

**MINISTRY OF HEALTHCARE OF UKRAINE  
HSEEU "Ukrainian Medical Stomatological Academy"**

**"Approved"**  
at the meeting of internal  
medicine №1 department  
Head of Department  
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Protocol № 4 from 13.10.2016

**GUIDELINES  
FOR STUDENTS  
INDEPENDENT WORK  
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Current practice of internal medicine
<i>Content module</i>	Management of the patients with main symptoms and syndromes in cardiology clinic
<i>Study subject</i>	<b>Management of the patients with chronic heart failure</b>
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

## **1. The aims of the training course:**

### **To Know:**

1. Tactic of patients treating.
2. Non-medicament, medication and surgical treatment.
3. Existing standards of treatment.
4. Primary and secondary prevention.
5. Weather and performance.

### **To be able to:**

- Conduct surveys and patients examination with major cardiological syndromes
- To draft survey the patients with heart diseases, to justify the use of major invasive and non-invasive diagnostic techniques which are using in cardiology, to identify indications and contraindications for their conduction, possible complications
- Identify different options for the course and complications of heart disease
- Carry out differential diagnosis, justify and formulate diagnoses for major cardiac syndromes based on laboratory analysis and test tool
- Prescribe treatment, determine prognosis, to conduct primary and secondary prevention in heart disease
- Register and interpret the ECG in 12 assignments
- Measure and interpret blood pressure
- Diagnose and assist in syncope
- Diagnose and assist in hypertensive crisis
- Diagnose and assist with arterial hypotension
- Diagnose and assist in the paroxysmal disorders of cardiac rhythm
- Diagnose and assist syndrome Morhany-Edems-Stoks
- Conduct pulmonary heart reanimation
- Demonstrate knowledge of moral principles medical specialist and professional principles of subordination

### **The contents of topic:**

#### **Text**

*Merck Manual Professional Version* <http://www.merckmanuals.com/professional>

Last full review/revision September 2013 by J. Malcolm O. Arnold, MD

## **Heart Failure**

Heart failure (HF) 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; the ventricles can be involved together or separately. Diagnosis is initially clinical, supported by chest x-ray, echocardiography, and levels of plasma natriuretic peptides. Treatment includes patient education, diuretics, ACE inhibitors, angiotensin II receptor blockers,  $\beta$ -blockers, aldosterone antagonists, digitalis, specialized implantable pacemakers and other devices, and correction of the underlying disorder.

HF affects about 5 million people in the US; > 500,000 new cases occur each year. About 23 million people are affected worldwide.

## **Physiology**

Cardiac contractility (force and velocity of contraction), ventricular performance, and myocardial  $O_2$  requirements are determined by preload, afterload, substrate availability (eg,  $O_2$ , fatty acids, glucose), heart rate and rhythm, and amount of viable myocardium. Cardiac output

(CO) is the product of stroke volume and 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 (LV) end-diastolic pressure, especially if higher than normal, is a reasonable measure of preload. LV 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 systolic BP at or shortly after the aortic valve opens represents peak systolic wall stress and approximates afterload.

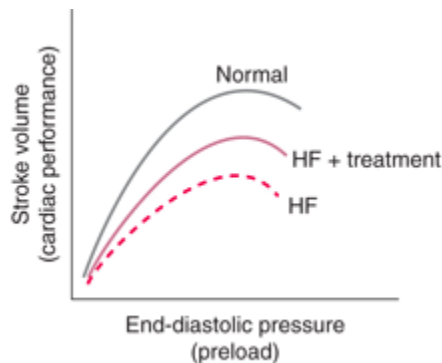
The Frank-Starling principle describes the relationship between preload and cardiac performance. It states that, normally, systolic contractile performance (represented by stroke volume or CO) is proportional to preload within the normal physiologic range. Contractility is difficult to measure without cardiac catheterization but is reasonably reflected by the ejection fraction (EF), which is the percentage of end-diastolic volume ejected with each contraction (stroke volume/end-diastolic volume). Contractility can generally be adequately assessed noninvasively with echocardiography, nuclear imaging, or MRI. EF is usually measured most accurately for the LV.

Cardiac reserve is the ability of the heart to increase its performance above resting levels in response to emotional or physical stress; body  $O_2$  consumption may increase from 250 to  $\geq 1500$  mL/min during maximal exertion. Mechanisms include increasing heart rate, systolic and diastolic volumes, stroke volume, and tissue extraction of  $O_2$  (the difference between  $O_2$  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 CO may increase from 6 to  $\geq 25$  L/min. At rest, arterial blood contains about 18 mL  $O_2$ /dL of blood, and mixed venous or pulmonary artery blood contains about 14 mL/dL.  $O_2$  extraction is thus about 4 mL/dL. When demand is increased, it may increase to 12 to 14 mL/dL. This mechanism also helps compensate for reduced tissue blood flow in HF.

## Cardiac Cycle

## Frank-Starling principle.

Normally (top curve), as preload increases, cardiac performance also increases. However at a certain point, performance plateaus, then declines. In heart failure (HF) due to systolic dysfunction (bottom curve), the overall curve shifts downward, reflecting reduced cardiac performance at a given preload, and, as preload increases, there is less of an increase in cardiac performance. With treatment (middle curve), performance is improved, although not normalized.



## Pathophysiology

In HF, 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. Although a primary abnormality can be a change in myocyte function, there are also changes in collagen turnover of the extracellular matrix. Cardiac structural defects (eg, congenital defects, valvular disorders), rhythm abnormalities (including persistently high heart rate), and high metabolic demands (eg, from thyrotoxicosis) also can cause HF.

## Systolic dysfunction

In systolic dysfunction (also called HF with reduced EF), the ventricle contracts poorly and empties inadequately, leading initially to increased diastolic volume and pressure and decreased EF. Many defects in energy utilization, energy supply, electrophysiologic functions, and contractile element interaction occur, with abnormalities in intracellular Ca modulation and cAMP production.

Predominant systolic dysfunction is common in HF due to MI, myocarditis, and dilated cardiomyopathy. Systolic dysfunction may affect primarily the LV or the right ventricle (RV); LV failure often leads to RV failure.

## Diastolic dysfunction

In diastolic dysfunction (also called HF with preserved EF), ventricular filling is impaired, resulting in reduced ventricular end-diastolic volume, increased end-diastolic pressure, or both. Contractility and hence EF remain normal; EF may even increase as the poorly filled LV empties more completely to maintain CO. Markedly reduced LV filling can cause low CO and systemic symptoms. Elevated left atrial pressures can cause pulmonary hypertension and pulmonary congestion.

Diastolic dysfunction usually results from impaired ventricular relaxation (an active process), increased ventricular stiffness, valvular disease, or constrictive pericarditis. Acute myocardial ischemia is also a cause of diastolic dysfunction. 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 predominates in hypertrophic cardiomyopathy, disorders with ventricular hypertrophy (eg, hypertension, significant aortic stenosis), and amyloid infiltration of the myocardium. LV filling and function may also be impaired if marked increases in RV pressure shift the interventricular septum to the left.

Diastolic dysfunction has increasingly been recognized as a cause of HF. Estimates vary, but about 50% of patients with HF have diastolic dysfunction and a normal EF; the prevalence increases with age and with diabetes.

## **LV failure**

In failure due to LV dysfunction, CO decreases and pulmonary venous pressure increases. When 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 ( $PaO_2$ ) 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 LV failure, pleural effusions characteristically develop in the right hemithorax and later bilaterally, further aggravating dyspnea. Minute ventilation increases; thus,  $PaCO_2$  decreases and blood pH increases (respiratory alkalosis). Marked interstitial edema of the small airways may interfere with ventilation, elevating  $PaCO_2$ —a sign of impending respiratory failure.

## **RV failure**

In failure due to RV dysfunction, 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 most severely affected, but the stomach and intestine also become congested; fluid accumulation in the peritoneal cavity (ascites) can occur. RV failure commonly causes moderate hepatic dysfunction, with usually modest increases in conjugated and unconjugated bilirubin, PT, and hepatic enzymes (eg, alkaline phosphatase, AST, ALT, gamma-glutamyl transpeptidase [GGT]). The impaired liver breaks down less aldosterone, further contributing to fluid accumulation. Chronic venous congestion in the viscera can cause anorexia, malabsorption of nutrients and drugs, 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 CO. As a result, the ventricles are remodeled over time: The LV becomes less ovoid and more spherical, dilates, and hypertrophies; the RV dilates and may hypertrophy. Initially compensatory, these changes eventually increase diastolic stiffness and wall tension (ie, diastolic dysfunction develops), compromising cardiac performance, especially during physical stress. Increased wall stress raises  $O_2$  demand and accelerates apoptosis (programmed cell death) of myocardial cells. Dilation of the ventricles can also cause mitral or tricuspid valve regurgitation with further increases in end-diastolic volumes.

## Hemodynamic responses

With reduced CO, O<sub>2</sub> delivery to the tissues is maintained by increasing O<sub>2</sub> extraction and sometimes shifting the oxyhemoglobin dissociation to the right to favor O<sub>2</sub> release.

Reduced CO 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 HF. 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 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 renal blood flow improves during rest, possibly contributing to nocturia.

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 HF.

The renin-angiotensin-aldosterone- vasopressin (antidiuretic hormone [ADH]) system causes a cascade of potentially deleterious long-term effects. Angiotensin II worsens HF by causing vasoconstriction, including efferent renal vasoconstriction, and by increasing aldosterone production, which not only enhances Na reabsorption in the distal nephron but also causes myocardial and vascular collagen deposition and fibrosis. Angiotensin II increases norepinephrine release, stimulates release of vasopressin, 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 HF. 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.

HF that causes progressive renal dysfunction (including that renal dysfunction caused by drugs used to treat HF) contributes to worsening HF and has been termed the cardiorenal syndrome.

## 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 ( $\alpha_1$ ,  $\beta_1$ ,  $\beta_2$ ,  $\beta_3$ , angiotensin II type 1 [AT<sub>1</sub>] and type 2 [AT<sub>2</sub>], muscarinic, endothelin, serotonin, adenosine, cytokine, natriuretic peptides); the roles of all of these receptors are not yet fully defined. In patients with HF,  $\beta_1$  receptors (which constitute 70% of cardiac  $\beta$  receptors) are downregulated, probably in response to intense

sympathetic activation. The result of downregulation is impaired myocyte contractility and increased heart rate.

Plasma norepinephrine levels are increased, largely reflecting sympathetic nerve stimulation as 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- vasopressin system.

Vasopressin is released in response to a fall in BP via various neurohormonal stimuli. Increased vasopressin decreases renal excretion of free water, possibly contributing to hyponatremia in HF. Vasopressin levels in patients with HF and 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 HF, the effect is blunted by decreased renal perfusion pressure, receptor downregulation, and perhaps enhanced enzymatic degradation.

Because endothelial dysfunction occurs in HF, fewer endogenous vasodilators (eg, nitric oxide, prostaglandins) are produced, and more endogenous vasoconstrictors (eg, endothelin) are produced, thus increasing afterload.

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  $\geq 10\%$ ), which may accompany severely symptomatic HF, and for other detrimental changes. The failing heart also undergoes metabolic changes with increased free fatty acid utilization and decreased glucose utilization; these changes may become therapeutic targets.

## **Changes with aging**

Age-related changes in the heart and cardiovascular system lower the threshold for expression of HF. Interstitial collagen within the myocardium increases, the myocardium stiffens, and myocardial relaxation is prolonged. These changes lead to a significant reduction in diastolic LV function, even in healthy elderly people. Modest decline in systolic function also occurs with aging. An age-related decrease in myocardial and vascular responsiveness to  $\beta$ -adrenergic stimulation further impairs the ability of the cardiovascular system to respond to increased work demands.

As a result of these changes, peak exercise capacity decreases significantly (about 8%/decade after age 30), and CO at peak exercise decreases more modestly. This decline can be slowed by regular physical exercise. Thus, elderly patients are more prone than are younger ones to develop HF symptoms in response to the stress of systemic disorders or relatively modest cardiovascular insults. Stressors include infections (particularly pneumonia), hyperthyroidism, anemia, hypertension, myocardial ischemia, hypoxia, hyperthermia, renal failure, perioperative IV fluid loads, nonadherence to drug regimens or to low-salt diets, and use of certain drugs (including NSAIDs,  $\beta$ -blockers, and certain Ca channel blockers).

## ***Etiology***

Both cardiac and systemic factors can impair cardiac performance and cause or aggravate HF.

## Causes of Heart Failure

Type	Examples
Cardiac	MI
	Myocarditis
Myocardial damage	Cardiomyopathy
	Some chemotherapy drugs
	Aortic stenosis
Valvular disorders	Mitral regurgitation
	Bradyarrhythmias
Arrhythmias	Tachyarrhythmias
	AV node block
Conduction defects	Left bundle branch block
Reduced substrate availability (eg, of free fatty acids or glucose)	Ischemia
	Amyloidosis
Infiltrative or matrix disorders	Chronic fibrosis
	Hemochromatosis
Systemic	Anemia
Disorders that increase demand for CO	Hyperthyroidism
	Paget disease
	Aortic stenosis
Disorders that increase resistance to output (afterload)	Hypertension
AV = atrioventricular; CO = cardiac output.	

## Classification

The traditional distinction between 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 HF and can be useful for initial evaluation and treatment. Other common descriptive terms include acute or chronic; congestive; high output or low output; systolic or diastolic; dilated or nondilated; and ischemic, hypertensive, or idiopathic dilated cardiomyopathy.

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

**RV failure** is most commonly caused by previous LV failure (which increases pulmonary venous pressure and leads to pulmonary arterial hypertension, thus overloading the RV) or by a



severe lung disorder (when it is called cor pulmonale. Other causes are multiple pulmonary emboli, RV infarction, primary pulmonary hypertension, tricuspid regurgitation or stenosis, mitral stenosis, pulmonary artery or valve stenosis, pulmonary venous occlusive disease, or congenital disorders such as Ebstein anomaly or Eisenmenger syndrome. Some conditions mimic RV failure, except cardiac function may be normal; they include volume overload and increased systemic venous pressure in polycythemia or overtransfusion, acute kidney injury with retention of Na and water, obstruction of either vena cava, and hypoproteinemia due to any cause resulting in low plasma oncotic pressure and peripheral edema.

**Biventricular failure** results from disorders that affect the whole myocardium (eg, viral myocarditis, amyloidosis, Chagas disease) or long-standing LV failure causing RV failure.

**High-output HF** results from a persistently high CO, which may eventually result in an inability of a normal heart to maintain adequate output. Conditions that may increase CO include severe anemia, beriberi, thyrotoxicosis, advanced Paget disease, arteriovenous fistula, and persistent tachycardia. CO 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. 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). The term is sometimes used to reflect etiology (eg, ischemic vs hypertensive cardiomyopathy). Cardiomyopathy does not always lead to symptomatic HF. It is often idiopathic and is classified as dilated, congestive, hypertrophic, infiltrative-restrictive, or apical-ballooning cardiomyopathy.

## Symptoms and Signs

Manifestations differ depending on the extent to which the LV and RV are initially affected. Clinical severity varies significantly and is usually classified according to the New York Heart Association (NYHA) system; the examples of ordinary activity may be modified for elderly, debilitated patients. Because HF has such a broad range of severity, some experts suggest subdividing NYHA class III into A or B. The American College of Cardiology classifies HF as A, B, C, or D.

- A: High risk of HF but no structural heart disease or symptoms
- B: Structural heart disease but no symptoms of HF
- C: Structural heart disease with symptoms of HF
- D: Refractory HF requiring specialized interventions

Severe LV failure may cause pulmonary edema or cardiogenic shock.

## New York Heart Association (NYHA) Classification of Heart Failure

NYHA Class	Definition	Limitation	Example
		Can complete any activity requiring $\leq 7$ MET:	
I	Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations.	None	<ul style="list-style-type: none"> <li>• Carry 11 kg up 8 steps</li> <li>• Carry objects weighing 36 kg</li> <li>• Shovel snow</li> <li>• Spade soil</li> <li>• Ski</li> </ul>

NYHA Class	Definition	Limitation	Example
			<ul style="list-style-type: none"> <li>• Play squash, handball, or basketball</li> <li>• Jog or walk 8 km/h</li> </ul> <p>Can complete any activity requiring <math>\leq 5</math> MET:</p>
II	Ordinary physical activity causes fatigue, dyspnea, palpitations, or angina.	Mild	<ul style="list-style-type: none"> <li>• Sexual intercourse without stopping</li> <li>• Garden</li> <li>• Roller skate</li> <li>• Walk 7 km/h on level ground</li> <li>• Climb one flight of stairs at a normal pace without symptoms</li> </ul> <p>Can complete any activity requiring <math>\leq 2</math> MET:</p>
III	Comfortable at rest; less than ordinary physical activity causes fatigue, dyspnea, palpitations, or angina.	Moderate	<ul style="list-style-type: none"> <li>• Shower or dress without stopping</li> <li>• Strip and make a bed</li> <li>• Clean windows</li> <li>• Play golf</li> <li>• Walk 4 km/h</li> </ul>
IV	Symptoms occur at rest; any physical activity increases discomfort.	Severe	Cannot do or cannot complete any activity requiring $\geq 2$ MET; cannot do any of the above activities

MET = metabolic equivalent task.

## History

**In LV failure**, the most common symptoms are dyspnea, reflecting pulmonary congestion, and fatigue, reflecting low CO. Dyspnea usually occurs during exertion and is relieved by rest. As HF 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 as HF advances. In paroxysmal nocturnal dyspnea (PND), dyspnea awakens patients several hours after they lie down and is relieved only after they sit up for 15 to 20 min. In severe HF, 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. Cheyne-Stokes breathing differs from PND in that the hyperpneic phase is short, lasting only 10 to 15 sec, but the cycle recurs regularly, lasting 30 sec to 2 min. PND is associated with pulmonary congestion, and Cheyne-Stokes respiration with low CO. Sleep-related breathing disorders, such as sleep apnea, are common in HF and may aggravate HF. Severely reduced cerebral blood flow and hypoxemia can cause chronic irritability and impair mental performance.

**In RV 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 HF symptoms include cool peripheries, postural light-headedness, nocturia, and decreased daytime micturition. 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.

In the elderly, presenting complaints may be atypical, such as confusion, delirium, falls, sudden functional decline, nocturnal urinary incontinence, or sleep disturbance. Coexisting cognitive impairment and depression may also influence assessment and therapeutic interventions and may be worsened by the HF.

## **Examination**

General examination may detect signs of systemic or cardiac disorders that cause or aggravate HF (eg, anemia, hyperthyroidism, alcoholism, hemochromatosis, atrial fibrillation with rapid rate, mitral regurgitation).

In LV failure, tachycardia and tachypnea may occur. Patients with severe LV failure may appear visibly dyspneic or cyanotic, hypotensive, and confused or agitated because of hypoxia and poor cerebral perfusion. Some of these less specific symptoms (eg, confusion) are more common in the elderly.

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  $O_2$  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 LV systolic dysfunction include a diffuse, sustained, and laterally displaced apical impulse; audible and occasionally palpable 3rd ( $S_3$ ) and 4th ( $S_4$ ) heart sounds, and an accentuated pulmonic component ( $P_2$ ) of the 2nd heart sound ( $S_2$ ). A pansystolic murmur of mitral regurgitation at the apex may occur. Pulmonary findings include early inspiratory basilar crackles that do not clear with coughing and, if pleural effusion is present, dullness to percussion and diminished breath sounds at the lung base(s).

Signs of RV 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 hepatjugular or abdominal-jugular reflux may be detected. Precordial palpation may detect the left parasternal lift of RV enlargement, and auscultation may detect the murmur of tricuspid regurgitation or the  $RV S_3$  along the left sternal border; both findings are augmented upon inspiration.

## **Diagnosis**

- Sometimes only clinical evaluation
- Chest x-ray
- Echocardiography, cardiac radionuclide scan, and/or MRI
- Sometimes NP/BNP or N-terminal-pro-BNP (NT-pro-BNP) levels
- ECG and other tests for etiology as needed

Clinical findings (eg, exertional dyspnea or fatigue, orthopnea, edema, tachycardia, pulmonary crackles, S<sub>3</sub>, jugular venous distention) suggest HF but are usually not apparent early. Similar symptoms may result from COPD or recurrent pneumonia or may be erroneously attributed to obesity or old age. Suspicion for HF should be high in patients with a history of MI, hypertension, or valvular disorders or murmurs and should be moderate in any patient who is elderly or has diabetes.

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

### **Chest x-ray**

Chest x-ray findings suggesting HF 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 (eg, COPD, pneumonia, interstitial pulmonary fibrosis, lung cancer).

### **ECG**

ECG findings are not diagnostic, but an abnormal ECG, especially showing previous MI, LV hypertrophy, left bundle branch block, or tachyarrhythmia (eg, rapid atrial fibrillation), increases suspicion for HF and may help identify the cause. An entirely normal ECG is uncommon in chronic HF.

### **Imaging**

**Echocardiography** can help evaluate chamber dimensions, valve function, EF, wall motion abnormalities, LV 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 LV diastolic dysfunction; tissue Doppler imaging is more accurate. Measuring LVEF can distinguish between predominant diastolic dysfunction (EF > 0.50) and systolic dysfunction (EF < 0.40). It is important to re-emphasize that HF can occur with a normal LVEF. 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 and is becoming more widely available. In many centers, multimode imaging (eg, stress MIBI [thallium and sestamibi stress tests] plus CT angiography) is becoming common, although there is growing concern about the radiation dose with CT angiography.

## **Blood tests**

Serum NP/BNP levels are high in HF; this finding may help when clinical findings are unclear or other diagnoses (eg, COPD) need to be excluded. It may be particularly useful for patients with a history of both pulmonary and cardiac disorders. NT-pro-BNP, an inactive moiety created when pro BNP is cleaved, can be used similarly to NP/BNP.

Recommended blood tests include CBC, 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.

## **Other tests**

Coronary angiography or CT coronary angiography is indicated when CAD is suspected or the etiology of HF is uncertain. Cardiac catheterization with intracardiac pressure measurements may be helpful in the diagnosis of restrictive cardiomyopathies and constrictive pericarditis.

Endocardial biopsy is sometimes done when an infiltrative cardiomyopathy is strongly suspected but cannot be confirmed with noninvasive imaging (eg, cardiac MRI).

## **Prognosis**

Generally, patients with HF have a poor prognosis unless the cause is correctable. Mortality rate at 1 yr from first hospitalization for HF is about 30%. In chronic HF, mortality depends on severity of symptoms and ventricular dysfunction and can range from 10 to 40%/yr. Specific factors that suggest a poor prognosis include hypotension, low EF, presence of CAD, troponin release, elevation of BUN, reduced GFR, hyponatremia, and poor functional capacity (eg, as tested by a 6-min walk test).

HF usually involves gradual deterioration, interrupted by bouts of severe decompensation, and ultimately death, although the time course is being lengthened with modern therapies. 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 and the risk of sudden cardiac death. For some patients, improving quality of life is as important as increasing quantity of life. Thus, it is important to determine patients' wishes about resuscitation (eg, endotracheal intubation, CPR) if their condition deteriorates, especially when HF is already 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 (when desired), who may be part of an interdisciplinary team or disease management program already in place, is particularly important in end-of-life care.

## **Treatment**

- Diet and lifestyle changes

- Treatment of cause
- Drugs (numerous classes)
- Sometimes device therapy (eg, implantable cardioverter-defibrillator, biventricular pacing)
- Multidisciplinary care

Immediate inpatient treatment is required for patients with acute or worsening HF due to certain disorders (eg, acute MI, atrial fibrillation with a very rapid ventricular rate, severe hypertension, acute valvular regurgitation), as well as for patients with pulmonary edema, severe symptoms, new-onset HF, or HF unresponsive to outpatient treatment. Patients with mild exacerbations of previously diagnosed HF can be treated at home.

The primary goal is to diagnose and to correct or treat the disorder that led to HF.

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

Long-term goals include correcting hypertension, preventing MI and atherosclerosis, improving cardiac function, reducing hospitalizations, and improving survival and quality of life. Treatment involves dietary and lifestyle changes, drugs, devices, and sometimes percutaneous coronary interventions or surgery.

Treatment is tailored to the patient, considering causes, symptoms, and response to drugs, including adverse effects. Treatment of systolic and diastolic dysfunction has become more similar, although there are more evidence-based therapies for systolic HF.

## **Disease management**

General measures, especially patient and caregiver education and diet and lifestyle modifications, are important for all HF patients.

- Education
- Na restriction
- Appropriate weight and fitness levels
- Correction of underlying conditions

Patient and caregiver education are critical to long-term success. The patient and family should be involved in treatment choices. They should be taught the importance of drug adherence, warning signs of decompensation, and how to link cause with effect (eg, increased salt in the diet with weight gain or symptoms).

Many centers (eg, specialized outpatient clinics) have integrated health care practitioners from different disciplines (eg, HF nurses, pharmacists, social workers, rehabilitation specialists) into multidisciplinary teams or outpatient HF management programs. These approaches can improve outcomes and reduce hospitalizations and are most effective in the sickest patients.

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  $< 2$  g/day by consuming only low-Na foods. Monitoring daily morning weight helps detect Na and water accumulation early. If weight increases  $> 2$  kg over a few days, patients may be able to adjust their diuretic dose themselves, but if weight gain continues or symptoms occur, patients should seek medical attention. Intensive case management, particularly by monitoring drug adherence and frequency of unscheduled visits to the physician or emergency department and

hospitalizations, can identify when intervention is needed. Specialized HF nurses are valuable in education, follow-up, and dosage adjustment according to predefined protocols.

Patients with atherosclerosis or diabetes should strictly follow a diet appropriate for their disorder. Obesity may cause and always aggravates the symptoms of HF; patients should attain a body mass index (BMI) of 21 to 25.

### **Clinical Calculator: Body Mass Index (Quetelet's index)**

Regular light activity (eg, walking), tailored to symptoms, is generally encouraged. Activity prevents skeletal muscle deconditioning, which worsens functional status; however, this measure does not appear to improve survival or decrease hospitalizations. Rest is appropriate during acute exacerbations. The role of formal exercise cardiac rehabilitation programs is being studied; initial results appear favorable.

Patients should have annual influenza vaccination because influenza can precipitate HF, particularly in the elderly.

If hypertension, persistent tachyarrhythmia, severe anemia, hemochromatosis, uncontrolled diabetes, thyrotoxicosis, beriberi, alcoholism, Chagas disease, or toxoplasmosis is successfully treated, patients may dramatically improve. Significant myocardial ischemia should be treated aggressively; treatment may include revascularization by percutaneous coronary intervention or bypass surgery. Management of extensive ventricular infiltration (eg, in amyloidosis) remains unsatisfactory.

## **Arrhythmias**

It is important to identify and treat the cause of an arrhythmia.

- Electrolytes are normalized.
- Atrial and ventricular rate are controlled.
- Sometimes antiarrhythmic drugs are given.

Sinus tachycardia, a common compensatory change in HF, usually subsides when HF treatment is effective. If it does not, associated causes (eg, hyperthyroidism, pulmonary emboli, fever, anemia, pain) 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; the target resting ventricular rate is typically  $< 80$  beats/min.  $\beta$ -Blockers are the treatment of choice, although rate-limiting Ca channel blockers may be used cautiously if systolic function is preserved. Adding digoxin, low-dose amiodarone, or other rhythm and/or rate controlling drugs may help some patients. Routine conversion to and maintenance of sinus rhythm has not been shown to be superior to rate control alone in a large clinical trial. If rapid atrial fibrillation does not respond to drugs, permanent pacemaker insertion with complete or partial ablation of the atrioventricular node, or other atrial fibrillation ablation procedures, may be considered in selected patients to restore a sinus or regular rhythm.

Isolated ventricular premature beats, which are common in HF, do not require specific treatment. However, optimization of HF treatments and correction of electrolyte abnormalities (especially K and Mg) reduce the risk of ventricular arrhythmias. Sustained ventricular tachycardia that persists despite correction of cause (eg, low K or Mg, ischemia) and optimal medical treatment of HF may require an antiarrhythmic drug. Amiodarone and  $\beta$ -blockers are the drugs of choice

because other antiarrhythmics have adverse proarrhythmic effects when LV systolic dysfunction is present. Because amiodarone increases digoxin levels, the digoxin dose should be decreased by half. Because long-term use of amiodarone can cause adverse effects, a low dose (200 mg po once/day) is used when possible; blood tests for liver function and thyroid-stimulating hormone are done every 6 mo. 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 may be required; to reduce risk of sudden death, a loading dose of 400 to 800 mg po bid is given for 1 to 3 wk until rhythm control is adequate, then dose is decreased over 1 mo to a maintenance dose of 400 mg po once/day. Dronedarone or other antiarrhythmic drugs can also be considered if close follow-up is available.

## **Device therapy**

Use of an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy is appropriate for some patients.

An 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 an LVEF persistently  $< 0.30$  while receiving good medical therapy.

CRT may relieve symptoms and reduce HF hospitalizations for patients who have HF, LVEF  $< 0.35$ , and a widened QRS complex ( $> 0.12$  sec—the wider the QRS, the greater potential benefit). Better ways of detecting ventricular dyssynchrony may help identify patients most likely to respond to CRT. CRT devices are effective but expensive, and patients should be appropriately selected. Many CRT devices also incorporate an ICD in their mechanism.

Ultrafiltration (venovenous filtration) can be useful in selected hospitalized patients with severe volume overload if they have not responded well to diuretic therapy and have rising serum creatinine (cardiorenal syndrome). Long-term benefits are still unclear.

An intra-aortic counterpulsation balloon pump is helpful in selected patients who have a good chance of recovery (eg, acute HF following MI). LV assist devices are implantable pumps that augment LV output. They were initially used only as a short-term intervention to maintain patients with severe HF awaiting transplant but are sometimes now used for extended periods (1 to 2 yr) in patients who are not transplant candidates. However, although survival can be prolonged, only a few of these patients (mainly those with acute, reversible symptoms) are able to recover sufficiently to tolerate device removal.

## **Surgery**

Surgery may be appropriate when certain underlying disorders are present. Usually, surgery in HF patients should be done in a specialized center. Surgical closure of congenital or acquired intracardiac shunts can be curative. Coronary artery bypass grafting to reduce ischemia did not improve survival in a large clinical trial of HF patients with ischemic systolic dysfunction. If HF 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 LV dilation, in whom myocardial function is likely to continue to be poor postoperatively. Surgery is preferably done before myocardial dilation and damage become irreversible.

Heart transplantation is the treatment of choice for patients  $< 60$  who have severe, refractory HF and no other life-threatening conditions and who are highly adherent to management recommendations. Some older patients with otherwise excellent health may be considered. Survival is 85 to 90% at 1 yr, and annual mortality thereafter is about 4%/yr; however, mortality



rate while waiting for a donor is 12 to 15%. Human organ donation remains low. LV assist devices continue to improve and can be a bridge to transplantation or recovery in carefully selected patients.

## **Experimental therapies**

Artificial hearts are not yet a long-term viable alternative. Stem cell transplantation is in early-stage trials. Surgical options studied include implantation of restraining devices to reduce progressive dilation and a modified aneurysmectomy called surgical ventricular restoration, but neither showed clinical benefit.

Dynamic cardiomyoplasty, endocardial laser therapy, and excision of segments of dilated myocardium are no longer recommended.

## **Persistent HF**

After treatment, symptoms often persist. Reasons include persistence of the underlying disorder (eg, hypertension, ischemia/infarction, valvular disease) despite treatment; suboptimal treatment of HF; drug nonadherence; excess intake of dietary Na or alcohol; and presence of an undiagnosed thyroid disorder, anemia, or supervening arrhythmia (eg, atrial fibrillation with rapid ventricular response, intermittent ventricular tachycardia). Also, drugs used to treat other disorders may interfere with HF treatment. NSAIDs, thiazolidinediones (eg, pioglitazone) for diabetes, and short-acting dihydropyridine or nondihydropyridine Ca channel blockers can worsen HF and should be avoided unless no alternative exists; patients who must take such drugs should be followed closely.

## ***Drugs for Heart Failure***

- Symptom relief: Diuretics, nitrates, or digoxin
- Long-term management and improved survival: ACE inhibitors,  $\beta$ -blockers, aldosterone antagonists, or angiotensin II receptor blockers (ARBs)

In systolic dysfunction, all these drug classes have been studied and have shown benefit.

In diastolic dysfunction, fewer drugs have been adequately studied. However, ACE inhibitors, ARBs, and  $\beta$ -blockers are generally used to treat diastolic HF. 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.

All patients should be given clear and explicit information about their drugs, including the importance of timely prescription renewal and adherence to therapy, how to recognize adverse effects, and when to contact their physician. Research is seeking plasma biomarkers that may predict which patients might respond best to which drug or drug combination.

## **Diuretics**

Diuretics are given to all patients with symptomatic systolic dysfunction and current or previous volume overload; dose is adjusted to the lowest dose that stabilizes weight and relieves symptoms. Loop diuretics are typically preferred. Furosemide is used most often, usually starting at 40 mg po once/day, increased up to about 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. IV infusion of furosemide (5 to 10 mg/h) may be helpful in selected patients with severe edema. Loop diuretics (particularly when used with metolazone) may cause hypovolemia with hypotension, hyponatremia, hypomagnesemia, and severe hypokalemia. The dose of diuretic required acutely can usually be gradually reduced; the target is the lowest dose that maintains stable weight and controls symptoms. When HF improves, the diuretic may be stopped if other drugs improve heart function and relieve HF symptoms. Using larger than required doses of diuretics lowers CO, impairs renal function, causes hypokalemia, and increases mortality. Serum electrolytes and renal function are monitored, initially daily (when diuretics are given IV) and subsequently as needed, particularly after a dose increase.

A K-sparing diuretic, either spironolactone or eplerenone (which are aldosterone antagonists), can be added to offset the K-losing effects of higher-dose loop diuretics. Hyperkalemia may result, especially when ACE inhibitors or ARBs are also taken, so electrolytes must still be monitored, especially during a dehydrating illness that could cause renal dysfunction. These drugs may have particular benefit in chronic RV failure, in which hepatic congestion results in elevated aldosterone levels as its metabolism is reduced.

Thiazide diuretics are not normally used as a single agent unless hypertension is present but may be added to a loop diuretic for added diuresis.

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.

Vasopressin (antidiuretic hormone) receptor antagonists are not frequently used even though hypokalemia and renal dysfunction may be less.

## **ACE inhibitors**

All patients with systolic dysfunction are given oral ACE inhibitors unless contraindicated (eg, by plasma creatinine > 2.8 mg/dL [ $> 250 \mu\text{mol/L}$ ], 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 LV filling pressure during rest and exercise, decreased systemic vascular resistance, and favorable effects on ventricular remodeling. ACE inhibitors prolong survival and reduce HF hospitalizations. For patients with atherosclerosis and a vascular disorder, these drugs reduce MI and stroke risk. For patients with diabetes, they delay onset of nephropathy. Thus, ACE inhibitors may be used in patients with diastolic dysfunction and any of these disorders.

The starting dose typically should be low (usually one fourth to one half of the target dose depending on BP and renal function); the dose is gradually adjusted upward over 8 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, and ramipril 5 mg bid; there are many others.

If the hypotensive effect (more marked in patients with hyponatremia or volume depletion) is troublesome, it can often be minimized by separating administration of other BP-lowering drugs, reducing the dose of concomitant diuretics, using a longer acting ACE inhibitor (eg, perindopril), or giving the dose at bedtime. ACE inhibitors often cause mild to moderate reversible serum creatinine elevation 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 closer monitoring, slower increases in dose, reduction in diuretic dose, or avoidance of NSAIDs. Because aldosterone's

effect is reduced, K retention may result, 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 occurs. Angioedema is rare but can be life threatening and is a contraindication to this class of drugs. Alternatively, ARBs can be used, although rarely cross-reactivity is reported. Both are contraindicated in pregnancy.

Serum 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, the ACE inhibitor dose may need to be reduced or the drug may be temporarily stopped.

## **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. ACE inhibitors and ARBs are equally effective post MI; however, their equivalence is less clear in chronic HF. 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, and the dose may need to be reduced or stopped temporarily during an acute dehydrating illness.

Adding an ARB to a regimen of an ACE inhibitor,  $\beta$ -blocker, and diuretic should be considered for HF patients with persistent symptoms and repeated hospitalizations. Such combination therapy requires increased monitoring of BP, serum electrolytes, and renal function.

## **Aldosterone antagonists**

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 antagonists (also termed mineralocorticoid receptor antagonists) are often used, particularly for patients with moderate to severe symptoms or signs of heart failure. Typical drugs include spironolactone 25 to 50 mg po once/day and eplerenone 10 mg po once/day (does not cause gynecomastia in males). Aldosterone antagonists can reduce mortality, including from sudden death, in patients with LVEF < 30% and chronic HF, or acute HF complicating acute MI. K supplements should be stopped. Serum K and creatinine should be checked every 1 to 2 wk for the first 4 to 6 wk and after dose 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  $\mu$ mol/L), or if ECG changes of hyperkalemia are present. These drugs are usually not used in patients receiving both an ACE inhibitor and an ARB because of the high risk of hyperkalemia and renal dysfunction. There is limited clinical trial experience with the combined use of ACE inhibitors, ARBs, and aldosterone antagonists.

## **$\beta$ -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. They are best started when the patient has no evidence of pulmonary congestion. Some of these drugs improve LVEF, 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 improving ventricular relaxation.

The starting dose should be low (one fourth of the target daily dose), then the dose is gradually increased over 8 wk as tolerated. The acute negative inotropic effects of  $\beta$ -blockade may initially cause cardiac depression and fluid retention. In such cases, a temporary increase in diuretic dose and slower upward titration of the  $\beta$ -blocker dose is warranted. Tolerance may improve over time, and efforts should be made to reach target doses. Usual oral target doses are carvedilol 25 mg bid (50 mg bid for patients  $\geq 85$  kg), bisoprolol 10 mg once/day, and 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 and most widely studied  $\beta$ -blocker but is more expensive in many countries. Some  $\beta$ -blockers (eg, bucindolol, xamoterol) do not appear beneficial and may be harmful.

During a severe, acute decompensation,  $\beta$ -blockers should not be started until patients are stabilized and have little evidence of fluid retention. For patients already taking a  $\beta$ -blocker, the dose may be temporarily reduced or, in severe decompensation, temporarily stopped but restarted and titrated again when patients are stable. For milder decompensations, the  $\beta$ -blocker dose should be continued with a temporary increase in diuretic dose.

After initial treatment, heart rate and myocardial  $O_2$  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 some patients after 6 to 12 mo but may take longer; EF and CO increase, and LV filling pressure decreases. Exercise capacity improves.

## 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. In black patients, when added to standard therapy, this combination has been shown to reduce mortality and hospitalization, and improve quality of life. 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 every 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-h 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 HF symptoms; patients can be taught to use sublingual nitroglycerin spray as needed for acute dyspnea and a transdermal patch for nocturnal or exertional dyspnea. Nitrates are safe, effective, and well tolerated and are particularly helpful in patients with HF and angina. Adverse effects include hypotension and headache.

Other vasodilators such as Ca channel blockers are not used to treat systolic dysfunction. Short-acting dihydropyridines (eg, nifedipine) and nondihydropyridines (eg, diltiazem, verapamil) may be deleterious. However, amlodipine and felodipine are better tolerated and may be useful for patients with HF 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 may be used in hypertrophic cardiomyopathy.

## Digitalis preparations

These drugs inhibit the Na-K pump ( $\text{Na}^+$ ,  $\text{K}^+$ -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 the 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 h in patients with normal renal function.

Digoxin has no proven survival benefit but, when used with diuretics and an ACE inhibitor, may help control symptoms and reduce the likelihood of hospitalization. Digoxin is most effective in patients with large LV end-diastolic volumes and an  $\text{S}_3$ . Acute withdrawal of digoxin may increase the hospitalization rate and worsen symptoms. 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 over 15 min followed by 0.25 mg IV at 8 and 16 h or with 0.5 mg po followed by 0.25 mg po at 8, 16, and 24 h. Prescription patterns vary widely by physician and by country, but in general, doses are lower than those used in the past, and a trough (8- to 12-h post-dose) digoxin level of 0.8 to 2 ng/mL is acceptable.

Toxicity is a concern, especially in patients with renal dysfunction and perhaps in women. These patients may need a lower oral dose, as may elderly patients, patients with a low lean body mass, and patients also taking amiodarone; patients > 80 kg may need a higher dose. Digoxin (and all digitalis glycosides) has a narrow therapeutic window. The most important toxic effects are life-threatening arrhythmias (eg, 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 still cause toxicity. Electrolyte levels should be monitored 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 HF but, except for digoxin, they increase mortality risk. These drugs can be grouped as adrenergic mode of action (norepinephrine, epinephrine, dobutamine, dopamine) or nonadrenergic (enoximone, milrinone, levosimendan [Ca sensitizers]). Regular outpatient IV infusions of inotropes (eg, dobutamine) increase mortality and are not recommended. Other drugs recently studied include Ca sensitizers (eg, levosimendan), cytokine blockers, endothelin blockers, matrix metalloproteinase (MMP) inhibitors, and immune modulators; none of these appear to improve outcomes compared to standard therapy. Anticoagulant drugs may be considered in patients with very large ventricles at risk of mural thrombus.

## **Key Points**

- HF involves ventricular dysfunction that ultimately leads to the heart not providing tissues with adequate blood for metabolic needs.
- In systolic dysfunction, the ventricle contracts poorly and empties inadequately; EF is low.
- In diastolic dysfunction, ventricular filling is impaired, resulting in reduced ventricular end-diastolic volume, and/or increased end-diastolic pressure; contractility and hence EF remain normal.
- Consider HF in patients with exertional dyspnea or fatigue, orthopnea, and/or edema, particularly in those with a history of MI, hypertension, or valvular disorders or murmurs.
- Do chest x-ray, ECG, and an objective test of cardiac function, typically echocardiography.
- Unless the cause is correctable, HF tends to progress and have a poor prognosis.
- Treatment includes education and lifestyle changes, control of underlying disorders, a variety of drugs, and sometimes implantable devices (pacemakers, ICDs).

Last full review/revision September 2013 by J. Malcolm O. Arnold, MD

### **Self preparation at class:**

Listen information;

Work with patients (with cardiac pathology);

Ask about the problems that have not been found in information given.

### **Self preparation at home:**

Compose the plan of your answer;

Answer the questions to the topic;

Do the test given above.

## **Questions**

1. Can an angiotensin II receptor blocker (ARB) be used instead of an ACE inhibitor?
2. What is the role of B-type natriuretic peptide (BNP)?
3. What is the optimal dosage and titration sequence for angiotensin converting enzyme (ACE) inhibitors and  $\beta$ -blockers in the treatment of chronic HF?

### **Recommended literature:**

#### **A. Main:**

1. "Harrison's principles of internal medicine", Editors: Anthony S. Fauci, Dennis L. Kasper, Stephen L Hauser, Dan L. Longo, Joseph Loscalzo, McGraw-Hill Education / Medical; 19 edition (April 8, 2015), 1-2 volumes, 3000 p.
2. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)
3. CURRENT Diagnosis and Treatment Emergency Medicine, Seventh Edition (LANGE CURRENT Series) by C. Keith Stone (May 23, 2011)
4. Goldman's Cecil medicine / [edited by] Lee Goldman, Andrew I. Schafer.—24th ed. Elsevier Sanders. Rev. ed. of: Cecil medicine. 23rd ed. — 2012. p.

## Answers

1. No; these 2 classes are not equivalent. Small mechanistic studies have suggested similar improvement in surrogate end points (eg, LV remodeling), but survival data are not comparable so far.<sup>14</sup> Two large-scale randomized controlled trials of losartan (Losartan Heart Failure Survival Study [ELITE II]<sup>15</sup>) and valsartan (Valsartan Heart Failure Trial [Val-HeFT]<sup>16</sup>) failed to show that these agents reduced mortality more than standard doses of ACE inhibitors. ACE inhibitors should therefore remain first-line agents for chronic HF unless contraindicated.

Routine combined use of ARBs, ACE inhibitors, and  $\beta$ -blockers is not recommended; patients in this tripletherapy subgroup in the Val-HeFT study had a higher overall mortality. This observation warrants further testing (eg, in the upcoming Valsartan in Acute Myocardial Infarction [VALIANT] trial).

Generally, patients with severe rash or intolerable cough resulting from ACE inhibitor use (about 5% to 8%) should be switched to an ARB. Because cough can sometimes be associated with the heart failure syndrome, careful evaluation is warranted before the switch is made. A similar incidence of renal insufficiency (serum creatinine greater than 3 mg/dL) and hyperkalemia (serum potassium greater than 6 mEq/dL) has been observed with ARBs and ACE inhibitors. Angioedema has also occurred with both agents, especially in African Americans. Consider a hydralazine-nitrate combination in patients with this potentially life-threatening side effect. It is unclear whether angioedema is likely to occur with an ARB if it has occurred with an ACE inhibitor, but such a cross-reaction is possible. - See more at:

<http://www.consultantlive.com/articles/chronic-heart-failure-10-questions-physicians-often-ask#sthash.r65PfFrJ.dpuf>

2. BNP belongs to a family of naturally occurring hormones that are synthesized in the cardiac ventricles. Plasma levels of BNP often correspond to the severity of underlying cardiac dysfunction and can provide relatively reliable prognostic information, thus making BNP measurement a potential “white cell count” for chronic HF.<sup>3</sup>

A bedside BNP assay. The recently approved point-of-care BNP assay enables clinicians to measure plasma BNP levels at the bedside. Women and elderly patients usually have higher normal baseline values of BNP. The assay, which uses an arbitrary cut-off of 100 pg/mL, is highly sensitive and specific in determining whether cardiac dysfunction is the cause of dyspnea.<sup>4</sup> If a patient presents with dyspnea and low BNP levels, it is unlikely that cardiac causes are involved. However, some patients with stable, well-managed chronic HF or those with flash pulmonary edema at symptom onset may present with normal levels of plasma BNP.

Despite the utility of BNP assays in ruling out cardiac causes of dyspnea, plasma BNP levels vary widely in patients with established cardiac conditions. In patients with decompensated HF, BNP levels are more than 50% above baseline, but a single measurement of plasma BNP may not accurately correlate with filling pressure or the degree of decompensation. Common conditions that may falsely elevate plasma BNP levels include age, significant renal dysfunction, and surgery (especially cardiothoracic procedures).

Significance of BNP levels. There is little doubt that elevated plasma BNP levels indicate a high risk of morbidity and mortality in patients with chronic HF<sup>5</sup> or with acute coronary syndrome.<sup>6</sup> Rehospitalization rates are usually lower among patients who achieve BNP levels below 400

pg/mL; those with BNP levels higher than 1000 pg/mL often have an especially poor prognosis. Additional laboratory-based BNP and Nterminal proBNP assays will soon be available for routine diagnostic use, but more data are needed to support the routine use of sequential plasma BNP assays to guide medical therapy.

Nesiritide. The BNP used for diagnosis is not to be confused with the vasodilator nesiritide, a human recombinant form of BNP given as a continuous infusion in patients with acute HF.<sup>8</sup> A number of studies have established that nesiritide effectively lowers intracardiac pressures during acute exacerbations of HF and has a good safety profile. The drug is relatively expensive; it costs about the same as milrinone but more than nitroglycerin or nitroprusside. Guidelines for patient selection for nesiritide therapy are still evolving. - See more at:

<http://www.consultantlive.com/articles/chronic-heart-failure-10-questions-physicians-often-ask#sthash.r65PffrJ.dpuf>

**3.** Consider both classes of drugs for every patient with chronic HF, regardless of disease severity.<sup>1</sup> Tens of thousands of patients with chronic systolic HF have been treated with these agents in clinical studies worldwide; results show a remarkable improvement in morbidity and mortality. Nevertheless, these agents remain relatively underused, in part because they can be difficult to titrate. In addition, although ACE inhibitors and  $\beta$ -blockers are likely to benefit patients with diastolic HF, the guidelines for using these drugs in such patients are not well defined.

Target drug dosages to those used in the clinical trials. Patients who experience adverse events from steady up-titration schedules may be able to tolerate a slower pace of increases. A schedule for up-titration of ACE inhibitors has never been clearly defined, but increasing the dosage on a weekly basis is reasonable.

The absence of clinical HF is not a compelling reason to stop up-titration, nor is mild to moderate renal insufficiency (serum creatinine levels of less than 3 mg/dL). Prerenal azotemia often occurs with ACE inhibitor up-titration, especially following aggressive diuresis. In such cases, the preferred strategy is slower up-titration and temporary discontinuation of diuretic therapy.

Several mechanistic and largescale mortality studies failed to demonstrate a clear-cut benefit of highdose ACE inhibition over the more commonly used low-dose regimens. For example, the Assessment of Treatment With Lisinopril and Survival (ATLAS) trial showed only a slight improvement in a composite end point of mortality and hospital admissions when high doses of lisinopril (32.5 to 35 mg/d) were compared with low doses (2.5 to 5 mg/d).<sup>11</sup>

The usual practice is to titrate the ACE inhibitor first and then start the  $\beta$ -blocker. However, there is no set rule, and separate titration serves mainly as a convenient way to monitor drug tolerability. Sometimes these agents can be initiated together (especially when  $\beta$ -blockers are likely to be beneficial, as in a hypertensive patient with tachycardia). Many experts initiate  $\beta$ -blockers before ACE inhibitors are fully maximized. A slow increase in  $\beta$ -blocker dosage on a biweekly to monthly basis is reasonable.

Contraindications to  $\beta$ -blocker therapy include cardiogenic shock, bradycardia with a high degree of heart block, active wheezing (in patients with bronchospasm), severe emphysema, and sustained symptomatic hypotension. Adjustments to diuretic dosage (eg, an increase to reduce fluid retention) and ACE inhibitor dosages (eg, a reduction to maintain adequate blood pressure) are often required during  $\beta$ -blocker up-titration when symptoms of light-headedness or fluid retention develop.



Data on the effects of down-titration of ACE inhibitors or  $\beta$ -blockers are limited, although several observational series have suggested adverse outcomes. In cases of acute exacerbation of HF or acute renal insufficiency, temporary withdrawal of these drugs may be necessary. - See more at: <http://www.consultantlive.com/articles/chronic-heart-failure-10-questions-physicians-often-ask#sthash.r65PffrJ.dpuf>

Methodical recommendations consisted by

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