

Smith Seminars
Continuing Education Credits
AARC-Approved for 2 CRCE
Congestive Heart Failure

Objectives

- Identify the physiology and pathophysiologic aspects of congestive heart failure
- List the classifications, etiology, signs and symptoms of CHF
- Review the diagnostic processes used in CHF
- Become aware of current treatments and drugs associated with CHF

Heart failure is a syndrome of ventricular dysfunction. Left ventricular failure causes shortness of breath and fatigue, and right ventricular failure causes peripheral and abdominal fluid accumulation; both ventricles are usually involved to some extent. Diagnosis is clinical, supported by chest x-ray and echocardiography. Treatment includes diuretics, ACE inhibitors, beta-blockers, and correction of the underlying disorder. Heart failure affects about 5 million people in the US; > 500,000 new cases occur each year.

Physiology

Cardiac contractility (force and velocity of contraction), ventricular performance, and myocardial O₂ requirements are determined by preload, afterload, substrate availability, (such as O₂, fatty acids, and glucose), heart rate and rhythm, and amount of viable myocardium. Cardiac output equals stroke volume times heart rate; it is also affected by venous return, peripheral vascular tone, and neurohumoral factors.

Preload is the loading condition of the heart at the end of its relaxation phase (diastole) just before contraction (systole). Preload represents the degree of end-diastolic fiber stretch and end-diastolic volume, which is influenced by ventricular diastolic pressure and the composition of the myocardial wall. Typically, left ventricular end-diastolic pressure, especially if above normal, is a reasonable measure of preload. Left ventricle dilation, hypertrophy, and changes in myocardial distensibility (compliance) modify preload.

Afterload is the force resisting myocardial fiber contraction at the start of systole; it is determined by chamber pressure, volume, and wall thickness at the time the aortic valve opens. Clinically, systemic BP at or shortly after the aortic valve opens represents peak systolic wall stress and approximates afterload.

The Frank-Starling principle describes the relationship between preload and cardiac performance. It states that, normally, systolic contractile performance (represented by stroke volume or cardiac output) is proportional to preload within the normal physiologic range. Contractility is difficult to measure without cardiac catheterization but is reasonably reflected by the ejection fraction, which is the percentage of end-diastolic volume ejected with each contraction (left ventricle stroke volume/end-diastolic volume). Cardiac reserve is the ability of the heart to increase its performance above resting levels in response to emotional or physical stress; body O₂ consumption may increase from 250 to = 1500 mL/min during maximal exertion. Mechanisms include increasing heart rate, systolic and diastolic volume, stroke volume, and tissue extraction of O₂ (the difference between O₂ content in arterial blood and mixed venous or pulmonary artery blood). In

well-trained young adults during maximal exercise, heart rate may increase from 55 to 70 beats/min at rest to 180 beats/min, and cardiac output may increase from 6 to = 25 L/min. At rest, arterial blood contains about 18 mL O₂/dL of blood, and mixed venous or pulmonary artery blood contains about 14 mL/dL. O₂ extraction is thus about 4.0 mL/dL, but when demand is increased, it may increase to 12 to 14 mL/dL. These mechanisms also help compensate for heart failure.

Pathophysiology

In heart failure, the heart may not provide tissues with adequate blood for metabolic needs, and cardiac-related elevation of pulmonary or systemic venous pressures may result in organ congestion. This condition can result from abnormalities of systolic or diastolic function or, commonly, both.

In systolic dysfunction, the ventricle contracts poorly and empties inadequately, leading initially to increased diastolic volume and pressure. Later, ejection fraction falls. Many defects in energy utilization, energy supply, electrophysiologic functions, and contractile element interaction occur, with abnormalities in intracellular Ca modulation and cyclic adenosine monophosphate (cAMP) production. Predominant systolic dysfunction is common in heart failure due to myocardial infarct. Systolic dysfunction may affect primarily the left ventricle or the right ventricle; left ventricle failure often leads to right ventricle failure.

In diastolic dysfunction, ventricular filling is impaired, resulting in reduced ventricular end-diastolic volume, increased end-diastolic pressure, or both. Contractility and hence ejection fraction remains normal; ejection fraction may even increase as the poorly filled left ventricle empties more completely to maintain cardiac output. Markedly reduced left ventricle filling can produce low cardiac output and systemic symptoms. Elevated left atrial pressures can produce pulmonary congestion. Diastolic dysfunction usually results from impaired ventricular relaxation (an active process), increased ventricular stiffness, constrictive pericarditis, or atrioventricular valve stenosis. Resistance to filling increases with age, probably reflecting myocyte loss and increased interstitial collagen deposition; thus, diastolic dysfunction is particularly common among the elderly. Diastolic dysfunction is presumed to be predominant in hypertrophic cardiomyopathy, disorders with ventricular hypertrophy (such as hypertension, significant aortic stenosis), and amyloid infiltration of the myocardium. Left ventricle filling and function may also be impaired if marked increases in right ventricle pressure shift the interventricular septum to the left.

In left ventricle failure, cardiac output decreases and pulmonary venous pressure increases. As pulmonary capillary pressure exceeds the oncotic pressure of plasma proteins (about 24 mm Hg), fluid extravasates from the capillaries into the interstitial space and alveoli, reducing pulmonary compliance and increasing the work of breathing. Lymphatic drainage increases but cannot compensate for the increase in pulmonary fluid. Marked fluid accumulation in alveoli (pulmonary edema) significantly alters ventilation-perfusion (V/Q) relationships: Deoxygenated pulmonary arterial blood passes through poorly ventilated alveoli, decreasing systemic arterial oxygenation (PaO₂) and causing dyspnea. However, dyspnea may occur before V/Q abnormalities, probably because of elevated pulmonary venous pressure and increased work of breathing; the precise mechanism is unclear. In severe or chronic left ventricle failure, pleural effusions characteristically develop in the right hemithorax and later bilaterally, further aggravating

dyspnea. Minute ventilation increases; thus, PaCO₂ decreases and blood pH increases (respiratory alkalosis). Marked interstitial edema of the small airways may interfere with ventilation, elevating PaCO₂, a sign of impending respiratory failure.

In right ventricle failure, systemic venous pressure increases, causing fluid extravasation and consequent edema, primarily in dependent tissues (feet and ankles of ambulatory patients) and abdominal viscera. The liver is affected most, but stomach and intestine also become congested; fluid accumulation in the peritoneal cavity (ascites) can occur. Right ventricle failure commonly causes moderate hepatic dysfunction, with usually modest increases in conjugated and unconjugated bilirubin and hepatic enzymes. The impaired liver breaks down less aldosterone, further contributing to fluid accumulation. Chronic venous congestion in the viscera can cause anorexia, malabsorption and protein-losing enteropathy (characterized by diarrhea and marked hypoalbuminemia), chronic GI blood loss, and rarely ischemic bowel infarction.

Cardiac response: If ventricular function is impaired, a higher preload is required to maintain cardiac output. As a result, the left ventricle is remodeled over time. It becomes less ovoid and more spherical, dilates, and hypertrophies. Initially compensatory, these changes eventually increase diastolic stiffness and wall tension, compromising cardiac performance, especially during physical stress. Increased wall stress raises O₂ demand and accelerates apoptosis (programmed cell death) of myocardial cells.

Hemodynamic responses: With reduced cardiac output, tissue O₂ delivery is maintained by increasing O₂ extraction and sometimes shifting the oxyhemoglobin dissociation curve to the right to favor O₂ release.

Reduced cardiac output with lower systemic BP activates arterial baroreflexes, increasing sympathetic tone and decreasing parasympathetic tone. As a result, heart rate and myocardial contractility increase, arterioles in selected vascular beds constrict, venoconstriction occurs, and Na and water are retained; these changes compensate for reduced ventricular performance and help maintain hemodynamic homeostasis in the early stages of heart failure. However, these compensatory changes increase cardiac work, preload, and afterload; reduce coronary and renal perfusion; cause fluid accumulation resulting in congestion; increase K excretion; and may cause myocyte necrosis and arrhythmias.

Renal responses: As cardiac function deteriorates, renal blood flow and GFR (Glomerular Filtration Rate) decrease, and blood flow within the kidneys is redistributed. The filtration fraction and filtered Na decrease, but tubular resorption increases, leading to Na and water retention. Blood flow is further redistributed away from the kidneys during exercise but improves during rest, possibly contributing to nocturia (the need to get up during the night in order to urinate).

Decreased perfusion of the kidneys (and possibly decreased arterial systolic stretch secondary to declining ventricular function) activates the renin-angiotensin-aldosterone system, increasing Na and water retention and renal and peripheral vascular tone. These effects are amplified by the intense sympathetic activation accompanying heart failure. The renin-angiotensin-aldosterone-(antidiuretic hormone [ADH]) system produces a cascade of potentially deleterious effects. Angiotensin II worsens heart failure by causing vasoconstriction, including efferent renal vasoconstriction, and by enhancing aldosterone production, which not only enhances Na reabsorption in the distal nephron

but also produces myocardial and vascular collagen deposition and fibrosis. Angiotensin II increases norepinephrine release, stimulates release of ADH, and triggers apoptosis. Angiotensin II may be involved in vascular and myocardial hypertrophy, thus contributing to the remodeling of the heart and peripheral vasculature, potentially worsening heart failure. Aldosterone can be synthesized in the heart and vasculature independently of angiotensin II (perhaps mediated by corticotropin, nitric oxide, free radicals, and other stimuli) and may have deleterious effects in these organs.

Neurohumoral responses: In conditions of stress, neurohumoral responses help increase heart function and maintain BP and organ perfusion, but chronic activation of these responses is detrimental to the normal balance between myocardial-stimulating and vasoconstricting hormones and between myocardial-relaxing and vasodilating hormones. The heart contains many neurohumoral receptors (alpha, beta 1, beta 2, beta 3, angiotensin II type 1 and type 2, muscarinic, endothelin, serotonin, adenosine, cytokine); the role of these receptors is not yet fully defined. In patients with heart failure, beta 1 receptors (which constitute 70% of cardiac beta receptors) are down-regulated, probably in response to intense sympathetic activation; the effect of down-regulation is to impair myocyte contractility.

Plasma norepinephrine levels are increased, largely reflecting sympathetic nerve stimulation since plasma epinephrine levels are not increased. Detrimental effects include vasoconstriction with increased preload and afterload, direct myocardial damage including apoptosis, reduced renal blood flow, and activation of other neurohumoral systems including the renin-angiotensin-aldosterone-ADH cascade.

ADH is released in response to a fall in BP via various neurohormonal stimuli. Increased ADH decreases renal excretion of free water, possibly contributing to hyponatremia in heart failure. ADH levels in heart failure with normal BP vary.

Atrial natriuretic peptide is released in response to increased atrial volume and pressure; brain (B-type) natriuretic peptide (BNP) is released from the ventricle in response to ventricular stretching. These peptides enhance renal excretion of Na, but in patients with heart failure, the effect is blunted by decreased renal perfusion pressure, receptor down-regulation, and perhaps enhanced enzymatic degradation.

Because endothelial dysfunction occurs in heart failure, fewer endogenous vasodilators (such as nitric oxide, prostaglandins) are produced, and more endogenous vasoconstrictors (such as endothelin) are produced.

The failing heart and other organs produce tumor necrosis factor (TNF)-alpha. This cytokine increases catabolism and is possibly responsible for cardiac cachexia (loss of lean tissue = 10%), which may accompany severely symptomatic heart failure, and for other detrimental changes.

Classification and Etiology

Both cardiac and systemic factors can impair cardiac performance and produce heart failure. Cardiac factors include myocardial damage (such as acute MI or myocarditis, chronic fibrosis due to various disorders), valvular disorders, arrhythmias (tachyarrhythmias or bradyarrhythmias), and reduced substrate availability (such as ischemia). Systemic factors include any disorder that increases demand for cardiac output (causing high-output heart failure) or resistance to output (afterload), such as systemic hypertension.

The traditional distinction of left and right ventricular failure is somewhat misleading because the heart is an integrated pump, and changes in one chamber ultimately affect the whole heart. However, these terms indicate the major site of pathology leading to heart failure and can be useful for initial evaluation and treatment.

Left ventricular failure characteristically develops in ischemic heart disease, hypertension, aortic stenosis, in most forms of cardiomyopathy, acquired mitral or aortic valvular regurgitation, and congenital heart disorders (such as ventricular septal defect, patent ductus arteriosus with large shunts).

Right ventricular failure is most commonly caused by previous left ventricular failure (which increases pulmonary venous pressure and leads to pulmonary arterial hypertension, thus overloading the right ventricle) or by a severe lung disorder (cor pulmonale). Other causes are multiple pulmonary emboli, pulmonary venous occlusive disease, right ventricular infarction, primary pulmonary hypertension, tricuspid regurgitation or stenosis, mitral stenosis, and pulmonary artery or valve stenosis. Some conditions mimic right ventricular failure, except cardiac function may be normal; they include volume overload and increased systemic venous pressure in polycythemia or overtransfusion, acute renal failure with Na and H₂O retention-induced overhydration, and obstruction of either vena cava.

Biventricular failure results from disorders that affect the whole myocardium (such as viral myocarditis, amyloidosis, Chagas' disease).

High-output heart failure results from a persistent need for a high cardiac output, which may eventually result in an inability of a normal heart to maintain adequate output.

Conditions that may increase cardiac output include severe anemia, beriberi, thyrotoxicosis, advanced Paget's disease, arteriovenous fistula, and persistent tachycardia. Cardiac Output is high in various forms of cirrhosis, but much of the observed fluid retention is due to hepatic mechanisms.

Cardiomyopathy is a general term reflecting disease of the myocardium and is sometimes used to reflect etiology (such as ischemic vs. hypertensive cardiomyopathy). Most commonly, the term refers to a primary disorder of the ventricular myocardium that is not caused by congenital anatomic defects; valvular, systemic, or pulmonary vascular disorders; isolated pericardial, nodal, or conduction system disorders; or epicardial coronary artery disease (CAD). Cardiomyopathy does not always lead to symptomatic heart failure. It is often idiopathic and is classified as dilated congestive, hypertrophic, or infiltrative-restrictive cardiomyopathy.

Symptoms and Signs

Presentation differs depending on the extent to which the right ventricle and left ventricle are initially affected. Severity varies significantly and is usually classified by the New York Heart Association system. Severe LV failure may produce pulmonary edema.

Class I: Ordinary physical activity does not cause undue fatigue, dyspnea, palpitation, or angina; No limitations; Examples: Can complete any activity requiring = 7 mets: carry 11 kg up 8 steps; carry objects weighing 36 kg; shovel snow; spade soil; ski; play squash, handball or basketball; jog/walk 8 km/hour

Class II: Ordinary physical activity causes fatigue, dyspnea, palpitation, or angina; Slight limitations; Examples: Can complete any activity requiring = 5 mets: sexual intercourse without stopping, garden, roller skate, walk 7 km/hour on level ground

Class III: Comfortable at rest; less than ordinary physical activity causes fatigue, dyspnea, palpitation, or angina; Moderate limitations; Examples: Can complete any activity requiring = 2 mets: shower or dress without stopping, strip and make bed, clean windows, play golf, walk 4 km/hour

Class IV: Symptoms at rest; any physical activity increases discomfort; Severe limitations; Examples: Cannot do or cannot complete any activity requiring = 2 mets; cannot do any of the above activities

In left ventricular failure, the most common symptoms are dyspnea, reflecting pulmonary congestion, and fatigue, reflecting low cardiac output. Dyspnea usually occurs during exertion and is relieved by rest. As heart failure worsens, dyspnea can occur during rest and at night, sometimes causing nocturnal cough. Dyspnea occurring immediately or soon after lying flat and relieved promptly by sitting up (orthopnea) is common. In paroxysmal nocturnal dyspnea, dyspnea awakens patients several hours after they lie down and is relieved only after they sit up for 15 to 20 min. In severe heart failure, periodic cycling of breathing (Cheyne-Stokes respiration) a brief period of increased breathing (hyperpnea) followed by a brief period of no breathing (apnea) can occur during the day or night; the sudden hyperpneic phase may awaken the patient from sleep. This breathing differs from paroxysmal nocturnal dyspnea in that the hyperpneic phase is short, lasting only a few seconds and resolving in < 1 min. Paroxysmal nocturnal dyspnea is associated with pulmonary congestion and Cheyne-Stokes respiration with low cardiac output. Sleep-related breathing disorders, such as sleep apnea, are common in heart failure and may aggravate heart failure. Severely reduced cerebral blood flow and hypoxemia can cause chronic irritability and impair mental performance.

In right ventricular failure, the most common symptoms are ankle swelling and fatigue. Sometimes patients feel a sensation of fullness in the abdomen or neck. Hepatic congestion can cause right upper quadrant abdominal discomfort, and stomach and intestinal congestion can cause anorexia and abdominal bloating.

Less specific heart failure symptoms include cool peripheries, postural light-headedness, nocturia, and decreased daytime urination. Skeletal muscle wasting can occur in severe biventricular failure and may reflect some disuse but also increased catabolism associated with increased cytokine production. Significant weight loss (cardiac cachexia) is an ominous sign associated with high mortality.

General examination may detect signs of systemic disorders that cause or aggravate heart failure (such as anemia, hyperthyroidism, alcoholism, and hemochromatosis).

In left ventricular failure, tachycardia and tachypnea may occur; patients with severe left ventricular failure may appear visibly dyspneic or cyanotic, hypotensive, and confused or agitated because of hypoxia and poor cerebral perfusion. Central cyanosis (affecting all of the body, including warm areas such as the tongue and mucous membranes) reflects severe hypoxemia. Peripheral cyanosis of the lips, fingers, and toes reflects low blood flow with increased O₂ extraction. If vigorous massage improves nail bed color, cyanosis may be peripheral; increasing local blood flow does not improve color if cyanosis is central.

Cardiac findings in left ventricular systolic dysfunction include a diffuse, sustained, and laterally displaced apical impulse; audible and occasionally palpable 3rd (S₃) and 4th (S₄) heart sounds, and an accentuated pulmonic component (P₂) of the 2nd heart sound (S₂). A pansystolic murmur of mitral regurgitation at the apex may occur. Pulmonary

findings include inspiratory basilar crackles and, if pleural effusion is present, dullness to percussion and diminished breath sounds at lung bases.

Signs of right ventricular failure include nontender peripheral pitting edema (digital pressure leaves visible and palpable imprints, sometimes quite deep) in the feet and ankles; an enlarged and sometimes pulsatile liver palpable below the right costal margin; abdominal swelling and ascites; and visible elevation of the jugular venous pressure, sometimes with large a or v waves that are visible even when the patient is seated or standing. In severe cases, peripheral edema can extend to the thighs or even the sacrum, scrotum, lower abdominal wall, and occasionally even higher. Severe edema in multiple areas is termed anasarca. Edema may be asymmetric if patients lie predominantly on one side.

With hepatic congestion, the liver may be palpably enlarged or tender, and hepato-jugular or abdominal-jugular reflux may be detected. Precordial palpation may detect the left parasternal lift of right ventricular enlargement, and auscultation may detect the murmur of tricuspid regurgitation or the right ventricle S3 along the left sternal border.

Diagnosis

Clinical findings (such as exertional dyspnea, orthopnea, edema, tachycardia, pulmonary rales, S3, jugular venous distention) suggest heart failure but are not apparent early. Similar symptoms may result from COPD or recurrent pneumonia or may be erroneously attributed to old age. Suspicion for heart failure should be high in patients with a history of MI, hypertension, or valvular disorders or murmurs and should be moderate in any elderly or diabetic patient.

Chest x-ray, ECG, and an objective test of cardiac function, typically echocardiography, should be done. Blood tests, except for B-type natriuretic peptide, are not used for diagnosis but are useful for identifying cause and systemic effects.

Chest x-ray findings suggesting heart failure include an enlarged cardiac silhouette, pleural effusion, fluid in the major fissure, and horizontal lines in the periphery of lower posterior lung fields (Kerley B lines). These findings reflect chronic elevation of left atrial pressure and chronic thickening of the intralobular septa due to edema. Upper lobe pulmonary venous congestion and interstitial or alveolar edema may also be present. Careful examination of the cardiac silhouette on a lateral projection can identify specific ventricular and atrial chamber enlargement. The x-ray may also suggest alternative diagnoses (such as COPD, interstitial pulmonary fibrosis, lung cancer).

ECG findings are not diagnostic, but an abnormal ECG, especially showing previous MI, left ventricular hypertrophy, left bundle branch block, or tachyarrhythmia (such as rapid atrial fibrillation), increases suspicion for heart failure and may help identify the cause.

Echocardiography can help evaluate chamber dimensions, valve function, ejection fraction, wall motion abnormalities, left ventricular hypertrophy, and pericardial effusion. Intracardiac thrombi, tumors, and calcifications within the heart valves, mitral annulus, and aortic wall abnormalities can be detected. Localized or segmental wall motion abnormalities strongly suggest underlying CAD but can also be present with patchy myocarditis. Doppler or color Doppler echocardiography accurately detects valvular disorders and shunts. Doppler studies of mitral and pulmonary venous inflow often help identify and quantify left ventricular diastolic dysfunction. Measuring left ventricular ejection fraction can distinguish between predominant diastolic dysfunction (ejection

fraction > 0.40) and systolic dysfunction (ejection fraction < 0.40), which may require different treatment. Three-dimensional echocardiography may become important but currently is available only in specialized centers.

Radionuclide imaging also can help assess systolic and diastolic function, previous MI, and inducible ischemia or myocardial hibernation. Cardiac MRI provides accurate images of cardiac structures but is not always available and is more expensive.

Recommended blood tests include CBC, blood creatinine, BUN, electrolytes (including Mg and Ca), glucose, albumin, and liver function tests. Thyroid function tests are recommended for patients with atrial fibrillation and for selected, especially elderly, patients. Serum BNP levels are high in heart failure; this finding may help when clinical findings are unclear or other diagnoses (such as COPD) need to be excluded. It may be particularly useful for patients with a history of both pulmonary and cardiac disorders. Cardiac catheterization and coronary angiography are indicated when CAD is suspected or when the diagnosis and etiology are uncertain.

Endocardial biopsy is usually done only when an infiltrative cardiomyopathy is strongly suspected.

Prognosis

Generally, patients with heart failure have a poor prognosis unless the cause is correctable. Mortality rate at 1 yr from 1st hospitalization for heart failure is about 30%. In chronic heart failure, mortality depends on severity of symptoms and ventricular dysfunction and can range from 10 to 40%/yr.

Heart failure usually involves gradual deterioration, interrupted by bouts of severe decompensation, and ultimately death. However, death can also be sudden and unexpected, without prior worsening of symptoms.

End-of-life care: All patients and family members should be taught about disease progression. For some patients, improving quality of life is as important as increasing quantity of life. Thus, determining patients' wishes about resuscitation (such as endotracheal intubation and CPR) if their condition deteriorates are important, especially when heart failure is severe. All patients should be reassured that symptoms will be relieved, and they should be encouraged to seek medical attention early if their symptoms change significantly. Involvement of pharmacists, nurses, social workers, and clergy, who may be part of an interdisciplinary team or disease management program already in place, is particularly important in end-of-life care.

Treatment

Immediate inpatient treatment is required for patients with heart failure due to certain disorders (such as acute MI, atrial fibrillation with a rapid ventricular rate, severe hypertension, acute valvular regurgitation), as well as for patients with pulmonary edema, severe symptoms, new-onset heart failure, or heart failure unresponsive to outpatient treatment. Patients with mild exacerbations of previously diagnosed heart failure can be treated at home. The primary goal is to diagnose and to correct or treat the disorder that led to heart failure.

Short-term goals include improving symptoms and hemodynamics; avoiding hypokalemia, renal dysfunction, and symptomatic hypotension; and correcting neurohumoral activation. Long-term goals include correcting hypertension, preventing

MI and atherosclerosis, reducing hospitalizations, and improving survival and quality of life. Treatment involves dietary and lifestyle changes, drugs, and sometimes surgery. Dietary Na restriction helps limit fluid retention. All patients should eliminate salt in cooking and at the table and avoid salted foods; the most severely ill should limit Na to < 1 g/day by consuming only low-Na foods. Monitoring daily morning weight helps detect Na and water accumulation early; if weight increases > 4.4 kg, patients may be able to adjust their diuretic dose themselves, but if weight gain continues or symptoms occur, they should seek medical attention. Patients with atherosclerosis or diabetes should strictly follow a diet appropriate for their disorder. Obesity may cause and always aggravates the symptoms of heart failure; patients should attain a BMI of 21 to 25. Regular light activity (such as walking), tailored to symptoms, is generally encouraged. Activity prevents skeletal muscle deconditioning, which worsens functional status; whether this measure improves survival is under study. Rest is appropriate during acute exacerbations.

Treatment is tailored to the patient, considering causes, symptoms, and response to drugs, including adverse effects. Treatment of systolic and diastolic dysfunction differs somewhat, although there is overlap. The patient and family should be involved in treatment choices. They should be taught the importance of drug compliance, warning signs of decompensation, and use of supplemental drug doses for symptom relief. Intensive case management, particularly by monitoring drug compliance and frequency of unscheduled visits to the physician or emergency department and hospitalizations, can identify when intervention is needed. Specialized heart failure nurses are valuable in education, follow-up, and dosage adjustment according to predefined protocols. Many centers (such as specialized outpatient clinics) have integrated health care practitioners from different disciplines (such as heart failure nurses, pharmacists, social workers, rehabilitation specialists) into multidisciplinary teams or outpatient heart failure management programs. These approaches can improve outcomes and reduce hospitalizations and are most effective in the sickest patients.

If hypertension, severe anemia, hemochromatosis, uncontrolled diabetes, thyrotoxicosis, beriberi, alcoholism, Chagas' disease, or toxoplasmosis is successfully treated, patients may dramatically improve. Management of extensive ventricular infiltration (such as in amyloidosis) remains unsatisfactory.

Surgery: Surgery may be appropriate when certain underlying disorders are present. Usually, surgery in heart failure patients should be performed in a specialized center. Surgical closure of congenital or acquired intracardiac shunts can be curative. Coronary artery bypass grafting to reduce ischemia may help some patients with ischemic cardiomyopathy. If heart failure is primarily due to a valvular disorder, valve repair or replacement is considered. Patients with primary mitral regurgitation are more likely to benefit than patients with mitral regurgitation secondary to left ventricular dilation, in which myocardial function is likely to continue to be poor postoperatively. Surgery done before myocardial dilation and damage become irreversible is preferable.

Heart transplantation is the treatment of choice for patients < 60 who have severe, refractory heart failure and no other life-threatening conditions. Survival is 82% at 1 yr and 75% at 3 yr; however, mortality rate while waiting for a donor is 12 to 15%. Human organ donation remains low. Left ventricular assist devices can be a bridge to transplantation or, in a few selected patients, permanent. Artificial hearts are not yet a

viable alternative. Surgical options under study include implantation of restraining devices to reduce progressive dilation and a modified aneurysmectomy called surgical ventricular restoration. Dynamic cardiomyoplasty and excision of segments of dilated myocardium (Batista procedure) are no longer recommended.

Arrhythmias: Sinus tachycardia, a common compensatory change in heart failure, usually subsides when heart failure treatment is effective. If it does not, associated causes (such as hyperthyroidism, pulmonary emboli, fever, and anemia) should be sought. If it persists despite correction of causes, a beta-blocker, given in gradually increasing doses, should be considered.

Atrial fibrillation with an uncontrolled ventricular rate must be treated. Beta-blockers are the treatment of choice although rate-limiting Ca channel blockers, used cautiously, may be used if systolic function is preserved. Adding digoxin or low-dose amiodarone may help some patients. If heart failure is mild, conversion to sinus rhythm may be no better than rate control, but some patients with heart failure benefit from being in sinus rhythm. If rapid atrial fibrillation does not respond to drugs, permanent pacemaker insertion with complete or partial ablation of the atrioventricular node may be considered in selected patients.

Isolated ventricular premature beats, which are common in heart failure, do not require specific treatment. Sustained ventricular tachycardia that persists despite optimal medical treatment of heart failure may require an antiarrhythmic drug. Amiodarone and beta-blockers are the drugs of choice because other antiarrhythmics have adverse proarrhythmic effects when left ventricular systolic dysfunction is present. Because amiodarone increases digoxin levels, the digoxin dose should be decreased by 1/2. Because long-term use of amiodarone can cause adverse effects, a low-dose (200 to 300 mg. PO once/day) is used when possible; blood tests for liver function and thyroid-stimulating hormone are done every 6 mo, and if chest x-ray is abnormal or dyspnea worsens significantly, chest x-ray and pulmonary function tests are done yearly to check for pulmonary fibrosis. For sustained ventricular arrhythmias, amiodarone 400 mg PO once/day may be required.

An implantable cardioverter-defibrillator (ICD) is recommended for patients with an otherwise good life expectancy if they have symptomatic sustained ventricular tachycardia (especially if it causes syncope), ventricular fibrillation, or a left ventricular ejection fraction < 0.30 after MI.

Refractory heart failure: After treatment, symptoms often persist. Reasons include persistence of the underlying disorder (such as hypertension, ischemia, valvular regurgitation) despite treatment, suboptimal treatment of heart failure, drug noncompliance, excess intake of dietary Na or alcohol, and presence of an undiagnosed thyroid disorder, anemia, or supervening arrhythmia (such as atrial fibrillation with rapid ventricular response, or intermittent ventricular tachycardia). Also, drugs used to treat other disorders may interfere with heart failure treatment; NSAIDs, thiazolidinediones (such as pioglitazone) for diabetes, and short-acting dihydropyridine or nondihydropyridine Ca channel blockers can worsen heart failure and usually should not be used. Biventricular pacing relieves symptoms for patients who have heart failure, severe systolic dysfunction, and a widened QRS complex.

Drugs

Drugs for symptom relief include diuretics, nitrates, and digoxin. ACE inhibitors, beta-blockers, aldosterone receptor blockers, and angiotensin II receptor blockers are effective for long-term management and improve survival. Different strategies are used for systolic and diastolic dysfunction. In patients with severe diastolic dysfunction, diuretics and nitrates should be used in lower doses because these patients do not tolerate reduced BP or plasma volume well. In patients with hypertrophic cardiomyopathy, digoxin is not effective and may be harmful.

Diuretics: Diuretics are given to all patients with symptomatic systolic dysfunction; dose is adjusted to the lowest dose that stabilizes weight and relieves symptoms. Loop diuretics are preferred. Furosemide is used most often, starting at 20 to 40 mg PO once/day, increased to 120 mg once/day (or 60 mg bid) if needed based on response and renal function. Bumetanide is an alternative. In refractory cases, furosemide 40 to 160 mg IV, ethacrynic acid 50 to 100 mg IV, bumetanide 0.5 to 2 mg PO or 0.5 to 1.0 mg IV, or metolazone 2.5 to 10 mg PO may have an additive effect. Loop diuretics (particularly when used with metolazone) may cause hypovolemia with hypotension, hyponatremia, hypomagnesemia, and severe hypokalemia.

Serum electrolytes are monitored, initially daily (when diuretics are given IV) and subsequently as needed, particularly after a dose increase. The K-sparing diuretics spironolactone or eplerenone (which are also aldosterone receptor blockers) can be added to offset the K-losing effects of higher-dose loop diuretics; hyperkalemia may result, especially when ACE inhibitors or angiotensin II receptor blockers are also taken, so electrolytes must still be monitored. Thiazide diuretics are not normally used unless hypertension is present.

Reliable patients are taught to take additional diuretic doses as needed when weight or peripheral edema increases. They should seek medical attention promptly if weight gain persists.

Experimental ADH blockers increase water excretion and serum Na levels and may cause less hypokalemia and renal dysfunction. They may become useful adjuncts to current diuretic therapy.

ACE inhibitors: All patients with systolic dysfunction are given oral ACE inhibitors unless contraindicated (such as by plasma creatinine > 2.8 mg/dL, bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, or previous angioedema due to ACE inhibitors).

ACE inhibitors reduce production of angiotensin II and breakdown of bradykinin, mediators that affect the sympathetic nervous system, endothelial function, vascular tone, and myocardial performance. Hemodynamic effects include arterial and venous vasodilation, sustained decreases in left ventricular filling pressure during rest and exercise, decreased systemic vascular resistance, and favorable effects on ventricular remodeling. ACE inhibitors prolong survival and reduce heart failure hospitalizations. For patients with atherosclerosis and a vascular disorder, these drugs may reduce MI and stroke risk. For diabetics, they delay onset of nephropathy. Thus, ACE inhibitors may be used in patients with diastolic dysfunction and any of these disorders.

The starting dose should be low (1/4 to 1/2 target dose depending on BP and renal function); the dose is gradually adjusted upward over 2 to 4 wk as tolerated, then

continued indefinitely. Usual target doses of representative drugs include enalapril 10 to 20 mg bid, lisinopril 20 to 30 mg once/day, ramipril 50 mg bid.

If the hypotensive effect (more marked in patients with hyponatremia or volume depletion) is troublesome, it can often be minimized by reducing the dose of concomitant diuretics. ACE inhibitors often cause moderate reversible renal insufficiency due to vasodilation of the efferent glomerular arteriole. An initial 20 to 30% increase in creatinine is no reason to stop the drug but does require slower increases in dose, reduction in diuretic dose, or avoidance of NSAIDs. K retention may result because aldosterone's effect is reduced, especially in patients receiving K supplements. Cough occurs in 5 to 15% of patients, probably because bradykinin accumulates, but other causes of cough should also be considered. Occasionally, rash or dysgeusia (dysfunction of the sense of taste) occurs. Angioneurotic edema is rare but can be life threatening and is a contraindication to this class of drugs. Alternatively, angiotensin II receptor blockers can be used, although rarely cross-reactivity is reported. Both are contraindicated in pregnancy.

Plasma electrolytes and renal function should be measured before an ACE inhibitor is started, at 1 mo, and after each significant increase in dose or change in clinical condition. If dehydration or poor renal function due to acute illness develops, an ACE inhibitor may need to be stopped temporarily.

Angiotensin II receptor blockers (ARBs): These drugs are not demonstrably superior to ACE inhibitors but are less likely to cause cough and angioedema; they may be used when these adverse effects prohibit ACE inhibitor use. Whether ACE inhibitors and ARBs are equally effective in chronic heart failure is unclear, and the best dose is still under study. Usual oral target doses are valsartan 160 mg bid, candesartan 32 mg once/day, and losartan 50 to 100 mg once/day. Introduction, upward titration, and monitoring of ARBs and ACE inhibitors are similar. Like ACE inhibitors, ARBs can cause reversible renal dysfunction. If dehydration or poor renal function due to acute illness develops, an ARB may need to be stopped temporarily.

Adding ARBs to ACE inhibitors, beta-blockers, and diuretics should be considered for heart failure patients with persistent symptoms and repeated hospitalizations. Such combination therapy requires increased monitoring of BP, plasma electrolytes, and renal function.

Aldosterone receptor blockers: Because aldosterone can be produced independently of the renin-angiotensin system, its adverse effects are not inhibited completely even by maximal use of ACE inhibitors and ARBs. Thus, the aldosterone receptor blockers spironolactone and eplerenone can reduce mortality, including from sudden death. Generally, spironolactone 25 to 50 mg PO once/day is given to patients with severe chronic heart failure, and eplerenone 10 mg PO once/day to patients who have acute heart failure with left ventricular ejection fraction < 30% after MI. K supplements should be stopped. Serum K and creatinine should be checked q 1 to 2 wk for the 1st 4 to 6 wk and after dosage changes; dose is lowered if K is between 5.5 and 6.0 mEq/L and stopped if K is > 6.0 mEq/L, if creatinine increases above 2.5 mg/dL (220 μ mol/L), or if ECG changes of hyperkalemia are present.

Beta-Blockers: Beta-blockers, unless otherwise contraindicated (by asthma, 2nd- or 3rd-degree atrioventricular block, or previous intolerance), are an important addition to ACE inhibitors for chronic systolic dysfunction in most patients, including the elderly, and for

diastolic dysfunction in hypertension and hypertrophic cardiomyopathy. Some of these drugs improve left ventricular ejection fraction, survival, and other major cardiovascular outcomes in patients with chronic systolic dysfunction, including those with severe symptoms. Beta-blockers are particularly useful for diastolic dysfunction because they reduce heart rate, prolonging diastolic filling time, and possibly improve ventricular relaxation.

During acute decompensation, beta-blockers must be used with caution. They are not started until patients are stabilized and have little evidence of fluid retention; for patients already taking a beta-blocker, the dose is temporarily withheld or reduced.

The starting dose should be low (1/8 to 1/4 of the target daily dose), then gradually increased over 6 to 8 wk as tolerated. Usual oral target doses are carvedilol 25 mg bid (50 mg bid for patients = 85 kg), bisoprolol 10 mg once/day, metoprolol 50 to 75 mg bid (tartrate) or 200 mg once/day (succinate extended-release). Carvedilol, a 3rd-generation nonselective beta-blocker, is also a vasodilator with alpha-blocking and antioxidant effects; it is the preferred beta-blocker but is more expensive in many countries. Some beta-blockers (such as bucindolol and xamoterol) do not appear beneficial and may be harmful.

After initial treatment, heart rate and myocardial O₂ consumption decrease, and stroke volume and filling pressure are unchanged. With the slower heart rate, diastolic function improves. Ventricular filling returns to a more normal pattern (increasing in early diastole), which appears less restrictive. Improved myocardial function is measurable in many patients after 6 to 12 mo; Ejection Fraction and cardiac output increase, and left ventricular filling pressure decreases. Exercise capacity improves.

When started, beta-blockers may require a temporary increase in diuretic dose if the acute negative inotropic effects of beta-blockade cause cardiac depression and fluid retention.

In such cases, slower upward titration of the beta-blocker dose is warranted.

Vasodilators: Hydralazine plus isosorbide dinitrate may help patients truly intolerant of ACE inhibitors or ARBs (usually because of significant renal dysfunction), although long-term benefit of this combination is limited. As vasodilators, these drugs improve hemodynamics, reduce valvular regurgitation, and increase exercise capacity without causing significant renal impairment. Hydralazine is started at 25 mg PO qid and increased q 3 to 5 days to a target total dose of 300 mg/day, although many patients cannot tolerate > 200 mg/day because of hypotension. Isosorbide dinitrate is started at 20 mg PO tid (with a 12-hour nitrate-free interval) and increased to a target of 40 to 50 mg tid. Whether lower doses (frequently used in clinical practice) provide long-term benefit is unknown. In general, vasodilators have been replaced by ACE inhibitors, which are easier to use, are usually better tolerated, and have greater proven benefit.

Nitrates alone can relieve heart failure symptoms; patients can be taught to use nitroglycerin spray as needed for acute symptoms and a patch for nocturnal dyspnea. In patients with heart failure and angina, nitrates are safe, effective, and well tolerated.

Other vasodilators such as Ca channel blockers are not used to treat systolic dysfunction. Short-acting dihydropyridines (such as nifedipine) and nondihydropyridines (such as diltiazem, verapamil) are deleterious. However, amlodipine and felodipine are well tolerated and may be useful for patients with heart failure and associated angina or hypertension. Both drugs may cause peripheral edema; rarely, amlodipine causes pulmonary edema. Felodipine should not be taken with grapefruit juice, which

significantly increases plasma levels and adverse effects by inhibiting cytochrome P-450 metabolism. In patients with diastolic dysfunction, Ca channel blockers may be used as needed to treat hypertension or ischemia or to control ventricular rate in atrial fibrillation. Verapamil is used in hypertrophic cardiomyopathy.

Digitalis preparations: These drugs inhibit the Na⁺-K⁺-ATPase. As a result, they cause weak positive inotropism, reduce sympathetic activity, block the atrioventricular node (slowing the ventricular rate in atrial fibrillation or prolonging PR interval in sinus rhythm), reduce vasoconstriction, and improve renal blood flow.

Digoxin is the most commonly prescribed digitalis preparation. It is excreted by the kidneys; elimination half-life is 36 to 40 hours in patients with normal renal function. Digitoxin is largely excreted in the bile. It is an alternative for patients with poor renal function but is infrequently prescribed.

Digoxin has no proven survival benefit but, when used with diuretics and an ACE inhibitor, may help control symptoms. Digoxin is most effective in patients with large left ventricular end-diastolic volumes and an S3. Acute withdrawal of digoxin may increase the hospitalization rate and worsen symptoms. Toxicity is a concern, especially in patients with renal dysfunction and perhaps in women. These patients may need a lower oral dose, as may the elderly, patients with a low lean body mass, and patients also taking amiodarone; patients > 80 kg may need a higher dose. In general, lower doses are used than in the past, and a trough (8 to 12 hours post dose) digoxin level of 1 to 1.2 ng/mL is acceptable. Prescription patterns vary widely by physician and by country.

In patients with normal renal function, digoxin (0.125 to 0.375 mg po once/day depending on age, sex, and body size) achieves full digitalization in about 1 wk (5 half-lives). More rapid digitalization can be achieved with digoxin 0.5 mg IV followed by 0.25 mg at 8 and 16 hours or with 0.5 mg PO followed by 0.25 mg at 8, 16, and 24 hours.

Digoxin (and all digitalis glycosides) has a narrow therapeutic window. The most important toxic effects are life-threatening arrhythmias (such as ventricular fibrillation, ventricular tachycardia, complete atrioventricular block). Bidirectional ventricular tachycardia, nonparoxysmal junctional tachycardia in the presence of atrial fibrillation, and hyperkalemia are serious signs of digitalis toxicity. Nausea, vomiting, anorexia, diarrhea, confusion, amblyopia, and, rarely, xerophthalmia may occur. If hypokalemia or hypomagnesemia (often due to diuretic use) is present, lower doses and serum levels can cause toxicity. Electrolyte levels must be monitored frequently in patients taking diuretics and digoxin, so that abnormalities can be prevented if possible; K⁺-sparing diuretics may be helpful.

When digitalis toxicity occurs, the drug should be stopped; electrolyte abnormalities should be corrected (IV if abnormalities are severe and toxicity is acute). Patients with severe toxicity are admitted to a monitored unit, and digoxin immune Fab (ovine antidigoxin antibody fragments) is given if arrhythmias are present or if significant overingestion is accompanied by a serum K of > 5 mEq/L. This drug is also useful for glycoside toxicity due to plant ingestion. Dose is based on the steady-state serum digoxin level or total amount ingested. Ventricular arrhythmias are treated with lidocaine or phenytoin. Atrioventricular block with a slow ventricular rate may require a temporary transvenous pacemaker; isoproterenol is contraindicated because it increases risk of ventricular arrhythmia.

Other drugs: Various positive inotropic drugs have been evaluated in heart failure, but except for digoxin, they increase mortality risk. Regular outpatient IV infusions of inotropes (such as dobutamine) increase mortality and are no longer recommended. Drugs under study include Ca sensitizers, cytokine blockers, endothelin blockers, matrix metalloproteinase (MMP) inhibitors, and immune modulators.

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