF by clinicians and the degree of BNP elevation, yet BNP levels are better predictors of 90-day outcome than physician judgment. High predischARGE BNP and NT-proBNP levels are strong, independent predictors of death or rehospitalization after decompensated HF.

NT-proBNP– and BNP-guided therapy reduces all-cause mortality and provides a strong measure of therapeutic response in chronic HF compared with usual care. Mildly elevated BNP levels may also be seen in right-sided HF related to cor pulmonale or pulmonary embolism. BNP levels are only slightly elevated in patients with end-stage renal disease, and in this setting marked elevation reflects ventricular dysfunction. Admission BNP and troponin levels are independent predictors of in-hospital mortality in acute decompensated HF. Increased concentrations of these and other biochemical markers of myocyte injury in the absence of discrete ischemic events in HF help identify patients most likely to have adverse outcomes. Plasma levels of cardiac troponins in stable HF also predict adverse outcomes.

The ESCAPE trial demonstrates that pulmonary artery catheterization in severe symptomatic HF increases anticipated adverse effects but does not affect overall mortality or duration of hospitalization. Noninvasive impedance cardiography appears to be an effective and developing technology to measure CO and other hemodynamic variables in HF and may obviate the need for a pulmonary artery catheter, although it cannot reliably measure LV filling pressures.

Bedside ultrasound can be an important ED screening tool in HF, with attention to wall motion abnormalities, EF, and valvular function, as well as exclusion of cardiac tamponade. Echocardiography is similarly useful and can provide detailed measurements of LV function and determine structural heart disease. Multidetector computed tomography coronary angiography can distinguish ischemic from other forms of cardiomyopathy but is rarely useful in acute HF. Radionuclide imaging and cardiac magnetic resonance imaging have an expanding role in evaluating chronic HF but no utility in the acute setting.

**TREATMENT OF ACUTE HEART FAILURE**

Of patients with HF in the ED, about 20% are experiencing their first episode of HF, and 80% have had prior hospital visits for the same condition. The approach focuses on (1) determining underlying cardiac pathology, (2) identifying the acute precipitant, and (3) mitigating the acute decompensation. The immediate therapeutic goals are to improve respiratory gas exchange, maintain adequate arterial saturation, and decrease LV diastolic pressure while maintaining adequate cardiac and systemic perfusion.

The acute congestive state can be controlled by (1) reducing cardiac workload through decreased preload and afterload, (2) controlling excessive retention of salt and water, and (3) improving cardiac contractility. Patients may have a wide spectrum of symptoms and signs ranging from mild dyspnea on exertion to full-blown cardiogenic shock with hypotension and concomitant respiratory failure.

**Acute Heart Failure**

Pulmonary edema is classified clinically into cardiogenic and noncardiogenic forms. Most patients in the emergency setting with pulmonary edema have the acute cardiogenic variety, resulting mainly from elevated LV end-diastolic pressure, forcing a protein-sparse plasma ultrafiltrate across the pulmonary capillary membrane into the pulmonary interstitium. Large amounts of edema accumulate, leading to alveolar flooding. Volumes as large as 1 or 2 L may leave the plasma over a short time and create serious respiratory compromise. Most commonly, cardiogenic pulmonary edema occurs with acute myocardial ischemia or infarction, cardiomyopathy, valvular heart disease, or hypertensive emergencies.

Patients with acute cardiogenic pulmonary edema have substantially lower plasma volumes than control patients. These changes are reflected by initial hemococoncentration as evidenced by higher hematocrits and colloid osmotic pressures. Despite the presence of pulmonary congestion, concomitant hypotension may require fluid challenge to rapidly restore preload, CO, systemic perfusion, and BP. Thus careful volume infusion with aliquots of normal saline is appropriate initial resuscitation for the hypoperfusing patient with acute-onset cardiogenic pulmonary edema.

In contrast, noncardiogenic pulmonary edema generally results from an alteration in the permeability characteristics of the pulmonary capillary membrane. The alteration may have such diverse causes as septic shock, inhalation injuries, drugs or toxins, aspiration syndromes, fat emboli syndrome, neurogenic causes, and high altitude.

**Acute Heart Failure with Adequate Perfusion**

Many patients with acute HF demonstrate adequate systemic perfusion with elevated BP because of activation of various compensatory mechanisms. The ability of the left ventricle to generate normal or elevated systolic pressures indicates the presence of considerable myocardial reserve and is associated with lower mortality in both acute and chronic HF. These patients should be quickly distinguished from those with pulmonary edema and evidence of hypoperfusion. Hypertensive pulmonary edema is easier to manage because afterload reduction with vasodilators is extremely effective.

Therapeutic interventions should decrease both preload and afterload. Excessive preload reduction may result in an abrupt decrease in CO, however, which could cause hypotension. This occurs more readily in patients with less compliant hearts. Fluid
TREATMENT OF ACUTE HEART FAILURE

Supplement oxygen/ventilate to get $P_{O_2} \geq 90\%$, escalating through the following as necessary:

- Nasal cannula
- Face mask
- Noninvasive ventilation
- Endotracheal intubation

Adequate perfusion

1. Position sitting upright
2. Vasodilator agents
   - Nitroglycerin
     - Sublingual 0.4 mg q5min
     - Intravenous starting at 5-10 µg/min and rapidly titrating up to obtain goals
   - Morphine sulfate IV in 2-5 mg boluses titrated to effect
3. Loop diuretics
   - Furosemide 0.5-1 mg/kg IV
   - Bumetanide 0.5-2 mg IV

Immediate treatment goals

1. Dyspnea relief
2. Improvement in oxygenation with decreasing supplementation
3. Reduction of pulmonary edema
4. Restoration/maintenance of adequate perfusion
5. Management of precipitating factors

Hypoperfusion

(Consider arterial catheter to monitor true blood pressure)

1. Consider careful crystalloid boluses (e.g., 250 cc NS)
2. Inotropic therapy (titrate to lowest adequate BP)
   - Noradrenaline: Initial 8-12 µg/min (preferred)
   - Dopamine: Initial 0.5-2 µg/kg/min
   - Epinephrine: Initial 1-4 µg/min
   - Dobutamine: Initial 0.5-1 µg/kg/min

Other considerations

1. Dialysis if severe renal failure
2. Blood transfusion if severe anemia (Hgb < 8 g/dL)
3. Rapid coronary revascularization if acute STEMI
4. Rate/rhythm control if aberrant rhythm

Oxygen and Ventilation

All patients with significant pulmonary edema have hypoxemia and require high-flow oxygen by face mask if spontaneously breathing and if oxygen saturation as measured by pulse oximetry ($Sp_{O_2}$) is below 90%. Excessive oxygen therapy, however, may significantly increase afterload and worsen cardiac function in decompenated HF. The typical acid-base disturbance of acute HF is mixed. Patients with fulminant APE may have lactic acidosis, and many also have concomitant respiratory alkalosis resulting from the tachypnea stimulated by metabolic acidosis, hypoxemia, and decreased pulmonary compliance. In more severe cases, respiratory acidosis ensues as the patient fatigues and respirations fail. The ratio of dead space to total ventilation ($V_D/V_T$) may be significantly increased owing to alveolar flooding. Patients with inadequate ventilation or with severe hypoxia which does not respond to supplemental oxygen require ventilatory support. Noninvasive ventilation (NIV) techniques are effective in treating severely compromised, but not agonal, APE patients (see Chapter 2.). Continuous positive airway pressure (CPAP) or biphasic positive airway pressure (BPAP) applied by an adjustable, snugly fitting face mask increases functional residual capacity, improves oxygenation, reduces work of breathing, and results in decreased LV preload and afterload by raising intrathoracic pressure (Fig. 81-6). These

Figure 81-5. A general therapeutic strategy for acute heart failure requires thoughtful application of interventions to achieve a reasonable improvement in early clinical treatment goals. Appropriate interpretation of the perfusion with use of clinical criteria and occasionally arterial pressure monitoring is central to the strategy. $BP$, blood pressure; $Hgb$, hemoglobin; $IV$, intravenously; $NS$, normal saline; $P_{O_2}$, pulse oximetry; STEMI, ST segment elevation myocardial infarction.

Figure 81-6. Noninvasive ventilation (NIV) techniques recruit collapsed alveoli and increase functional residual capacity (FRC), which improves oxygenation and reduces work of breathing (WOB). These factors tend to reduce sympathetic tone, heart rate (HR), and blood pressure (BP), relieving myocardial ischemia. NIV also acts as an afterload-reducing agent, which tends to directly improve cardiac index (CI), systemic oxygen delivery (DO$_2$), partial pressure of oxygen in arterial blood (PaO$_2$), and ventilation-perfusion ratio ($V/Q$). Preload is also reduced by NIV.
techniques result in more rapid restoration of normal vital signs and oxygenation than supplemental oxygen alone. Even in studies using only CPAP, fewer patients will require endotracheal intubation. The addition of pressure support (BPAP) further reduces the work of breathing and more rapidly improves hypercarbia than CPAP alone. Selected patients may benefit greatly from these techniques when appropriately applied in conjunction with pharmacotherapy. These ventilatory therapies do not increase the risk of MI in APE. A large multicenter trial demonstrated that NIV provides earlier improvement in respiratory distress and related metabolic abnormalities than supplemental oxygen alone in APE but does not improve short-term mortality.

Patients too ill for noninvasive ventilation are supported with bag-valve-mask assisted oxygenation in preparation for tracheal intubation. Intubation is indicated for apneic patients and those with respiratory distress, agitation, or hypoxemia not responsive to high-flow oxygen or NIV. Most spontaneously breathing patients respond rapidly to medical therapy, and the majority of alert hypercarbic patients can also be managed without mechanical ventilation.

Vasodilator Agents

Nitrates and Nitroprusside

Organic nitrates activate the enzyme guanylate cyclase, leading to accumulation of cGMP, which relaxes vascular smooth muscle by sequestering calcium in the sarcoplasmic reticulum. At lower doses, nitrates are primarily venodilators. They effectively decrease preload and are therefore very effective in the initial therapy of APE. At higher doses, intravenous nitroglycerin also causes arteriolar dilation that decreases BP and afterload. Thus, pump function is improved while myocardial oxygen demand is decreased. Nitroglycerin may further reduce myocardial ischemia by its direct coronary vasodilator effect and is particularly effective when myocardial ischemia is contributing to the acute decompensation. Prolonged nitrate therapy over hours to days leads to tachyphylaxis secondary to depletion of intracellular sulfhydryl groups.

Nitroglycerin may be initiated by the sublingual route, followed by titrated intravenous administration. Intravenous nitroglycerin has rapid onset and offset of action. Hypotension from excessive preload reduction or vagally mediated idiosyncratic reactions may occur. Nitroglycerin should be avoided in patients who have taken impotence medications (PDE type 5 inhibitors) within the previous 24 hours (up to 48 hours for tadalafil), as the combination may precipitate refractory hypotension. Transcutaneous absorption may be erratic because of diaphoresis and poor skin perfusion, so ointment should not be used as a delivery mechanism until the patient’s condition has stabilized. Also, transcutaneous nitroglycerin patches may ignite during defibrillation. Sodium nitroprusside works similarly to nitroglycerin, acting as a balanced vasodilator to reduce both preload and afterload. Continuous intra-arterial pressure monitoring is preferred in patients receiving this drug to avoid precipitous hypotension. Nitroprusside is useful for patients with pulmonary edema and significant systemic hypertension. In the presence of acute myocardial ischemia or infarction, however, nitroglycerin is preferable because it avoids the coronary steal syndrome, in which normal vessels dilate and divert flow from more diseased vessels. These patients are also particularly vulnerable to unintended hypotension, an event more likely to occur with nitroprusside than nitroglycerin. Patients with renal failure may experience thiocyanate toxicity from high-dose nitroprusside infusions. Cyanide toxicity, recognized clinically by the presence of agitation and lactic acidosis, may occur in individuals with a genetic predisposition. Nitroglycerin is thus preferred over nitroprusside in HF.

Morphine Sulfate

Morphine sulfate, an opioid analgesic, reduces pulmonary congestion through a central sympatholytic effect and release of vasoactive histamine, causing peripheral vasodilatation and reduced preload. In addition, through reduced systemic catecholamines, morphine decreases HR, BP, cardiac contractility, and myocardial oxygen consumption. Patients with APE tend to be agitated as a result of air hunger. The calming effect of morphine is advantageous in this setting. Morphine is administered in repeated 2- to 5-mg intravenous doses carefully titrated to effect. If oversedation results in hypoventilation, gentle stimulation usually restores ventilatory effort. In APE, mild carbon dioxide (CO₂) retention does not contraindicate morphine use because it results from acute alveolar flooding that is improved by the mechanisms just delineated. Airway support should be considered, however, before morphine use in obtunded HF patients.

Nesiritide

Nesiritide, a recombinant human BNP, is a balanced vasodilator that reduces aldosterone and ET levels while increasing sodium and water excretion, without a resultant reflex tachycardia. Nesiritide, however, is not superior to nitroglycerin, nor does it provide additional benefit when added to a treatment regimen that includes intravenous nitroglycerin. Treatment of acute HF with nesiritide did not reduce return to the ED or 30-day hospitalization in one ED study. Meta-analyses of studies using nesiritide in acute HF suggest the possibility of increased drug-related mortality. Nesiritide is not indicated in the emergency department treatment of episodes of acute HF.

Loop Diuretics

Loop diuretics inhibit sodium resorption from renal filtrate, resulting in significant increases in salt and water excretion. In patients with volume overload, this diuretic action lowers plasma volume, decreasing preload and pulmonary congestion. Although the renal effects of intravenously administered loop diuretics begin within 10 minutes, symptom relief in patients with APE often occurs much faster, probably the result of diuretic-induced neurohumoral changes. Furosemide acts as a vasodilator, promoting both renal PGE₂ and natriuretic peptide secretion, and as a vasoconstrictor, stimulating renin release. Loop diuretics (furosemide or bumetanide) should be administered to patients with hypertensive APE. The half-life of furosemide in patients with APE is double that in healthy volunteers, and caution is required with frequent administration. Continuous infusion of furosemide is not superior to bolus therapy.

Patients with abrupt onset of APE who do not have underlying chronic HF may have low plasma volumes at presentation, and diuresis in this group of patients may be unnecessary. Patients who fail to respond to loop diuretic administration may have severely compromised renal perfusion. In these situations, invasive hemodynamic monitoring may be beneficial. Diuretic therapy causes depletion of the important cations K⁺ and Mg²⁺, which may be significant in patients in whom these cations are already depleted by chronic diuretic therapy or other agents. High-dose diuretic therapy in APE is associated with deterioration in renal function and increased mortality.

Other Therapies

Most patients with APE and adequate systemic perfusion respond promptly to treatment with oxygen, nitrates, morphine, and diuretics. Hemodialysis is useful in patients with renal insufficiency. Blood transfusion candidates in acute HF have worse
clinical features but derive some benefit from RBC repletion for hemoglobin levels below 8 g/dL. Therapies such as ET receptor antagonists, vasopressin receptor antagonists, beta-endorphins, adenosine receptor antagonists, and other agents have undefined therapeutic potential. Urotilatin, a synthetic renin natriuretic peptide, has effectiveness in acutely decompensated HF. Levosimendan, a calcium-sensitizing drug that opens ATP-dependent potassium channels, provides prompt hemodynamic improvement in acute HF. In cardiogenic shock treated with percutaneous coronary intervention (PCI), levosimendan improves cardiovascular hemodynamics compared with conventional inotropic therapy. Relaxin, a vasodilating hormone produced in pregnant women, shows promise in the treatment of decompensated HF. Trials with a tumor necrosis factor antagonist have failed to demonstrate benefit in HF. Historical therapies (e.g., rotating tourniquets, phlebotomy, and theophylline) have no demonstrated efficacy in APE. Endotracheal intubation should be reconsidered if the patient develops severe respiratory deterioration unresponsive to NIV, significant cardiac dysrhythmias, or low CO or has ongoing chest pain.

**Treatment of Acute Heart Failure in Hypotensive Patients**

Patients with acute cardiogenic pulmonary edema and apparent systemic hypotension present a therapeutic dilemma. Coronary perfusion in patients depends on the pressure gradient between the aorta and LV chamber in diastole. The combination of hypotension and elevated left-sided filling pressure dramatically decreases coronary perfusion, particularly with coronary artery disease, leading to further impairment of contractility from increased ischemia. Vasopressor administration to maintain coronary perfusion pressure is necessary if this set of conditions truly exists. Vasopressors, however, can increase afterload, decrease CO, increase myocardial oxygen demand, exacerbate ischemia, and precipitate dysrhythmias. As previously discussed, an intra-arterial catheter provides more accurate and immediate BP monitoring and is helpful in guiding therapy.

If the patient is truly hypoperfusing, initial measures should aim to maintain or restore coronary perfusion pressure. In this setting, the patient is either in true cardiac shock (pulmonary edema, hypotension, and decreased peripheral perfusion) or is volume depleted. Patients in true cardiac shock have lost as much as 40% of their ventricular muscle mass. Nearly 25% of patients with acute MI and clinical evidence of systemic hypoperfusion, however, have low preload, indicating the presence of hypovolemia. Fluid challenge alone in these patients restores hemodynamic stability in half. Hypotensive patients with APE should receive a judicious fluid challenge in the form of 250-mL crystalloid boluses over 5 to 10 minutes. If respiratory status is not deteriorating, repeated aliquots may be administered. If hypovolemia is contributing to hypotension, this intervention should restore BP and systemic perfusion without need for vasopressors. If the patient has true cardiac shock, more intensive interventions, including vasopressor therapy, intra-aortic balloon counterpulsation, and endotracheal intubation with mechanical ventilation, may be needed. APE with systemic hypoperfusion in the setting of acute coronary syndrome represents ischemic cardiogenic shock. Emergency coronary revascularization is the treatment of choice.

**Inotropic or Vasopressor Therapy**

Inotropic agent use in HF increases myocardial oxygen demand, cardiac arrhythmias, and mortality. Intravenous inotropic agents with vasoactive properties should be reserved for hypoperfused patients with low CO despite a high LV filling pressure. In patients with acute MI or ischemia and severe LV dysfunction, the use of a catecholamine may be counterproductive, as all increase myocardial cell work and thus further injure ischemic myocardium. Revascularization to reperfuse stunned or hibernating myocardium is preferable.

In hypotensive patients who are adequately volume repleted (true cardiogenic shock), norepinephrine is the pressor of choice. It raises BP and coronary perfusion pressure (alpha-vasoconstrictor effect) with a modest beta effect for inotropy and the least overall increase in HR and contractility, which could further increase myocardial oxygen demand. In cardiac shock, norepinephrine administration is a temporizing maneuver to maintain coronary perfusion pending rescue strategies, such as angioplasty, intra-aortic balloon pumping, or cardiac surgery.

Dopamine is a naturally occurring catecholamine and a norepinephrine precursor. It has a dose-dependent effect on peripheral vascular tone and is a positive inotropic and chronotropic agent. Despite previous impressions, dopamine in HF has no clinically significant perfusion-sparing effect on the kidneys at any dose. Epinephrine is a potent alpha- and beta-agonist that maintains BP and increases CO. In cardiac surgery patients, it combats myocardial stunning after cardiopulmonary bypass. Dobutamine is a synthetic catecholamine that is mainly a beta-receptor agonist with some beta- and alpha-agonist activity. It is an inotropic vasodilator at therapeutic doses and should be used with caution in patients with borderline hypotension because it occasionally reduces BP further. Isoproterenol is a potent beta-agonist that causes profound tachycardia and vasodilation, which would be dangerous in HF.

Aminodone and milrinone are PDE type III inhibitors that increase cyclic adenosine monophosphate (cAMP) in the myocardium and peripheral smooth muscle. These intravenous vasodilating inotropic agents increase CO and reduce LV pressures without producing significant changes in HR and BP. The positive inotropic effects of aminodone and dobutamine are additive, and concomitant use of both drugs appears to be better tolerated than high doses of dobutamine alone, with lower metabolic costs. Aminodone and milrinone may be useful on a short-term basis in patients awaiting heart transplantation. They should be used with caution in selected patients—in general in the context of invasive hemodynamic monitoring. These agents are proarrhythmic, and long-term use of PDE type III inhibitors reduces survival in HF.

**Rate and Rhythm Controllers**

Rate and rhythm control is occasionally necessary in HF. Compensatory tachycardia is the rule in HF, unless the patient is taking beta-blocking agents. Noncompensatory tachycardia increases myocardial oxygen consumption while reducing coronary perfusion and is a particular problem with atrial flutter or fibrillation with rapid ventricular response. As with other causes of HF, diastolic filling is a more prompt and safe alternative to digoxin in normotensive patients. Electrical cardioversion is indicated when a new-onset tachydysrhythmia is causing or exacerbating HF, especially with hypoperfusion or ongoing evidence of myocardial ischemia. Transcutaneous pacing may be necessary in severe bradyarrhythmias with hypotension.

**Chronic Heart Failure**

Chronic HF often involves a more gradual onset of symptoms, with a slow increase in dyspnea on exertion, progressive orthopnea, fatigue, and other symptoms. Patients with chronic HF often have complex multiorgan dysfunction and comorbidities for which polydrug medical regimens are used. In this clinical setting, the potential impact of any therapeutic intervention on the
entire spectrum of disease and compensatory mechanisms should be considered. For example, adding an NSAID to the medical regimen of a patient with chronic HF may negatively affect renovascular function and precipitate increased fluid retention and pulmonary edema.89 U.S. guidelines approved by the AHA and ACC reflect a new classification system for chronic HF that includes four categories: patients at risk, patients with asymptomatic LV dysfunction, patients with symptomatic HF, and those with refractory HF. The number of patients with asymptomatic LV dysfunction is approximately fourfold greater than the number of patients with symptomatic HF.131 Echocardiography is a very useful modality in screening for asymptomatic LV dysfunction in high-risk subgroups.82

A main goal in the management of HF is to modify long-term maladaptive responses as well as achieve short-term functional improvement.133 Treatment should ideally be initiated in patients at risk to prevent disease progression. Atherosclerotic coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, cocaine or ethanol abuse, smoking, and obesity are significant risk factors for HF.134 Hypertension precedes HF in 75% of patients, particularly in blacks. Control of hypertension reduces the risk of development of HF,135 as does improvement of dyslipidemias in patients with atherosclerosis. Approximately two thirds of patients with systolic HF have significant coronary artery disease. Those with diabetes mellitus have more than a threefold increased risk of cardiac ischemic events and HF.136 High dietary sodium is associated with impaired diastolic relaxation.137 Appropriate lifestyle changes, including smoking cessation, weight reduction, restriction of salt and water intake, and modest exercise programs, reduce symptoms in HF and may delay progression. Excessive lipid accumulation within the myocardium is directly cardiotoxic and causes LV remodeling and dilated cardiomyopathy.138 Substantial weight loss in patients with HF associated with obesity produces a reversal of many of the clinical manifestations and improves NYHA functional class in most patients.139,140 Paradoxically, however, overweight and obese patients have lower cardiovascular mortality in chronic HF.141

The LV remodeling process is triggered by volume or pressure overload as well as loss of cardiac myocytes (e.g., MI). Therapeutic interventions in HF aim to slow remodeling. Ventricular remodeling correlates with poor clinical outcomes in HF.142 Serial measurements of various neurohormones may serve as surrogate markers of ventricular remodeling.143 Various antihypertensive therapies allow regression of LV hypertrophy and reduce the rate of sudden cardiac death.144 Reverse remodeling is a concept in which progressive LV dysfunction is not simply arrested but also partially reversed.145 Beta-blockers, ACE inhibitors, aldosterone antagonists, and angiotensin receptor blockers (ARBs) all inhibit or reverse remodeling.146,147

The mainstay of treatment for chronic HF and asymptomatic LV dysfunction is vasodilator therapy, which benefits pump function by reducing both afterload and preload. The most important vasodilators for chronic HF are ACE inhibitors, angiotensin II receptor antagonists, and nitrates.

**Common Therapeutic Agents in Chronic Heart Failure**

**Angiotensin-Converting Enzyme Inhibitors.** ACE inhibitors provide the most effective therapy for LV dysfunction. They increase survival in all classes of chronic HF and reduce development of HF in patients with MI and asymptomatic LV dysfunction.148-150 ACE inhibitors are natriuretic vasodilators that block production of angiotensin II and aldosterone secretion, reducing diuretic and potassium supplementation requirements. Additional ACE inhibitor effects include inhibition of bradykinin degradation and reduction of intrinsic ET-dependent vasoconstriction.151 Unlike other vasodilators, they do not induce reflex tachycardia.

The main side effects of ACE inhibitors are hypotension, deterioration of renal function, chronic cough, and upper airway angioedema. ACE inhibitors should be initiated at low doses with careful attention to the potential for hypotension, with concomitant reduction in diuretic and potassium supplementation. Optimization of ACE inhibitor dosage appears to be neglected in many patients with HF, particularly the elderly.152,153 In patients with chronic HF, high-dose aspirin (>325 mg/day) may impair some clinical benefits of ACE inhibitors.154

**Angiotensin II Receptor Blockade.** In HF patients intolerant of ACE inhibitors, angiotensin type I (AT1) receptor blockers are useful.155 In a meta-analysis of 17 trials comparing angiotensin II receptor blockers with ACE inhibitors, both ACE inhibitors and ARBs allowed reverse remodeling in HF156 and reduced the risk of development of AF.157 ARBs were not superior to ACE inhibitors in reducing mortality or hospitalization for HF.158,159 The combination of an ARB and an ACE inhibitor, however, increases hyperkalemia and hypotension and worsens renal function. Because of marginal benefit and increased side effects, dual renin-angiotensin blockade with an ACE inhibitor and an ARB is no longer recommended in HF.160 ARBs are most useful in patients intolerant of ACE inhibitors155 and have reduced side effects of cough and bradycardia accumulation.161,162

**Beta-Blocker and Combined Alpha-, Beta-Blocker Therapy.** Despite the apparent paradox of use of agents that reduce myocardial contractility, beta-adrenergic blocking agents have significant efficacy in chronic HF. Long-term activation of the sympathetic nervous system in HF, activation of the RAAS, myocardial beta-adrenergic receptor downregulation, and direct cardiotoxicity because of elevated norepinephrine levels are associated with adverse effects. An extensive meta-analysis revealed that beta-blockers in chronic HF significantly increase EF and decrease mortality.163,165 HR reduction with use of beta-blockers correlates with improvement in LVEF and reduced death rate in HF.166,167 AHA/ACC guidelines recommend beta-blockers for all patients with symptomatic LV systolic dysfunction.168

Beta-blockers should not normally be initiated in acute HF. They are most useful in chronic HF associated with conditions having indications for beta-blocker therapy, including hypertension, angina pectoris, and significant dysrhythmias. Slow upward titration of beta-blocker therapy facilitates maximal tolerability.169 Vasodilating beta-blockers such as carvedilol and nebivolol may have special use in chronic HF.170,171 Carvedilol, a third-generation alpha- and beta-blocker with antioxidant properties, may be a particularly effective agent in chronic HF.172-174 In one large study comparing metoprolol with carvedilol for HF, the number needed to treat was 15 to prevent one excess death at 5 years for carvedilol.175 Nebivolol is a beta1-receptor blocker with NO-potentiating vasodilatory effects that improves hemodynamics and prognosis in chronic HF.170

**Diuretics.** Patients with chronic HF exhibit a reduced ability to exert a sodium and water load, with abnormal cardiac and hemodynamic adaptations to salt excess.176 Low-dose diuretics are one of the most effective treatments to prevent recurrence of HF.177 Loop diuretics, although commonly used, are associated with significant side effects, including hypovolemia, electrolyte disturbances (low K+, Mg++, and Na+), hyperuricemia, worsening renal function, and metabolic alkalosis. Torasemide may block the aldosterone cascade, unlike furosemide, and may be clinically a better loop diuretic in chronic HF.178 The addition of thiazide diuretic therapy to loop diuretics greatly increases sodium and fluid excretion but increases side effects.179

In patients hospitalized for HF exacerbation, admission serum sodium is an independent predictor for increased days of hospitalization for cardiovascular causes and increased mortality
within 60 days of discharge. Persistent hyponatremia is an independent predictor of mortality, hospitalization for HF, and death or rehospitalization, despite clinical and hemodynamic improvements similar to those in patients without hyponatremia.\(^\text{183,184}\)

The hypokalemia and hypomagnesemia secondary to diuretic therapy are proarrhythmic. The use of potassium-sparing diuretics in HF is associated with a reduced risk of death. Spironolactone and eplerenone directly antagonize aldosterone. They significantly reduce mortality while improving LV function in patients with severe HF (EF below 35%) already being treated with an ACE inhibitor and a loop diuretic, with or without digoxin.\(^\text{185,186}\) Spironolactone reverses remodeling in patients with mild to moderate chronic systolic HF.\(^\text{187,188}\) Eplerenone, when used in addition to standard therapy, results in significant reduction in morbidity and mortality in patients after acute MI.\(^\text{189-191}\) Aldosterone antagonists may lead to serious hyperkalemia in the presence of significant renal insufficiency or in patients taking supplemental potassium.

Nitrates. Nitrates, by virtue of a direct vasodilator effect, improves exercise tolerance in chronic HF and offers potential hemodynamic improvement.\(^\text{192}\) Isosorbide used in combination with the arteriolar dilator hydralazine prolongs survival in patients with HF, but less so than ACE inhibitors. ACE inhibitors, however, are less effective in African Americans. A fixed-dose isosorbide–hydralazine regimen is particularly effective in chronic HF in African Americans,\(^\text{193}\) reducing hospitalization and mortality by about 40%,\(^\text{194}\) with these positive effects sustained over time.\(^\text{195,196}\) The main problem with nitrate therapy appears to be rapid drug tolerance, which can be partially addressed by daily nitrate drug-free intervals.

Cardiac Glycosides. The cardiac glycosides inhibit the adenosine triphosphatase–dependent sodium-potassium pump in the cell membrane of the cardiac myocyte. This inhibition increases the availability of intracellular calcium to contractile proteins in myocardial cells, with modest positive inotropic effect. Digoxin is of benefit in patients with all degrees of chronic HF by reducing symptoms and improving quality of life and exercise tolerance.\(^\text{197}\) Digoxin reduces the rate of hospitalization in chronic HF, and it decreases mortality when added to an ACE inhibitor and diuretic therapy.\(^\text{198,199}\) Digoxin should be used in low doses for most persistently symptomatic HF patients whose treatment already includes ACE inhibitors, diuretics, and beta-blocker therapy when HF is caused by systolic or diastolic dysfunction.\(^\text{200}\)

Other Considerations in Chronic Heart Failure

Electrical Therapy. Implantable cardioverter-defibrillators (ICDs) have a substantial mortality advantage over antiarrhythmics in chronic HF,\(^\text{9,201}\) particularly in patients with previous MI and low LVEF. Prophylactic placement in appropriate patients undergoing coronary artery bypass grafting (CABG), however, has been found to be ineffective in reducing mortality in the first 6 months after surgery.\(^\text{202}\) Although a meta-analysis of ICD therapy continues to show benefit in MI patients with low EF, the economic impact is unclear.

Patients with severe HF and significant LV dyssynchrony benefit from atioventricular sequential pacing.\(^\text{203,204}\) RV apical pacing is often used in chronic HF but creates abnormal LV contraction, hypertrophy, and reduced pump function.\(^\text{205}\) Cardiac resynchronization therapy (CRT) via LV or biventricular pacing attempts to coordinate the activation of the interventricular septum and left ventricle free wall in HF. LV or biventricular pacing allows more physiologic LV contraction, and both are equally effective.\(^\text{206,207}\) CRT improves HF symptoms and exercise capacity and can reverse chronic cardiac dilation.\(^\text{208-210}\) CRT combined with ICD use greatly reduces risk of sudden cardiac death\(^\text{211-213}\) and other cardiac events.\(^\text{214}\) Cardiac resynchronization in patients with AF is also effective in improving EF as well as functional outcome\(^\text{215}\) and appears more effective than pharmacologic therapy.\(^\text{216}\) CRT also reduces functional mitral regurgitation at rest.\(^\text{217}\)

Intrathoracic impedance monitoring is available on some devices to continuously monitor hemodynamic status in HF\(^\text{218,219}\) Potential roles for telemonitoring in chronic HF are evolving.

Antidysrhythmic Therapy. From 70 to 95% of patients with cardiomyopathy and HF have frequent premature ventricular beats, and 40 to 80% develop nonsustained ventricular tachycardia,\(^\text{220}\) with an associated increased risk of sudden death. Amiodarone and classmate dronedarone are useful in acute management of sustained ventricular tachyarrhythmias. In chronic HF, amiodarone prevents the development of AF and converts significantly more patients with AF to sinus rhythm.\(^\text{221}\) In patients with AF and HF, however, rhythm control was not found to reduce the cardiovascular death rate compared with rate control.\(^\text{222}\) Unfortunately, amiodarone and other antidysrhythmic agents have significant toxicities and may be proarrhythmic, and none demonstrates decreased mortality in HF.\(^\text{223,224}\) Dronedarone has been found to similarly increase mortality and worsen HF in patients with LV systolic dysfunction.\(^\text{225}\) In patients with post-MI LV systolic dysfunction with or without HF, amiodarone is associated with increased early and late all-cause cardiovascular mortality.\(^\text{226,227}\) ICD therapy is also superior to amiodarone in terms of psychological well-being and quality of life in HF.\(^\text{228}\)

Rate control of sinus rhythm is recognized as an avenue for therapeutic intervention in HF.\(^\text{229,230}\) In patients with LV dysfunction and stable coronary artery disease, elevated HR above 70 beats/min is associated with higher cardiovascular mortality and admission for MI or HF.\(^\text{231}\) In particular, for every increase of 5 beats/min above 70 beats/min, there are increases in cardiovascular death, admission for HF or MI, and coronary revascularization. Icabradine, a selective sinus node inhibitor, demonstrates reduced hospitalization and death rates in chronic HF with resting HR over 70 beats/min and EF below 35%.\(^\text{232}\)

Calcium Channel Blockers. First-generation calcium channel blockers (verapamil, diltiazem, and nifedipine) do not improve survival in chronic HF and may precipitate clinical deterioration.\(^\text{233}\) Second-generation dihydropyridines (nicardipine and amlodipine) have more moderate negative inotropic effects. Amlodipine reduces fatal and nonfatal cardiac events in nonischemic but not in ischemic heart disease.\(^\text{234}\) Calcium channel blockers used to treat hypertension increase the incidence of HF compared with other regimens.\(^\text{235}\) There is no compelling evidence for the use of calcium channel blockers in chronic HF, although they may be needed in patients intolerant of beta-blockers, ACE inhibitors, ARBs, and combined nitrates plus hydralazine.\(^\text{236}\) Calcium channel blockers are indicated for the treatment of hypertension, angina, and dysrhythmias, but benefits may be reduced in patients with associated chronic HF.\(^\text{237}\)

Ultrafiltration and Renal Dialysis. Ultrafiltration reduces volume overload when diuretic therapy is inadequate.\(^\text{238,239}\) In decompensated HF, ultrafiltration may be more effective than intravenous diuretics in volume overloaded states.\(^\text{240-242}\) Renal dialysis is important for HF treatment in end-stage renal disease. Potential complications of renal disease that may require special consideration include fluid overload, severe hyperkalemia, iatrogenic hyperkalemia, uremic pericardial effusion, and drug toxicity (e.g., digitalis).

Coronary Artery Bypass Grafting and Angioplasty. Although there is little consensus regarding the role of revascularization in the management of ischemic cardiomyopathy, registry data suggest a benefit of CABG over PCI in HF.\(^\text{243}\) In patients with coronary artery disease amenable to CABG and EF below 35%, CABG combined with medical therapy, compared with medical therapy alone, reduced death from cardiovascular causes but not all-cause mortality.\(^\text{244}\) Another study shows no advantage in preventing HF,
immunomodulatory effects that are beneficial in patients with chronic HF.298,299 They should be used only in hypoperfusion states unresponsive to other therapies. PDE type 5 inhibition with sildenafil, used commonly for erectile dysfunction, is safe in HF and may have other beneficial effects, including better CO and exercise capacity.277,278 Long-term use of sildenafil in chronic HF improves exertional ventilation and aerobic efficiency.261,262

Phosphodiesterase Inhibitors. There is no indication for long-term PDE type 3 inhibitors (amrinone or milrinone), which increase morbidity and mortality in patients with severe chronic HF.25,256 They should be used only in hypoperfusion states unresponsive to other therapies. PDE type 5 inhibition with sildenafil, used commonly for erectile dysfunction, is safe in HF and may have other beneficial effects, including better CO and exercise capacity.277,278 Long-term use of sildenafil in chronic HF improves exertional ventilation and aerobic efficiency.261,262

Statins and Polyunsaturated Fatty Acids. Statins improve endothelial function and have anti-inflammatory, antioxidative, and immunomodulatory effects that are beneficial in patients with chronic HF.263-266 Early use of statin therapy after acute MI reduces risk of HF,269 and use in nonischemic HF improves LVEF and NYHA classification and reduces serum levels of multiple inflammatory markers.270-271 A statin reduces risk of HF substantially in high-risk populations and also decreases risk of major vascular effects.272 Statin therapy is associated with lower hospitalizations, reduced inflammatory markers, improved EF, and decreased mortality among patients with severe HF.273-275 High-dose statin therapy adds benefit to lower doses in HF.276 Polyunsaturated fatty acids (n-3 PUFA) show improved LV systolic function and functional capacity and reduced hospitalizations in patients with dilated cardiomyopathy.277 In patients with HF from any cause, n-3 PUFA use leads to a small decrease in mortality and admissions for cardiovascular reasons.278

Anemia. Anemia is present in about one-third of chronic HF patients279 and is associated with increased mortality in both systolic and diastolic HF.61 An aggressive approach to anemia in chronic HF using iron supplements and intermittent erythropoietin improves LV systolic function, LV remodeling, BNP levels, NYHA class,63,280 sleep-related breathing disorders,49 and renal function, as well as need for hospitalization.281-283

Sleep Apnea-Related Respiratory Support. Hypoxemia and related hemodynamic stress underlies the impact of sleep disorders in HF.284 Obstructive sleep apnea is more prevalent in chronic HF than previously recognized, and treatment with CPAP can be therapeutic,285-287 even improving LVEF and heart transplant-free survival.288,289 CPAP for central sleep apnea and HF improves nocturnal oxygenation, EF, and exercise capacity but is not proven to increase survival.290,291 BPAP is superior to CPAP in improving EF in systolic HF with obstructive sleep apnea.292

Exercise Programs. Cardiopulmonary exercise testing provides prognostic information in patients with HF.293 Various exercise programs in chronic HF show benefits in terms of functional status and quality of life, and reduce rehospitalization rates.294-297 Growth hormone and testosterone replacement in HF increase exercise capacity and quality of life.298,299

Left Ventriculoplasty, Ventricular Assist Devices, and Transplantation. After a promising beginning, left ventriculoplasty has largely been abandoned because of failure to demonstrate long-term efficacy in HF. A study of ventriculoplasty during coronary artery bypass surgery also failed to show functional improvement or reduced mortality in HF.300 In contrast, LV aneurysm repair is useful in HF.301

Multiple implantable LV assist devices are in trials for chronic HF as a bridge to transplantation and as a surgical alternative to chronic medical management.302-307 Heart transplantation is still the most effective therapy for end-stage HF, with 88% survival at 8 years in one study in which statins were used to prevent vasculopathy,308 with rejection also reduced by immunosuppressive therapy.309 The limited availability of donors (2500 heart transplants per year in the United States), however, makes alternative surgical techniques of interest in end-stage HF.310 There is increasing evidence that stem cell therapy may offer promise in chronic HF.311,312 Mononuclear bone marrow cell transplantation during CABG surgery in patients with ischemic HF improves cardiac function and regional perfusion.313 Autologous stem cell transplantation leads to significant improvement in cardiac function in patients undergoing CABG for ischemic cardiomyopathy.314-316 Myoblast transplantation in coronary surgery patients with depressed LV function, however, fails to improve EF and increases postoperative arrhythmias.317

Psychosocial Factors. Depression is common in patients with HF and increases cardiovascular mortality. Treatment is challenging. Palliative care is important to manage multiple sources of distress in end-of-life issues related to end-stage HF.318

Admission Criteria and Predictors of Readmission in Heart Failure

In general, exacerbations of chronic HF require admission if the cause of the exacerbation cannot be readily recognized and corrected, if the disease process is unstable because of increased ischemia or new dysrhythmia, or if clinical deterioration appears likely. Many patients in the ED with acute decompensated HF are admitted because of comorbidities, inability to identify those at low risk for poor outpatient outcomes, or difficulty providing proper bedside HF education and close follow-up. In-hospital mortality for acute decompensated HF is about 4% but higher with increased age, elevated HR, hyponatremia, hypotension, LV systolic dysfunction, increased blood urea nitrogen (BUN) or creatinine, troponin, natriuretic peptides, or HF as the primary cause for admission.319 Precipitating events, including acute coronary syndrome, concomitant pneumonia, or worsening renal function increase hospital mortality and should prompt admission. Several risk factors predict poor postdischarge outcome, including ischemic ECG changes, elevated troponins or natriuretic peptide levels, hyponatremia, elevated BUN or creatinine, and low systolic BP.320 Worsening renal function during HF hospitalization is an independent predictor for early readmission and mortality.321 Conversely, those with rectifiable dietary or medication noncompliance issues may occasionally be discharged with close follow-up. Observation units may have a substantial role in avoiding HF admission.

The difficulties of outpatient HF management range from compliance and understanding of the multifactorial therapeutic strategies to optimization of care after hospital discharge including diet, medications, and weight monitoring. Patients with HF are frequently readmitted for both cardiac and unrelated causes.322 Several studies have demonstrated reduced readmission rates with individualized, comprehensive discharge planning,323,324 structured postdischarge follow-up,325 telemonitoring,326 and directed home self-management.326 A meta-analysis of 18 studies that used an international patient population demonstrated reduced readmission rates for those with comprehensive discharge planning and postdischarge support versus standard therapy. There is significant variability in the adherence to HF quality-of-care issues in the United States.320 Initiation of proven therapeutic modalities at hospitalization leads to early benefits, including decreased risks of mortality and rehospitalization for HF.330

SUMMARY

Evaluation and management of patients with HF remains a challenge in emergency medicine. HF exacerbation remains among the most frequent conditions resulting in ED visits and hospital admissions. APE requires deliberate consideration of multiple different diagnostic entities. Recognition of common precipitating
The references for this chapter can be found online by accessing the accompanying Expert Consult website.
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