

# The Syndrome of Heart Failure

T. Nagendran, MD, FACS

**H**ear failure has been compared to the mythical multiheaded beast Hydra because of its many causes and varied clinical presentation.<sup>1</sup> Heart failure is defined as the inability of the heart either to pump a sufficient amount of blood to the metabolizing tissues or to do so without an increased filling pressure (**Table 1**). The American College of Cardiology/American Heart Association<sup>2</sup> and the Agency for Health Care Policy and Research<sup>3</sup> issued clinical guidelines in 1995 and 1994, respectively, for the management of heart failure, especially systolic dysfunction. In 1999, a supplement to the current guidelines was published.<sup>4</sup> These guidelines recommend early and routine use of angiotensin-converting enzyme (ACE) inhibitors in all patients with heart failure. According to an analysis of office visits by patients with heart failure through 1994, only 31% of these patients were receiving ACE inhibitor therapy.<sup>5</sup> This article describes the epidemiology, etiology, pathogenesis, and management of patients with heart failure.

## EPIDEMIOLOGY

Today, 4 million patients are living with symptomatic heart failure in the United States.<sup>6</sup> The incidence of heart failure doubles in the general population each decade in patients 65 years and older and increases 9-fold in patients older than 80 years.<sup>7</sup> Heart failure is more common in elderly patients, in men, and in African Americans<sup>7</sup> than in other population groups.

There are 400,000 to 700,000 new cases of heart failure diagnosed in the United States each year: 3 per 1000 persons in the general population, 10 per 1000 persons 65 years and older, and 27 per 1000 persons 85 years and older. In 1970, 170,000 patients were discharged from hospitals in this country with the diagnosis of heart failure; by 1990, the number had increased to 700,000. This apparent increase in incidence may be the result of better management of hypertension and myocardial infarction, the 2 most common causes of heart failure,<sup>7</sup> which has resulted in patients living longer.

Each year in the United States, 5 million inpatient hospital days and 4 million office visits are related to the treatment of heart failure.<sup>7</sup> Approximately 1.5 million hospital admissions each year involve patients with

heart failure, and each hospital admission costs approximately 6,000 to 12,000 dollars.<sup>6</sup> The 3-month readmission rate for treatment of heart failure is 20% to 50%. The mortality rate for heart failure also is extremely high, with the overall 2-year mortality reported to be 35%<sup>7</sup>; approximately 50% of men with symptomatic heart failure will be dead within 2 years of developing the condition. In the United States, 300,000 persons die each year of heart failure, 40% of them suddenly.

## ETIOLOGY AND CLASSIFICATION OF HEART FAILURE

Myocardial dysfunction resulting from coronary artery disease and hypertension is the most common cause of heart failure in United States.<sup>8</sup> Myocardial infarction specifically causes 50% of cases of heart failure.<sup>1</sup> Causes of heart failure are listed in **Table 2**.

Clinically, heart failure is generally described as left ventricular failure, right ventricular failure, and biventricular failure; the precise term used depends on whether there is an increase in left or right atrial pressure, or both. Left ventricular failure is associated with either systolic dysfunction or diastolic dysfunction. In systolic dysfunction, the ejection fraction is low (usually less than 40%), and there is an increase in filling pressure. In diastolic dysfunction, the ejection fraction is usually normal or even elevated; the ventricular wall is stiff and noncompliant and fails to relax during diastole, thus impairing diastolic filling.<sup>6,9,10</sup>

Left ventricular failure is caused primarily by 4 diseases: (1) coronary artery disease, (2) hypertension, (3) cardiomyopathy, and (4) valvular heart diseases. Right-sided heart failure, in the majority of cases, is caused by left-sided heart failure. Pure right-sided heart failure occurs either in parenchymal lung diseases (such as chronic obstructive pulmonary disease) or in primary pulmonary hypertension (ie, cor pulmonale).<sup>10</sup>

*Forward heart failure* is the term used when symptoms are related to low cardiac output, and *backward heart failure* denotes a "back-damming" of blood, producing pulmonary and systemic venous congestion.

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Dr. Nagendran is Medical Director, Smiths Station Medical Clinic, Smiths, AL.

**Table 1.** Definitions of Key Terms

**Heart failure**

Inability of the heart to pump a sufficient amount of blood to metabolizing tissues or the ability to do so only with an increased filling pressure

**Ejection fraction**

Measure of myocardial contractility: the proportion of the end-diastolic volume that is ejected into the aorta during systole (normally, 56% to 78%)

**Systolic dysfunction**

Presence of reduced ejection fraction (less than 40%) together with increased left ventricular filling pressure

**Diastolic dysfunction**

Presence of increased left ventricular filling pressure together with normal ejection fraction

**Forward failure**

Heart failure associated with low cardiac output

**Backward failure**

Heart failure associated with increased left ventricular filling pressure and pulmonary and systemic venous congestion

Functional classification of heart failure is based on the criteria developed by the New York Heart Association.<sup>11</sup> Class I patients become symptomatic only with greater than normal activity. Class II patients develop symptoms during normal exercise. Class III patients are asymptomatic at rest and become symptomatic with minimal activity. Class IV patients are symptomatic at rest.

**PHYSIOLOGY OF HEART FUNCTION**

Unlike other vital organs such as brain and liver, the heart is capable of 2 different levels of function.<sup>1,12</sup> The first is an intrinsic function of contraction and relaxation, which occurs at rest. The second is a modulated function by which the heart is able to increase its output 2- to 10-fold; in other words, a cardiac output that is 4 to 6 L per minute at rest can be increased to a much higher level when needed.

Cardiac output is determined by both heart rate and stroke volume. Stroke volume depends on venous return to the heart (also called *preload*), which is measured as left ventricular end-diastolic volume. Myocardial contractility is measured as ejection fraction. Normal myocardial contractility forces 56% to 78% of end-diastolic volume into the aorta (provided there is no valvular deformity), resulting in a normal ejection

**Table 2.** Major Causes of Heart Failure

Coronary artery disease

Hypertension

Valvular heart disease

Nonischemic cardiomyopathy

Constrictive pericarditis

High-output failure

fraction of 56% to 78%. The force against which the heart has to pump is known as *afterload*.<sup>8</sup> At rest, the healthy heart pumps the preload—no matter what the volume happens to be—without back-damming of the blood. This is accomplished by the *Frank-Starling mechanism*: the longer the cardiac muscle fibers are stretched by an increase in preload volume, the greater the force of contraction of muscle fiber to eject it.

With the modulated function that results from sympathetic stimulation, the strength of myocardial contraction increases, regardless of the amount of preload volume. This occurrence is known as *inotropy*. The sympathetic stimulus also increases heart rate, a circumstance known as *chronotropy*.

**PATHOPHYSIOLOGY OF HEART FAILURE**

Heart failure is associated with low cardiac output and elevated filling pressure. When cardiac output is low, either acutely (eg, in myocardial infarction) or chronically (eg, in hypertension), multiple compensatory mechanisms come into play (**Figure 1**). In acute situations, blood pressure decreases, the baroreceptor reflex is activated, and sympathetic stimulation occurs. Epinephrine is released to increase inotropy and chronotropy, thus maintaining adequate blood supply to vital organs. If low cardiac output is not corrected but continues to persist, then additional compensatory changes take place. These changes include activation of the renin-angiotensin-aldosterone mechanism, hypertrophy of the myocardium, and release of atrial natriuretic peptides.

**Renin-Angiotensin-Aldosterone Mechanism**

As a result of low cardiac output, the glomerular filtration rate decreases and renin is released. Renin converts angiotensinogen to angiotensin I, which in turn is converted into angiotensin II by ACE. Angiotensin II is a powerful vasoconstrictor that increases afterload and stimulates production of aldosterone; aldosterone promotes salt and water retention, thus increasing preload.

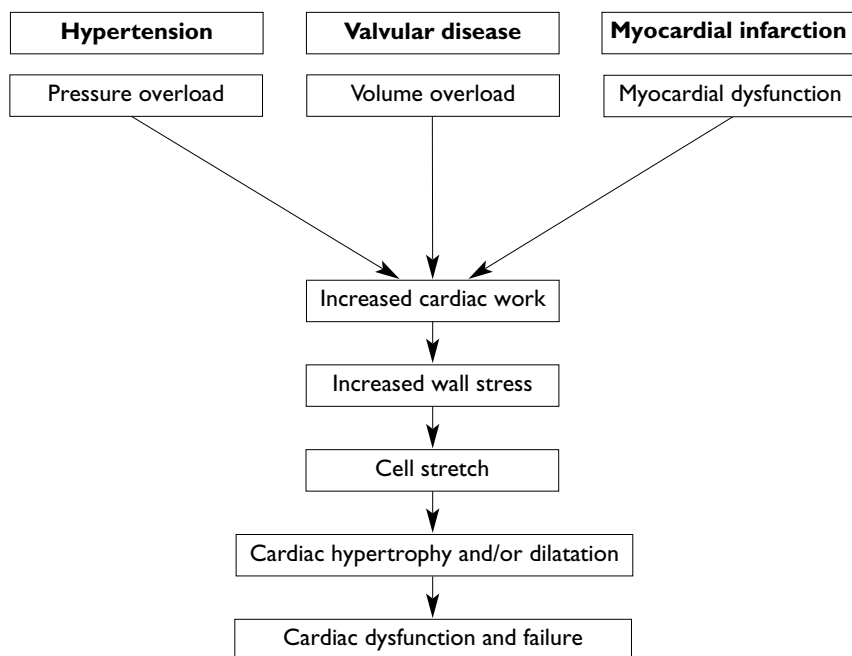


Figure 1. Algorithm depicting the pathophysiology of heart failure.

### Hypertrophy of the Myocardium

Because adult cardiomyocytes cannot divide, hyperplasia does not occur when additional workload is needed to increase the cardiac output in a failing heart. In some cases, myocardial hypertrophy occurs instead. Myocardial hypertrophy can develop in various settings: myocardial infarction in which the noninfarcted myocardium has to compensate for the infarcted myocardium; volume overload associated with mitral and aortic regurgitation; and pressure overload associated with aortic stenosis and hypertension. In cases of volume overload, myocardial hypertrophy involves ventricular dilatation; in cases of pressure overload, concentric hypertrophy takes place.<sup>9</sup>

Although the hypertrophy initially is helpful to increase cardiac output, it subsequently contributes to ventricular dysfunction<sup>9</sup> by a loss of myocytes caused by apoptosis, synthesis of dysfunctional proteins, decreased capillary-to-myocyte ratio, and decreased calcium availability.

### Atrial Natriuretic Peptide

Atrial natriuretic peptide normally is stored in the atrial muscle wall and is released when there is increased atrial pressure, as occurs in heart failure.<sup>7,13</sup> The normal atrial natriuretic peptide level in the plasma is 10 to 70 pg/mL. Measurement of this peptide can be used to assess the severity of heart failure.<sup>14</sup> The potential role of this peptide in the management of heart failure has led to the development of a recombi-

nant form called *nesiritide*, which will be available for clinical use in the near future.<sup>14</sup>

### CLINICAL PRESENTATION OF HEART FAILURE

Risk factors for the development of heart failure are listed in **Table 3**. Specific signs and symptoms of heart failure will depend on both the severity and type of heart failure in individual patients.<sup>7</sup> Half of the patients who have left ventricular systolic dysfunction are either asymptomatic or have only minimal symptoms. Moreover, it is extremely difficult to diagnose heart failure in the elderly because of confounding factors such as existing chronic, comorbid conditions (eg, chronic obstructive pulmonary disease), illnesses that cause physical deconditioning (eg, arthritis), and the multiple medications patients may be taking to treat other conditions. Consequently, it is crucial to obtain a detailed history, especially in patients with numerous risk factors.

### Signs and Symptoms

In patients with heart failure, symptoms can be caused by either elevated filling pressure or low cardiac output (or by a combination of the two). Elevated filling pressure gives rise to congestive symptoms such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema (**Table 4**). Low cardiac output causes fatigue, weakness not relieved by rest, and decreased exercise tolerance.<sup>10</sup>

Dyspnea, or shortness of breath, involves an abnormal awareness of breathing.<sup>13</sup> In heart failure, dyspnea

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**Table 3.** Risk Factors for Developing Heart Failure

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Advanced age
African American race
Cigarette smoking
Coronary artery disease
Diabetes mellitus
Hyperlipidemia
Hypertension
Male gender
Obesity

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progresses slowly over a period of weeks or months. Produced by pulmonary venous and capillary hypertension, dyspnea generally precedes coughing in patients with heart failure, whereas in patients with chronic obstructive pulmonary disease, coughing and expectoration precede dyspnea.

Peripheral edema in heart failure is bilateral and symmetrical. It usually occurs late in the course of the disease, only after 7 to 10 L of water have been retained by the patient.<sup>10,15</sup> In patients who are bedridden, edema occurs in the sacral area. Severe heart failure is associated with anasarca or generalized edema.

Fatigue, low exercise tolerance, and weakness are typical symptoms in patients with heart failure associated with low cardiac output. Anorexia, weight loss, and cachexia occur in patients with advanced heart failure.

**Clinical Findings**

There are numerous clinical signs of heart failure, particularly of left-sided heart failure, that can be detected on thorough physical examination.<sup>16</sup> Those discussed below, although not exhaustive, comprise the major signs. Table 4 and Table 5 list typical clinical findings in heart failure associated with increased filling pressure and decreased ejection fraction, respectively.

Examination of the neck veins to detect jugular venous distension, a classic sign of left ventricular systolic dysfunction, is best performed with the patient in the supine position and the examiner standing on the right side of the patient.<sup>13</sup> The head of the patient is raised or lowered until the top of the venous column is seen clearly. Although the venous column of the external jugular vein usually can be seen fairly easily, an accurate determination of distension is made only by observing the internal jugular vein. Normal jugular venous pressure is 5 to 8 cm H<sub>2</sub>O; it is usually measured above the level of sternal angle of Louis, which is

**Table 4.** Findings in Patients with Increased Filling Pressure

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<b>Signs and symptoms</b>
Dyspnea
Orthopnea
Peripheral edema
<b>Clinical findings</b>
Jugular venous distension
Tachycardia
Proportional pulse pressure less than 25%
<b>Imaging findings</b>
Cardiomegaly and redistribution of vessels on chest radiograph

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5 cm above the right atrium. Elevated jugular venous pressure is a reflection of elevated filling pressure.

Measurement of various pressures should be obtained in patients suspected of having heart failure. During inspiration, negative intrathoracic pressure typically causes the venous pressure to decrease. In patients with right ventricular failure and constrictive pericarditis, however, the venous pressure increases during inspiration (*Kussmaul's sign*). Likewise, under normal conditions of rest, an inspiratory decrease in arterial systolic pressure of less than 10 mm Hg occurs. A decrease in systolic pressure of more than 10 mm Hg on inspiration (*pulsus paradoxus*) occurs in patients with constrictive pericarditis and right-sided heart failure.<sup>17,18</sup> Lastly, proportional pulse pressure is the difference between systolic and diastolic pressure divided by systolic pressure. If the value obtained is less than 32%, it indicates a decreased ejection fraction and left ventricular systolic dysfunction.<sup>16</sup>

Regularly placed, alternating strong and weak pulses—termed *pulsus alternans*—is an uncommon clinical finding. When present, it indicates severe left-sided heart failure.<sup>10</sup> Mackenzie<sup>19</sup> described a technique to document pulsus alternans: by inflating the blood pressure cuff above the systolic pressure level and releasing it slowly, one hears perfectly even and regular soft beats at a rate that is half the pulse rate; as the cuff is further deflated, these beats get louder and alternate with an additional set of soft beats at the regular pulse rate. Unlike a bigeminal pulse, which is irregular and produced by premature ventricular beats, pulsus alternans is regular.

The *apical impulse* is normally felt or seen in the fourth or fifth left intercostal space and is perceived as

a brief tap<sup>16</sup>; it is best appreciated when the patient is lying in a 45-degree left lateral decubitus position and is exhaling. A downward, laterally shifted, and sustained impulse indicates left ventricular systolic dysfunction. Simultaneous auscultation allows the quantification of the duration of a sustained impulse (ie, lasting more than three fourths of systole). Percussion of the cardiac borders will confirm left ventricular enlargement. In cases of right ventricular hypertrophy, the apical impulse is shifted medially towards the left parasternal border.

A left ventricular third heart sound (S<sub>3</sub>) is another indication of left ventricular systolic dysfunction. Heard during rapid filling of the ventricles during diastole and produced by ventricular vibration, an S<sub>3</sub> also is best heard when a patient is in a 45-degree left lateral decubitus position. The bell of the stethoscope is well suited for auscultating this heart sound.<sup>16</sup> A sustained apical impulse and S<sub>3</sub> can be visually demonstrated by placing a tongue depressor over the heart and holding it in place with the diaphragm of the stethoscope.<sup>16</sup>

Another method of detecting heart failure involves blood pressure and Valsalva's maneuver. With the patient in a supine position or in a semiupright position, the blood pressure cuff is inflated 15 mm Hg above the systolic pressure and the patient is asked to perform Valsalva's maneuver. In contrast to healthy patients, patients with the left ventricular systolic dysfunction and increased filling pressure will produce a Korotkoff sound, audible during the straining phase of the maneuver.<sup>15,16</sup>

Finally, in patients with right ventricular failure, pressing on the right upper quadrant of the abdomen will increase the jugular venous pressure, producing the hepatojugular reflux.

Once examination of the patient is completed, an attempt should be made to establish the type of heart failure (ie, left ventricular, right ventricular, biventricular; systolic or diastolic dysfunction). Often, however, clinical assessment alone is insufficient and further diagnostic work-up is necessary before a complete diagnosis can be made.<sup>11,20</sup>

#### **DIAGNOSTIC IMAGING**

Imaging tools that can help establish a diagnosis of heart failure include echocardiography with Doppler flow studies, electrocardiography, and chest radiography.<sup>11</sup> Among these, echocardiography is the most useful diagnostic tool.

Echocardiography helps measure the ejection fraction, provides quantitative assessment of the dimen-

**Table 5.** Findings in Patients with Decreased Ejection Fraction

#### **Signs and symptoms**

Dyspnea

Peripheral edema

#### **Clinical findings**

Jugular venous distension

Proportional pulse pressure less than 32%

Pulse rate more than 90 bpm

Abnormal apical impulse

#### **Imaging findings**

Cardiomegaly and redistribution of vessels seen on chest radiograph

Anterior Q wave and/or left bundle branch block seen on electrocardiogram

sions, geometry, thickness, and regional motion of the ventricles, and enables qualitative assessment of the valves and pericardium.<sup>11</sup> This procedure should be performed in all patients suspected of having heart failure. Patients with increased filling pressure and left ventricular hypertrophy but normal ejection fractions generally have diastolic dysfunction.

Electrocardiography can help identify ventricular hypertrophy, atrial enlargement, conduction abnormalities, arrhythmias, and prior myocardial infarction.<sup>11</sup>

Cardiomegaly and redistribution of pulmonary vessels can be detected on a radiograph of the chest.<sup>16</sup> Cardiomegaly is present when the cardiothoracic ratio, measured by dividing the cardiac width by the largest width of the thoracic cavity,<sup>15</sup> is more than 50. Redistribution of pulmonary vessels is best assessed by comparing the upper lobe vessels with the lower lobe vessels. This assessment should be performed at an equal distance above and below the hilum. In patients with heart failure, the upper lobe vessels are larger than the lower lobe vessels. Pleural effusion may be present in patients with severe heart failure.

#### **MANAGEMENT OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION**

Management of heart failure should be based on its severity, etiology, coexisting conditions, and precipitating factors (**Table 6**).<sup>9</sup> Because left ventricular systolic dysfunction is the most common type of heart failure encountered today, this article addresses its management first and most completely. Every attempt should be made to diagnose left ventricular dysfunction in all

**Table 6.** Common Precipitating Factors of Heart Failure

Anemia
Arrhythmias
Dietary or medical noncompliance
Drugs (eg, nonsteroidal anti-inflammatory drugs)
Fluid overload
Hypertension
Myocardial infarction
Myocardial ischemia
Pregnancy
Systemic infections
Toxins (eg, alcohol)

high-risk patients (Table 3) by echocardiography, even if they are clinically asymptomatic. Once identified, patients with left ventricular systolic dysfunction should be started on ACE inhibitors because these agents have been shown to delay the onset of symptoms.<sup>1</sup>

#### General Measures

The goals of management in cases of left ventricular systolic dysfunction include alleviating congestive symptoms, improving exercise tolerance, preventing further deterioration of cardiac function,<sup>1</sup> prolonging life,<sup>20</sup> and identifying correctable causes.<sup>6,13</sup> Some correctable causes and their management are listed in Table 7.

Short-term bed rest can be useful in treating heart failure. Bed rest reduces the myocardial oxygen demand and helps to mobilize fluid from the periphery, which in turn increases venous return to heart. However, prolonged bed rest should be discouraged because it increases the muscular weakness of cardiac patients. When patients are on bed rest, they should be protected against deep vein thrombophlebitis either by passive leg exercises, anticoagulant therapy, or both.

Salt and water restriction can also help manage left ventricular systolic dysfunction. Because a major aspect of heart failure is water and salt retention by the renin-angiotensin-aldosterone mechanism, all patients should be strongly encouraged to restrict their intake of both; if possible, salt intake should be limited to 2 g daily and water to 1.5 L daily. Patients also should be told to monitor their weight daily.

To prevent further injury to the left ventricle, patients with heart failure should be encouraged to stop smoking or drinking alcohol and, if overweight, to

**Table 7.** Correctable Causes of Heart Failure and Their Management

Causes	Management
Coronary heart disease	Revascularization
Valvular heart disease	Valve replacement
Left ventricular aneurysm	Aneurysmectomy
End-stage cardiomyopathy	Heart transplantation, left ventricular assistive devices
Heart blocks (profound bradycardia, atrioventricular conduction defects)	Dual chamber pacemaker
Arrhythmias (atrial and ventricular)	Administration of anti-arrhythmic agents, cardioversion, therapeutic ablation, implantable defibrillator
Drugs and other toxins	Discontinuation of their use

reduce their weight. Moreover, control of hypertension, reduction of hyperlipidemia, and control of diabetes mellitus are all extremely important in further reducing the risk of injury to the left ventricle.<sup>9</sup> When acute symptoms are relieved, patients should be encouraged to engage in moderate physical exercise. Isometric exercises must be avoided, however, because they increase oxygen demand on the myocardium.

Vaccination against influenza and pneumococcal pneumonia should be provided to all patients with heart failure. Chronic anticoagulation therapy is needed in heart failure patients who have had previous thromboembolic complications, atrial fibrillation, or myocardial infarction. In cases of extreme heart failure, thoracentesis and paracentesis are helpful, and in acute cases of fluid overload in patients with renal and heart failure, hemodialysis should be used.

#### Pharmacologic Management

Drugs are used in patients with left ventricular systolic dysfunction to decrease preload and afterload and to increase myocardial contractility and heart rate. Medications generally fall into 5 groups: diuretics, ACE inhibitors, vasodilators, digoxin, and  $\beta$ -blockers. Specific drugs and recommended dosages in each of these classes are listed in Table 8.

**Diuretics.** Virtually all patients with left ventricular systolic dysfunction require diuretics. Diuretics can improve clinical symptoms of heart failure caused by increased filling pressure, but a subsequent reduction in intravascular volume will diminish renal function. The

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**Table 8.** Commonly Used Drugs (and Dosages) in the Management of Heart Failure

**Diuretics**

Hydrochlorothiazide (12.5–50 mg daily)

Furosemide (20–200 mg daily)

Bumetanide (0.5–4 mg daily)

Ethacrynic acid (25–100 mg daily)

Torsemide (5–100 mg daily)

**ACE inhibitors**

Captopril (6.25–150 mg daily)

Enalapril (2.5–40 mg daily)

Lisinopril (2.5–40 mg daily)

Ramipril (2.5–10 mg daily)

Quinapril (5–20 mg daily)

**Angiotensin II receptor blockers**

Losartan (25–100 mg daily)

**Vasodilators**

Hydralazine (25–200 mg daily)

Isosorbide (10–120 mg daily)

**β-Blockers**

Carvedilol (3–50 mg daily)

**Intravenously administered drugs**

Nitroglycerin (0.5–10 µg/kg body weight per min)

Nitroprusside (0.5–10 µg/kg per min)

Dopamine (2–20 µg/kg per min)

Dobutamine (2.5–10 µg/kg per min)

ACE = angiotensin-converting enzyme.

3 major groups of diuretics used in heart failure patients include thiazides, loop diuretics, and potassium-sparing diuretics. The type and dosage of diuretic used need to be tailored to the specific patient according to severity of heart failure, functional renal status, and serum electrolyte levels. In the treatment of acute pulmonary edema, for example, ideal daily diuresis should result in a 0.5 to 1.0 kg reduction in body weight; in chronic cases, patients should be taught to adjust their dosage on a daily basis, according to their body weight.

Diuretics are always used in conjunction with ACE inhibitors, β-blockers, and/or digoxin. In severe heart failure, diuretics administered orally may not be absorbed because of congestion and edema of mucosa of the gastrointestinal tract. Dopamine administered in small doses can act as a diuretic by causing dilatation of the renal vessels. Torsemide, a newer diuretic, is more potent and effective, even in cases of renal insufficiency.

Thiazides inhibit salt and water reabsorption at the level of the distal convoluted tubule. They are used in patients with mild to moderate congestive symptoms and normal renal function. Unlike other thiazides, metolazone works at both proximal and distal convoluted tubules<sup>8</sup> and is an excellent choice when combined with a loop diuretic, even in patients with reduced glomerular filtration rate. Potential complications of thiazides include hypokalemia, hypercalcemia, hyperuricemia, pancreatitis, vasculitis, and increased levels of low-density lipoproteins.

Loop diuretics are extremely useful when significant diuresis is needed and the patient's renal function is compromised. Furosemide and bumetanide are sulfa derivatives, but ethacrynic acid is not. Ethacrynic acid is highly ototoxic.

Potassium-sparing diuretics are useful when combined with thiazides or loop diuretics. The serum potassium level should be monitored to avoid fatal hyperkalemia, which can also occur when these agents are used with ACE inhibitors. Recently, it has been shown that the potassium-sparing diuretic spironolactone prolongs survival in patients with severe heart failure.<sup>21</sup>

**ACE inhibitors.** ACE inhibitors have been shown to slow the progression of heart failure and reduce mortality in patients with the disorder.<sup>1</sup> These drugs also effectively relieve symptoms of heart failure and improve the clinical status of patients. They delay development of symptoms in clinically asymptomatic patients with left ventricular systolic dysfunction and prevent development of heart failure in patients who develop a decreased ejection fraction after myocardial infarction. Captopril 50 mg 3 times daily (or an equivalent dosage of any other ACE inhibitor) seems to provide maximum hemodynamic, neurohumoral, and symptomatic benefits.

Other beneficial effects of ACE inhibitors are most likely related to their pharmacologic modulation of neuroendocrine activity at all stages of heart failure. These drugs effectively reduce heart size, mortality, and the number of hospitalizations resulting from heart failure; they also can be used safely with other drugs to treat heart failure.<sup>1</sup> Higher doses of ACE inhibitors are associated with lower mortality. Generally, it is recommended that ACE inhibitors be started at a lower dose and titrated to the maximum tolerated dose. All patients with left ventricular systolic dysfunction, as evidenced by a reduced ejection fraction, should be started on ACE inhibitors without fail.

Adverse effects of ACE inhibitors include chronic cough, angioedema, chronic renal failure, and

hypotension. Hypotension also is common in patients receiving diuretics, patients with hyponatremia, and patients who are on dialysis. It is advisable to discontinue diuretics for 24 hours before starting ACE inhibitors. If hypotension occurs, there is no need to discontinue the ACE inhibitor, but careful monitoring of the patient is essential. An increase in blood urea nitrogen level might occur but is usually reversible with discontinuation of the diuretics, increasing the intake of salt, and reducing the dosage of the ACE inhibitor. Caution must be exercised in using ACE inhibitors in patients with renal artery stenosis because they are prone to develop acute renal failure. A dry cough occurs in 20% of patients taking these drugs and is not dose related; often, ACE inhibitors need to be discontinued in patients with this symptom.<sup>2</sup> The dosage of ACE inhibitors needs to be adjusted in patients with low creatinine clearance or hyperkalemia. ACE inhibitors should be used with great caution when combined with potassium-sparing diuretics because they can lead to the development of life-threatening hyperkalemia. The concomitant use of nonsteroidal anti-inflammatory drugs and ACE inhibitors is associated with high incidence of renal failure. ACE inhibitors are contraindicated in pregnant patients.<sup>2</sup>

Patients who are unable to tolerate ACE inhibitors should be given angiotensin II receptor blockers, which have similar pharmacologic benefits with minimal adverse effects. Also, such patients might be candidates for vasodilator therapy.

**Vasodilators.** Nitrates and hydralazine are the 2 most commonly used vasodilators in patients with systolic dysfunction. Nitrates primarily dilate the veins, thus reducing preload volume and relieving symptoms related to increased filling pressure.

Hydralazine is an arteriolar dilator that reduces afterload. Consequently, hydralazine can help relieve symptoms related to low cardiac output. The combination of hydralazine and nitrates relieves symptoms of both increased filling pressure and low cardiac output.<sup>10</sup>

**Digoxin.** Digoxin is extremely helpful in patients who have dilated cardiomyopathy or who have heart failure associated with atrial fibrillation. Although digoxin decreases the number of recurrent hospitalizations, it does not reduce the mortality associated with heart failure. However, it does seem to increase the quality of life in patients with heart failure. It should always be combined with ACE inhibitors and diuretics in the management of left ventricular systolic dysfunction.<sup>1</sup>

**$\beta$ -Blockers.**  $\beta$ -Blockers have been found to reduce mortality in patients with systolic dysfunction.<sup>1</sup> Initially,

these agents make symptoms of heart failure worse. For this reason, they should not be given to patients with Class IV heart failure or to patients whose symptoms have recently become worse. These agents thus are not usually given to hospitalized patients. Carvedilol, a  $\beta_1$ -,  $\beta_2$ -, and  $\alpha_1$ -blocker, has been recently approved by the US Food and Drug Administration for use in patients with systolic dysfunction.  $\beta$ -Blockers should be started at very low dose and titrated up to the optimum dose.<sup>1</sup> Bronchial asthma is a contraindication for these agents.

**Other agents.** The calcium-channel blockers amlodipine and felodipine are helpful in patients with heart failure and angina or heart failure and hypertension. Their role in treating other types of systolic dysfunction is uncertain at this time, however.<sup>1</sup>

### **MANAGEMENT OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION**

If echocardiography confirms isolated left ventricular diastolic dysfunction, then every attempt should be made to rule out occult ischemic heart disease.<sup>7</sup> The congestive symptoms should be relieved by optimizing the patient's volume status<sup>7</sup> without causing hypovolemia. In hypertensive heart disease, ACE inhibitors, calcium-channel blockers, central sympatholytic agents, and/or  $\beta$ -blockers should be used to reduce left ventricular mass. Heart rate should be kept between 55 to 60 bpm by using a  $\beta$ -blocker or calcium-channel blocker to increase the duration of diastole and, thus, ventricular filling.

### **CARDIOGENIC PULMONARY EDEMA**

#### **Pathogenesis**

Cardiogenic pulmonary edema (ie, pulmonary edema resulting from left-sided heart failure) results from increased hydrostatic pressure in pulmonary capillaries secondary to left ventricular dysfunction. Common causes include myocardial infarction, hypertension, and acute fluid overload. Clinical signs of pulmonary edema include severe dyspnea, tachypnea, tachycardia, hypoxemia, and hypercarbia.

One quick way of determining whether pulmonary edema results from a cardiac cause is to perform the test described on page 50, in which the patient performs a Valsalva's maneuver during measurement of blood pressure; if the pulmonary edema is cardiogenic, a Korotkoff sound will be heard.<sup>22</sup>

#### **Management**

Patients with cardiogenic pulmonary edema should be placed in a semiupright position. Supplemental

oxygen should be administered in all cases, although some concern has been expressed in the literature that supplemental oxygen can reduce cardiac output and might increase systemic vascular resistance.<sup>23</sup>

Morphine administered intravenously can reduce anxiety and increase cardiac output by decreasing systemic vascular resistance. If blood pressure is normal or elevated, nitrates can be extremely helpful in reducing pulmonary congestion by increasing venous capacitance and thus decreasing preload. Nitrates are equally effective given sublingually, transdermally, or intravenously. ACE inhibitors can be given sublingually to reduce afterload volume. Captopril has been used for this purpose as well<sup>24,25</sup>; in our institution, captopril at a dosage of 12.5 mg has been used effectively.

Diuretics, especially furosemide, should be given intravenously. However, if diuretics are administered before preload volume is reduced with nitrates and before afterload volume is reduced with ACE inhibitors, they will actually increase the pulmonary wedge pressure and systemic vascular resistance.<sup>26</sup> Thiamine also can be administered intravenously, especially in patients who are on chronic diuretic therapy,<sup>27</sup> because thiamine deficiency causes depression of left ventricular function.<sup>28</sup> Intravenous magnesium therapy might also be appropriate<sup>29</sup>; hypomagnesemia caused by chronic diuretic therapy can cause ventricular arrhythmia and sudden death. Hypotensive patients should be treated first with dopamine and then with dobutamine, and hypertensive patients should be treated with sodium nitroprusside.

## CONCLUSION

The prevalence of left ventricular systolic dysfunction—the most common type of heart failure—is increasing in the United States, most likely because patients are receiving better treatment of associated underlying diseases such as myocardial infarction and hypertension and are thus generally living longer. ACE inhibitors, when used early and in appropriate doses, slow the progression of heart failure and reduce mortality. All primary care practitioners should perform echocardiography in high-risk patients in order to diagnose left ventricular systolic dysfunction early and should start affected patients on the maximum tolerated dosage of ACE inhibitors.<sup>4</sup>

HP

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