

ST-segment deviation has a lower reported accuracy in women. Therefore, stress testing with imaging provides better accuracy in women (see Diagnostic Testing in Cardiology). Because of these differences, the same guideline recommendations apply to both women and men.

Reports from observational studies and substudies of randomized controlled trials suggest that women have worse outcomes after STEMI presentation. The cause of these differences is thought to be delays in recognition of symptoms and longer overall ischemic time. Complication rates are also reported to be higher in women who undergo reperfusion therapy for STEMI. The COURAGE trial demonstrated that among patients with stable angina treated with percutaneous coronary intervention, women had lower rates of overall mortality and a nonfatal MI but a higher rate of complications compared with men. Overall, treatment guidelines do not differ between men and women.

Diabetes Mellitus

Diagnosis and Evaluation

Diabetes has been proposed as a CAD equivalent because age-adjusted risk for CAD events is two- to threefold higher in patients with diabetes. Cardiovascular morbidity and mortality are also significantly higher in this population, especially in patients with type 2 diabetes. Much of the risk has been attributed to the higher incidence of known cardiovascular risk factors; however, evidence suggests that underlying vascular dysfunction may play an important role.

Patients with diabetes may present with atypical cardiac symptoms, such as dyspnea or nausea, requiring a high index of suspicion for CAD during their evaluation. The diagnostic accuracy of noninvasive stress testing in symptomatic patients with diabetes is similar to that in patients without diabetes. Although traditional risk factors for CAD should be aggressively managed in patients with diabetes, screening for CAD in asymptomatic persons is controversial, and routine stress testing is not recommended.

Medical Therapy and Secondary Prevention

Medical therapy for patients with diabetes and CAD includes aggressive risk factor reduction, glucose control, and secondary prevention. The American College of Cardiology/American Heart Association recommend antihypertensive treatment with a target blood pressure below 130/80 mm Hg for patients with diabetes. In contrast, the American Heart Association recommends a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg for most patients. Lower systolic and diastolic blood pressure targets may be appropriate for patients at high risk for cardiovascular disease, if they can be achieved without undue treatment burden. ACE inhibitors and ARBs are preferred in the setting of hypertension because of their kidney-protective effects. High-intensity statin therapy is indicated in most patients with diabetes and CAD.

Aspirin is recommended for secondary prevention in all patients with diabetes and CAD. Primary prevention is recommended for patients with diabetes with a 10-year cardiovascular risk greater than 10% or one additional risk factor.

Tight glycemic control reduces microvascular complications; however, it does not reduce the risk for MI. In a recent study, liraglutide, a glucagon-like peptide-1 analogue, was associated with reduced risk for cardiovascular death in patients with type 2 diabetes and high cardiovascular risk. Initial studies suggested thiazolidinediones, specifically rosiglitazone, were associated with an elevated risk for cardiovascular events, although a subsequent clinical trial demonstrated no elevated risk for MI or death. Consequently, the FDA has removed the restriction on rosiglitazone use in patients with type 2 diabetes and CAD. Metformin does not have any cardiovascular effects, but caution should be exercised in patients undergoing coronary angiography, patients who have had an MI, and patients with heart failure because of concern for potentially fatal lactic acidosis.

Invasive Treatment

The choice of revascularization strategy (PCI or CABG) in patients with diabetes is based on many factors, including the severity and extent of CAD, comorbid conditions, and degree of atherosclerotic narrowing of small, distal vessels. Mortality rates are similar between the two procedures; however, CABG is generally preferred because it is associated with lower rates of repeat revascularization. In patients who undergo PCI, drug-eluting stent placement is recommended to reduce the occurrence of target vessel revascularization because of higher rates of restenosis in patients with diabetes.

- Stress testing is not routinely recommended in asymptomatic patients with diabetes mellitus to detect subclinical coronary artery disease.
- Coronary artery bypass grafting is the preferred mode of revascularization in patients with diabetes mellitus.

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Heart Failure

Pathophysiology of Heart Failure

Heart failure is a clinical syndrome characterized by signs and symptoms of fluid overload and decreased cardiac output. Heart failure can result from systolic or diastolic dysfunction. In cases of systolic dysfunction, multiple causes result in reduced stroke volume and ejection fraction, termed heart failure with reduced ejection fraction (HFrEF). Common causes of HFrEF include coronary artery disease (CAD), myocarditis, valvular heart disease, infiltrative processes, and hypertension. Diastolic dysfunction is usually characterized by a stiffened left ventricle with abnormal relaxation during diastole, resulting in an increase in left

ventricular preload. Ejection fraction classically remains normal in this setting, known as heart failure with preserved ejection fraction (HFpEF). Common causes of HFpEF include hypertension, aging, obesity, diabetes mellitus, and CAD. Often, patients with heart failure have concomitant systolic and diastolic dysfunction. The outcome of both processes is increased left ventricular filling pressures, which are transmitted to the lungs and subsequently to the right ventricle and the body. The increase in pressures causes the classic signs and symptoms of heart failure, including dyspnea, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, crackles on pulmonary auscultation, elevated jugular venous pressure, and an S_3 .

In patients with heart failure, compensatory mechanisms activate to adapt to the reduction in cardiac output and elevated pressures. The heart dilates in response to an increase in preload to improve myocardial contraction (Frank-Starling mechanism). To combat the increase in wall stress that occurs with dilatation and high filling pressures, the myocytes hypertrophy, initially reducing wall stress but eventually leading to reduced left ventricular compliance. These changes improve or maintain stroke volume at first; however, in the long term, they contribute to worsening cardiac function.

Another compensatory mechanism is the upregulation of the renin-angiotensin-aldosterone system to produce angiotensin II and aldosterone. Angiotensin II causes vasoconstriction, which improves blood pressure and stimulates thirst. Aldosterone increases fluid retention by increasing sodium resorption. The adrenergic nervous system is stimulated, resulting in release of epinephrine, norepinephrine, and vasopressin. The hormones cause an increase in heart rate, contractility, and vascular resistance, and vasopressin causes additional water retention. These mechanisms improve blood pressure and forward flow initially; however, over time, they become deleterious. The increase in blood pressure causes an increase in afterload, leading to reduced stroke volume and increased ventricular preload. The increase in volume results in an increase in preload and left ventricular distention, followed by a rise in pulmonary pressures and enlarged heart size owing to both myocyte hypertrophy and elongation. Elevated levels of neurohormones also cause myocyte injury and adversely promote remodeling. The result is a cycle of slowly worsening left ventricular function with decreasing forward flow and increasing pulmonary and right-sided pressures.

- Common causes of heart failure with reduced ejection fraction include coronary artery disease, myocarditis, valvular heart disease, infiltrative processes, and hypertension.
- Heart failure with preserved ejection fraction is commonly caused by hypertension, aging, obesity, diabetes mellitus, or coronary artery disease.

Screening and Prevention

Patients at risk for heart failure (such as those with hypertension, diabetes, or vascular disease), but without heart failure symptoms or left ventricular dysfunction, should be screened with B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement followed by early intervention with appropriate therapy in those with elevated levels. BNP assays are typically used to establish or exclude heart failure as the cause of dyspnea. Small studies have shown that aggressive guideline-based medical therapy in patients with elevated BNP or NT-proBNP levels can help prevent future left ventricular dysfunction or new-onset heart failure. Additional research is needed to identify the effects of screening on mortality as well as the cost effectiveness of such interventions.

Evidence has shown that heart failure incidence can also be reduced by significantly lowering blood pressure in at-risk patients. The American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America recommend targeting an optimal blood pressure of less than 130/80 mm Hg for heart failure prevention.

Diagnosis and Evaluation of Heart Failure

Clinical Evaluation

Clinical evaluation of patients suspected of having heart failure should include a comprehensive history and physical examination, focusing on assessment of fluid and perfusion status. Most patients with heart failure present with volume overload and normal cardiac output. The second most common presentation is low cardiac output with volume overload; rarely, patients have signs and symptoms of low cardiac output without volume overload. Volume overload is associated with crackles, jugular venous distention, peripheral edema, increased abdominal girth (ascites), dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Patients with heart failure typically develop exertional dyspnea first, followed by orthopnea and paroxysmal nocturnal dyspnea. Elevated jugular venous pressures and orthopnea are most predictive of elevated pulmonary capillary wedge pressure, which suggests left-sided heart failure. Signs of low cardiac output include low pulse pressure, cool extremities, and reduced cognition. Although worsening kidney or liver function may be a sign of low cardiac output, end-organ dysfunction can also be caused by vascular congestion.

Diagnosis

Initial diagnostic testing should include electrocardiogram to evaluate for ischemia and arrhythmia, chest radiogram to exclude pulmonary causes of dyspnea, and a BNP or NT-proBNP assay to establish the presence and severity of heart failure. In patients with dyspnea, BNP can effectively differentiate cardiac from pulmonary causes. BNP levels are

elevated in patients with increased right or left ventricular filling pressures and systolic or diastolic heart failure (typically >400 pg/mL [400 ng/L]), whereas BNP levels are low to normal in patients with pulmonary disease (typically <100 pg/mL [100 ng/L]). Studies have shown that an elevated BNP level has a sensitivity for heart failure of 95% to 97% and a negative predictive value of 90% to 97%. Between 100 pg/mL and 400 pg/mL (100-400 ng/L), BNP concentrations are neither sensitive nor specific for excluding or confirming the diagnosis of heart failure. Other factors that increase BNP levels include kidney failure, older age, and female sex. BNP levels are reduced in patients with an elevated BMI.

Laboratory assessment should also include a complete blood count, serum electrolytes and kidney function tests, glucose and lipid levels, liver chemistry tests, and serum thyroid-stimulating hormone level. Thyroid-stimulating hormone measurement is indicated to evaluate for occult hypo- or hyperthyroidism as a reversible cause of heart failure. In hyperthyroidism in particular, the predominant manifestation of thyroid dysfunction may be cardiac symptoms, which will abate when the hyperthyroidism is treated.

Echocardiography is the primary diagnostic test in the evaluation of heart failure. An echocardiogram provides information on heart size, systolic and diastolic function, regional wall motion abnormalities, and valvular disease. Findings on echocardiography can provide information on underlying causes of heart failure as well. Regional wall motion abnormalities suggest CAD, and changes in the myocardium can suggest conditions such as cardiac amyloid. Echocardiography may also provide prognostic information, particularly in the setting of severely depressed ejection fraction.

Evaluation for Ischemia

CAD is the leading cause of heart failure in the United States (>50% of patients) and should be considered in all patients with newly diagnosed heart failure. The decision to evaluate for CAD depends on the patient's symptoms and risk factors (family history, male sex, diabetes, hypertension, tobacco use). Additionally, findings on electrocardiography and echocardiography may suggest an ischemic cause for left ventricular dysfunction. Patients with exertional chest pain, history of myocardial infarction, or other symptoms suggesting CAD should undergo further evaluation with stress testing or cardiac catheterization as clinically appropriate (see Diagnostic Testing in Cardiology). Identification of significant CAD is important, as left ventricular dysfunction caused by ischemia may improve or resolve with percutaneous or surgical revascularization. **□**

Classification

The severity of heart failure is categorized according to the New York Heart Association (NYHA) functional classification (Table 12) and the ACC/AHA heart failure stages (Table 13). Patients can move back and forth between NYHA classes

TABLE 12. New York Heart Association Functional Classification

Class	Description
I	No limitations of physical activity
II	Slight limitation of physical activity
III	Marked limitation of physical activity
IIIA	Symptoms with less than ordinary activity
IIIB	Symptoms with minimal exertion
IV	Unable to carry on any physical activity without symptoms

TABLE 13. American College of Cardiology/American Heart Association Stages of Heart Failure

Stage	Description
Stage A	At risk for heart failure but without structural heart changes (e.g., patients with diabetes mellitus, coronary artery disease, hypertension, or vascular disease)
Stage B	Structural heart disease (e.g., reduced ejection fraction, left ventricular hypertrophy, chamber enlargement) but without heart failure symptoms
Stage C	Structural heart disease with current or prior heart failure symptoms
Stage D	Refractory heart failure requiring advanced intervention (e.g., biventricular pacemaker, left ventricular assist device, transplantation)

Information from Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391-479. [PMID: 19324966] doi:10.1161/CIRCULATIONAHA.109.192065

depending on fluid status and progression of heart failure; however, they may only progress in the ACC/AHA stages. Both the patient's functional class and stage affect the choice of therapy.

- B-type natriuretic peptide measurement is a sensitive and specific test for the diagnosis of heart failure in patients with dyspnea.
- In patients suspected of having heart failure, echocardiography should be performed to assess ejection fraction and identify possible causes of heart failure.

Medical Therapy for Systolic Heart Failure

The treatment of patients with HFReF (systolic heart failure) includes treatment of acute exacerbations followed by long-term therapy to decrease morbidity and mortality and improve symptoms in patients with chronic heart failure.

A ACE Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors reduce morbidity and mortality in patients with HFrEF and are the cornerstone of long-term therapy for both symptomatic and asymptomatic patients. ACE inhibitors block the conversion of angiotensin I to angiotensin II, inhibiting the upregulation of the aldosterone pathway. The ATLAS trial examined the effects of low-dose versus high-dose ACE inhibitor therapy (lisinopril) in patients with systolic heart failure and found no difference in overall mortality; however, high-dose lisinopril was associated with a significant reduction in the composite endpoint of mortality and hospitalizations from heart failure and for any cause. On the basis of these results, the general consensus is to uptitrate ACE inhibitors to maximal doses or until the onset of symptomatic hypotension.

The primary adverse effects associated with the use of ACE inhibitors are kidney dysfunction, ACE inhibitor-induced cough, and angioedema. Although ACE inhibitors should be considered in every patient with HFrEF, elevations in creatinine levels may prevent use of maximal doses. Many physicians do not recommend increasing the dosage once the creatinine level rises to 2.5 mg/dL (221 μ mol/L) or the estimated glomerular filtration rate falls below 30 mL/min/1.73 m². The estimated glomerular filtration rate should be monitored for decline during uptitration of ACE inhibitor or angiotensin receptor blocker (ARB) therapy and should be rechecked before discontinuation of these drugs, as other conditions or drugs may confound the assessment of kidney function. Hyperkalemia may also result from ACE inhibitor or ARB therapy in patients with pre-existing chronic kidney disease and may require dosage reduction or discontinuation. Development of ACE inhibitor-induced cough is the primary reason to switch a patient from an ACE inhibitor to an ARB. Although fewer data support the use of ARBs in asymptomatic patients with a reduced ejection fraction, there is general consensus that all patients who cannot tolerate ACE inhibitor therapy should receive an ARB. Patients who develop angioedema while taking an ACE inhibitor are often switched to an ARB; however, there are rare reports of ARB-induced angioedema, and patients should be informed of this risk.

Angiotensin Receptor-Nepriylisin Inhibitor

The angiotensin receptor-nepriylisin inhibitor (ARNI) valsartan-sacubitril belongs to a relatively new drug class that combines an ARB with a nepriylisin inhibitor. Nepriylisin is a neutral endopeptidase that degrades several vasoactive peptides, including natriuretic peptides and bradykinin. Inhibition of nepriylisin increases levels of these substances, leading to enhanced diuresis, natriuresis, and myocardial relaxation. In the PARADIGM-HF trial, patients with symptomatic heart failure (elevated BNP or NT-proBNP level or a heart failure hospitalization within 12 months) and an ejection fraction below 40% were randomly assigned to receive valsartan-sacubitril or the ACE inhibitor enalapril. The patients who

received valsartan-sacubitril had a reduction in morbidity and mortality. However, 12% of patients withdrew from the trial during the run-in phase, primarily because of hypotension, kidney dysfunction, cough, and hyperkalemia. During the trial, 16.7% of patients had symptomatic hypotension, and in 4.8% of patients, creatinine level increased to higher than 2.5 mg/dL (221 μ mol/L).

Guidelines currently recommend replacing an ACE inhibitor or ARB with valsartan-sacubitril in patients with chronic symptomatic HFrEF who tolerate ACE inhibitor or ARB therapy well. Caution should be used when initiating this drug in patients with hypotension or kidney impairment, and kidney function should be followed closely. Valsartan-sacubitril should not be administered concurrently with an ACE inhibitor or within 36 hours of the last dose of an ACE inhibitor owing to the risk for angioedema.

β -Blockers

β -Blockers should be initiated in all patients with HFrEF. β -Blockers improve remodeling, increase ejection fraction, and reduce hospitalization and mortality when added to ACE inhibitor and diuretic therapy. In contrast to ACE inhibitors, the benefits of β -blocker therapy do not appear to be a class effect, and one of the three agents shown to have a mortality benefit (bisoprolol, carvedilol, and metoprolol succinate) should be used.

β -Blockers are generally well tolerated, but they should be initiated only when the patient is euvolemic or nearly euvolemic. These agents have negative inotropic properties and may exacerbate heart failure in patients with volume overload. Consequently, β -blockers should be initiated at low doses and slowly uptitrated over weeks (not days) until the patient achieves a heart rate of around 60/min or has symptomatic hypotension (Table 14). In general, hospitalized patients should be started on β -blocker therapy before discharge. In patients with reactive airways disease or COPD, β -blocker therapy should not be initiated if the patient has bronchospasm or evidence of an exacerbation of pulmonary disease.

Initiating and Managing ACE Inhibitor and β -Blocker Therapy

ACE inhibitors and β -blockers are indicated in all patients with HFrEF. Either drug may be initiated first. Studies have shown that patients receive additive benefit from the second

TABLE 14. Therapeutic Dosages of β -Blockers for Treatment of Heart Failure with Reduced Ejection Fraction

Agent	Target Dosage
Carvedilol	25 mg twice daily (50 mg twice daily if weight >85 kg [187 lb])
Metoprolol succinate	200 mg daily
Bisoprolol	10 mg daily

agent regardless of which agent is started earlier. It is reasonable to select the first agent based on patient factors. For example, a β -blocker should be initiated first in patients with CAD or atrial fibrillation who require heart rate control. Conversely, an ACE inhibitor should be started first in patients with diabetes for the additional renal benefits. Regardless of the agent first initiated, the second drug should be started before the dosage of the first agent is maximized, especially if the patient has low blood pressure or is at risk for hypotension.

Recent guidelines recommend treating to a systolic blood pressure of less than 130/80 mm Hg in patients with HFrEF. Although randomized controlled trials have not specifically evaluated a goal blood pressure in patients with HFrEF, studies have shown that patients with lower blood pressure have fewer adverse cardiovascular events.

Diuretics

Loop diuretics are the mainstay of treatment for volume overload in patients with heart failure because of the increased potency of these agents compared with other diuretics. Of the four loop diuretics, furosemide is most commonly used; however, some studies have shown torsemide to be more effective, which may be attributable to its increased bioavailability and longer half-life. Occasionally, loop and thiazide diuretics are combined to potentiate diuresis. The lowest dosage that achieves euolemia should be used. The primary side effects include hypokalemia and hypomagnesemia; therefore, electrolyte levels should be monitored.

Digoxin

Digoxin is used in patients with HFrEF and concomitant atrial fibrillation for rate control and in patients who continue to have symptoms of heart failure despite optimal therapy with ACE inhibitor and β -blocker therapies. Digoxin reduces the risk for hospitalization in patients with heart failure, and its discontinuation is associated with worsening heart failure symptoms. Unlike neurohumoral antagonists (including ACE inhibitors, β -blockers, and aldosterone antagonists), digoxin does not improve survival. The use of digoxin in patients with heart failure has decreased over the past 20 years, primarily because of its lack of mortality benefit and the dangerous side effects associated with digoxin toxicity. Digoxin should be managed carefully in patients with impaired kidney function, older adults, and women. It should be dosed to achieve a serum level of less than 1.0 ng/mL (1.28 nmol/L).

Aldosterone Antagonists

Aldosterone antagonists (spironolactone, eplerenone) reduce mortality and heart failure hospitalizations in patients with symptomatic heart failure (NYHA functional class II-IV symptoms) and patients with heart failure after an acute myocardial infarction. Despite their proven efficacy, they are underused, probably because of concerns of hyperkalemia and associated death raised by observational studies of spironolactone. Both drugs require that patients be monitored for hyperkalemia,

and these agents should be used carefully in patients with kidney dysfunction. In clinical trials, potassium supplementation was routinely discontinued at the beginning of therapy, and electrolyte measurement was repeated within 1 week of initiation.

Although spironolactone and eplerenone are both effective, their differences may guide drug selection. Spironolactone is a nonspecific antagonist that has antiandrogen and antiprogesterone side effects. It is extensively metabolized in the liver, and the half-life can increase in the setting of hepatic congestion. Eplerenone is a selective antagonist that is metabolized by cytochrome P-450 isoenzyme 3A4 (CYP3A4) and is subject to substantial drug interactions with both inhibitors and inducers of this isoenzyme.

Current guidelines recommend these agents as first-line therapy, along with ACE inhibitors and β -blockers, in patients with symptomatic heart failure. Generally, the doses of both the ACE inhibitor and β -blocker should be uptitrated to maximal levels before spironolactone or eplerenone is added. Aldosterone antagonists should not be considered diuretic therapy, and patients with volume overload will also need to be treated with a loop or thiazide diuretic.

Isosorbide Dinitrate-Hydralazine

Isosorbide dinitrate-hydralazine is superior to placebo in reducing hospitalization but inferior to ACE inhibitors for survival benefit in patients with symptomatic HFrEF. Therefore, this combination should be considered in patients intolerant of ACE inhibitors and ARBs, especially those with chronic kidney disease. In black patients with NYHA functional class III to IV symptoms, isosorbide dinitrate-hydralazine should be used in combination with optimal therapy, including ACE inhibitors, β -blockers, and aldosterone antagonists, to reduce mortality. Headache is a common adverse effect. Because many patients will not adhere to the dosage regimen of three doses daily, clinicians should strongly encourage patients to comply. Nonadherence issues may prompt clinicians to consider switching the patient to once-daily nitrate therapy, but once-daily therapy has not been studied in clinical trials to prove similar efficacy.

Calcium Channel Blockers

The nondihydropyridine calcium channel blockers verapamil and diltiazem both have detrimental effects in patients with systolic heart failure, probably related to negative inotropic effects, and these agents should not be used. Amlodipine and felodipine have shown neither benefit nor harm in patients with heart failure. Therefore, these two drugs are safe but should be used only in patients with hypertension despite therapy with other agents at maximal dosage.

Ivabradine

Ivabradine is a sinoatrial node modulator that selectively inhibits the I_f current in the sinoatrial node, causing a reduction in heart rate. It has no negative inotropic effects. In



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patients with chronic symptomatic heart failure and left ventricular ejection fraction less than or equal to 35% who are in sinus rhythm and taking maximally tolerated doses of a β -blocker, ivabradine reduces heart failure-associated hospitalizations and the combined endpoint of mortality and heart failure hospitalization. Ivabradine has been approved for use in the United States and should be considered for patients who have an elevated heart rate (≥ 70 /min) in sinus rhythm despite maximally tolerated doses of β -blocker therapy.

Key Points

- Guidelines currently recommend replacing an ACE inhibitor or angiotensin receptor blocker (ARB) with valsartan-sacubitril in patients with chronic symptomatic heart failure with reduced ejection fraction who tolerate ACE inhibitor or ARB therapy well.
- β -Blockers are generally well tolerated in patients with heart failure, but these agents should be initiated only when the patient is euvolemic or nearly euvolemic.
- Ivabradine should be considered for patients with symptomatic heart failure and an ejection fraction less than or equal to 35% who have an elevated heart rate (≥ 70 /min) in sinus rhythm despite maximally tolerated doses of β -blocker therapy.
- Aldosterone antagonists reduce mortality and heart failure hospitalizations in patients with symptomatic heart failure.

Management of Heart Failure with Preserved Ejection Fraction

The prototypical presentation of HFpEF is an elderly woman with long-standing hypertension associated with left ventricular hypertrophy; however, patients with CAD, diabetes, kidney disease, or other conditions may also present with signs and symptoms of heart failure and a normal ejection fraction. The primary therapies for HFpEF are diuretics to control symptoms of volume overload and antihypertensive agents to target a systolic blood pressure of less than 130 mm Hg in the setting of hypertension. In patients with worsened symptoms of heart failure and atrial fibrillation, restoration of sinus rhythm or rate control may reduce symptoms.

Despite many studies of therapeutic agents, no drug has been shown to reduce morbidity or mortality in patients with HFpEF, which may reflect the heterogeneity of etiology. The recent TOPCAT trial showed no difference in the primary combined endpoint of death, aborted cardiac arrest, or heart failure hospitalization in patients treated with spironolactone compared with those who received a placebo. In retrospective analysis, there was a mortality advantage with use of spironolactone in the United States, whereas in Europe, evidence showed spironolactone to be less effective. However, the clinical characteristics of the enrolled patients were statistically different in these two regions. Some clinicians have suggested

that spironolactone should be used routinely for this condition with no other proven treatments; however, spironolactone therapy for HFpEF is not supported by current evidence.

- The primary therapies for heart failure with preserved ejection fraction are diuretics to control symptoms of volume overload and antihypertensive agents to target a systolic blood pressure of less than 130 mm Hg.

Device Therapy

Implantable Cardioverter-Defibrillator Therapy for Prevention of Sudden Cardiac Death

Arrhythmias are a common cause of death in patients with heart failure, and implantable cardioverter-defibrillators (ICDs) improve survival when used for both primary and secondary prevention of arrhythmias. Current guidelines recommend ICD placement in patients receiving guideline-directed medical therapy who have an ejection fraction less than or equal to 35% and NYHA functional class II or III heart failure symptoms. Patients with class IV symptoms should only undergo ICD placement if they are candidates for heart transplant or left ventricular assist device (LVAD) placement. It is important to reassess both ejection fraction and symptoms after guideline-directed medical therapy (40 days after myocardial infarction, 3 months in all others). Many patients with new-onset heart failure experience substantial improvements in ejection fraction with medical therapy and may not require or benefit from ICD insertion.

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT), or biventricular pacing, involves traditional pacing of the right ventricular apex and pacing of the left ventricular lateral wall via a lead inserted through the coronary sinus into a lateral cardiac vein. In patients with dyssynchrony (demonstrated in most trials by a widened QRS interval or left bundle branch block [LBBB]), CRT has improved ejection fraction, reduced heart failure symptoms, and reduced mortality. Retrospective analysis of many trials has shown that patients with LBBB are most likely to benefit from CRT. Based on these findings, CRT is indicated in patients with an ejection fraction less than or equal to 35%, NYHA functional class II to IV heart failure symptoms despite guideline-directed medical therapy, sinus rhythm, and LBBB with a QRS complex of 150 ms or greater. Patients with no LBBB but a QRS complex of 150 ms or greater may derive a lesser benefit from CRT.

- Placement of an implantable cardioverter-defibrillator is recommended in patients with heart failure who have an ejection fraction less than or equal to 35% and New York Heart Association functional class II or III symptoms while taking guideline-directed medical therapy.

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Cardiac resynchronization therapy is indicated in patients with an ejection fraction less than or equal to 35%, New York Heart Association functional class II to IV heart failure symptoms despite guideline-directed medical therapy, sinus rhythm, and left bundle branch block with a QRS complex of 150 ms or greater.

Assessment of Chronic Heart Failure

Patients with chronic heart failure should be serially assessed for progression of disease in the outpatient setting. Each follow-up visit should include evaluation of current symptoms and functional capacity; assessment of volume status, electrolytes, and kidney function; and review of the patient's medication regimen for adequacy (both appropriate doses and the appropriate medications as heart failure progresses). Of equal or greater importance is repeated patient education, including reminding patients to take their medications as prescribed, measure their weight daily, avoid dietary sodium, watch their fluid intake, and exercise regularly. Patients who appropriately take their medications and avoid sodium and excess fluid intake can greatly improve their functional status.

Sleep disorders frequently occur in patients with heart failure and are often underdiagnosed. Recognizing these disorders and distinguishing between central and obstructive sleep apnea are important for improving quality of life in patients with heart failure and for potentially improving heart failure-related outcomes. Current guidelines support obtaining a formal sleep assessment in patients with symptomatic heart failure (NYHA functional class II-IV) and excessive daytime sleepiness or those who are suspected of having sleep-disordered breathing (see MKSAP 18 Pulmonary and Critical Care Medicine). Treatment with continuous positive airway pressure in patients with obstructive sleep apnea improves sleep quality and reduces the apnea-hypopnea index. In contrast, therapy for central sleep apnea with adaptive servoventilation has been shown to cause harm.

Serial B-Type Natriuretic Peptide Assessment

Measurement of BNP levels is helpful in determining whether dyspnea is related to heart failure or a different cause. For outpatients with chronic heart failure in whom volume status is uncertain on physical examination, BNP level can be useful in diagnosing fluid overload. BNP measurement in patients with stable heart failure also can provide information about prognosis and disease severity. However, serial measurements and treatment based on BNP levels have not been shown to reduce hospitalizations or mortality in patients with heart failure. Currently, BNP measurement should be used to aid in the diagnosis of heart failure and acute volume overload, but it should not be used serially in the inpatient or outpatient setting to guide care.

Echocardiography in Chronic Heart Failure

Echocardiography is the most common method for assessing left ventricular function. For patients with new-onset heart failure, guidelines suggest repeating assessment of left ventricular function after optimization of medical therapy. If the patient's ejection fraction is less than or equal to 35%, the patient may be a candidate for ICD or biventricular pacemaker placement. Current guidelines recommend routine echocardiography every 1 to 2 years in stable patients or when clinical status changes; however, routine echocardiography every 3 to 6 months is not indicated.

Assessing Prognosis

Many prognostic models have been developed to assist in predicting morbidity and mortality in patients with heart failure. These models are usually derived from retrospective analyses of clinical trials or large admission databases. To some extent, the models reflect the unique patient populations enrolled in clinical trials, which tend to have fewer comorbid conditions. Unfortunately, no one tool has been found to be more predictive than the others, and questions remain regarding the utility of these models for the individual patient. It has been suggested that these tools be used in addition to, not in place of, the clinician's judgment for heart failure management.

Clinical indicators associated with worse outcomes in the 1 to 2 years after diagnosis include heart failure hospitalization, poor exercise tolerance, ICD firings, serum sodium level less than 135 mEq/L (135 mmol/L), worsening kidney function, cardiac cachexia, required diuretic doses of more than 1 mg/kg, and symptomatic hypotension necessitating reduction in the dosage of heart failure medications. Heart failure hospitalizations are associated with a mortality rate of 10% to 20% over the next 6 months. In patients with poor prognosis, a frank discussion of advanced therapies, such as LVAD placement or heart transplantation, should occur. For patients who are ineligible for or uninterested in such therapies, end-of-life goals should be discussed, and palliative care or hospice should be considered.

- Serial B-type natriuretic peptide measurements should not be used to guide the care of patients with chronic heart failure. HVC
- Echocardiography should be performed every 1 to 2 years in stable patients with heart failure or when clinical status changes.

Inpatient Management of Heart Failure

Acute Decompensated Heart Failure

Initial management of patients hospitalized for acute decompensated heart failure should focus on identifying the cause of the heart failure exacerbation, determining the patient's



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current physiologic state, removing fluid to improve congestion, and optimizing medical therapy before discharge.

Determining the cause of acute heart failure can be challenging. Common causes include fluid overload in the setting of nonadherence to dietary fluid or salt intake recommendations and recurrent ischemia in patients suspected of having ischemic cardiomyopathy. Fluid overload can sometimes be related to an unintentional increase in foods with higher salt content or an inability to tolerate previous levels of fluid and salt intake due to progression of left ventricular dysfunction. Other causes of decompensation include hypertension, concurrent illness, and nonadherence to medication regimens, including but not limited to diuretics. An understanding of the cause of the decompensation may identify opportunities to prevent recurrence.

Patients hospitalized for heart failure should be evaluated for volume overload. Typical symptoms include orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, weight gain, and progressive exertional dyspnea. On physical examination, jugular venous distention is usually present. Patients may have crackles (which are much more likely in acute than chronic heart failure), ascites, or peripheral edema. Perfusion should also be assessed, and patients may be classified as “warm” (adequate perfusion) or “cold” (inadequate perfusion). Signs and symptoms of poor perfusion include cool extremities, a narrow pulse pressure, poor mentation, and worsening kidney function. Intravenous inotropes or other advanced therapies should be considered in patients with signs of poor perfusion to help improve cardiac function.

Diuretic therapy is the principal treatment for patients with decompensated heart failure and fluid overload. A recent study evaluated different strategies for diuresis, including varied diuretic dosages and bolus versus continuous therapy. Administration of high-dose diuretics (2.5 times the outpatient oral daily dosage) was associated with increased diuresis but also transient worsening of kidney function. No differences were observed between bolus and continuous intravenous infusion groups, and length of stay did not differ regardless of the strategy used. Providing effective diuresis is essential and often requires intravenous administration. If the current dosage of loop diuretic is inadequate, increasing the dosage or adding a thiazide diuretic may be considered. Notably, administering low-dose dopamine to improve diuresis and preserve kidney function offers no benefit.

In patients with acute kidney dysfunction at the time of admission, it is still important to treat with diuretic therapy. The most likely cause of the dysfunction is poor kidney perfusion due to vascular congestion, and kidney function will often improve with diuresis. In contrast, withholding ACE inhibitors and aldosterone antagonists may be reasonable until kidney function improves. If a patient receiving diuretic therapy develops worsening kidney function when approaching euvolemia, withholding diuretics for 1 day to allow extravascular fluid to

redistribute into the vascular space should be considered. Once euvolemia has been achieved, creatinine often also increases, which may indicate decongestion.

Standard heart failure therapy, including ACE inhibitor or ARB therapy, β -blockers, and aldosterone antagonists, should either be maintained throughout hospitalization or be restarted before discharge. If β -blockers are discontinued upon admission because of signs of low cardiac output, therapy should not be reinitiated until the patient nears euvolemia. If the patient is admitted with volume overload without signs of low cardiac output, β -blocker therapy can usually be maintained at the same or a lower dosage during hospitalization.

BNP level should be measured upon admission and before discharge for prognostic purposes because high levels are linked with increased mortality and rehospitalization. Likewise, patients with BNP levels that fail to decrease during an admission have a higher mortality rate. Serum troponin measurement upon admission can also be used for prognostication; patients with elevated troponin levels have worse clinical outcomes and a higher risk for death. Currently, there are no absolute cutoff values for these biomarkers, and measurement data should be used in combination with clinical judgment in advising the patient with heart failure.

Cardiogenic Shock

Cardiogenic shock is characterized by signs and symptoms of low cardiac output and end-organ compromise, with acute worsening of kidney and liver function. Patients with cardiogenic shock often require intravenous inotropic agents to improve hemodynamic status, including increasing cardiac output and urine output (Table 15). Routine use of invasive pulmonary artery catheterization to monitor hemodynamics does not improve survival or reduce future hospitalization in patients with decompensated heart failure. Therefore, pulmonary artery, or “right heart,” catheterization should be used only when hemodynamic and volume status is not evident from physical examination findings or other noninvasive tests, or when hemodynamic data may lead to advanced mechanical circulatory support or consideration of heart transplantation.

The use of percutaneous mechanical support during acute exacerbation has greatly increased in the past few years. Intra-aortic balloon pumps, percutaneous ventricular assist devices, and extracorporeal membrane oxygenators can be quickly placed to support the critically ill patient. Treatment by a team composed of a heart failure physician, critical care physician, and cardiac surgeon is suggested to rapidly deploy therapy and care for the patient in the following days. Decisions regarding longer-term options for advanced heart failure (heart transplantation or permanent or “destination” LVAD) are an important aspect in the use of mechanical support in the acute setting. In patients who do not show clinical improvement, there should be daily discussions about treatment options and goals of care, including



CONT.



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TABLE 15. Intravenous Vasoactive Medications Used for Treatment of Cardiogenic Shock

Medication	Mechanism	Inotropy	Vasodilation
Milrinone	Phosphodiesterase inhibition	++	+
Dobutamine	β_1, β_2 Receptor agonism	++	(+) (at low dose) - (vasoconstriction, at high dose)
Nesiritide	Natriuretic peptide receptor agonism	0	++
Sodium nitroprusside	Nitric oxide production	0	++
Nitroglycerin	Nitric oxide production	0	++ (mainly venous)
Vasopressin	Arginine vasopressin receptor (V receptor) agonism	-	- (vasoconstriction)
Dopamine	Dopaminergic receptor (D receptor) agonism	+	- (vasoconstriction, at high dose)
	β_1 Receptor agonism at intermediate dose		
	α_1 Receptor agonism at high dose		
Norepinephrine	α_1, α_2 Receptor agonism greater than β_1 receptor agonism	+	- (vasoconstriction)

Strength of effect: ++ indicates very strong; + indicates strong; (+) indicates weak; 0 indicates neutral; - indicates opposite effect.

transplantation, permanent device placement, or palliative care or hospice.

Strategies to Prevent Readmission

The first step in preventing heart failure readmission is to treat any reversible causes of the exacerbation. Medication reconciliation before discharge should ensure that the patient is taking the appropriate medications, particularly those that reduce mortality and morbidity in heart failure. Patients should not be discharged until they have achieved euvolemia with diuresis. Patients should be educated on heart failure physiology, the importance of medication and dietary adherence, signs and symptoms of worsening heart failure, and when to contact a physician. Finally, an early follow-up appointment (within 7 days) should be scheduled to review the medication list, assess the patient's volume status and adherence to diet and medications, and reinforce patient education points. 

KEY POINTS

- Management of patients with acute decompensated heart failure focuses on identifying the cause of the heart failure exacerbation, determining the patient's current physiologic state, treating fluid overload, and optimizing medical therapy before discharge.
- In patients hospitalized with acute heart failure, scheduling an early follow-up appointment (within 7 days) to review the medication list, assess the patient's volume status and adherence to diet and medications, and reinforce patient education points reduces the risk for heart failure readmission.
- Routine invasive pulmonary artery catheterization for hemodynamic monitoring is not recommended in patients with decompensated heart failure.

Advanced Refractory Heart Failure

Once heart failure has progressed to ACC/AHA stage D, characterized by persistent severe symptoms despite maximum therapy, advanced treatments should be considered. Cardiac transplantation remains the gold standard therapy for patients with end-stage heart failure. Unfortunately, because of a lack of appropriate donors, fewer than 3000 heart transplantations are performed in the United States each year. Indications for transplantation generally include age younger than 65 to 70 years, no medical contraindications (such as diabetes with end-organ complications, malignancies within 5 years, kidney dysfunction, or other chronic illnesses that will decrease survival), and good social support and adherence. The use of an LVAD as "destination therapy" should be considered for patients who are not transplant candidates. Many patients awaiting transplant also require an LVAD for support until an organ becomes available. Hospice may be considered as an option in shared decision-making discussions.

Mechanical Circulatory Support

In the past 10 years, clinical outcomes of patients with advanced heart failure have markedly improved with the use of LVADs. With newer continuous-flow devices, patients have 1-year survival approximating that of cardiac transplant recipients and substantial improvements in functional capacity and quality of life. Because these devices provide continuous flow, most patients no longer have a palpable pulse, and blood pressure must be measured by Doppler. Typical therapy includes anticoagulation to prevent pump thrombus formation, continued heart failure therapy with ACE inhibitors (or ARBs) and β -blockers, and management of fluid overload with diuretics.

LVADs are associated with important complications related to both the driveline, which passes through the skin and connects the internal pump to a power source, and the

pump itself. Major complications include hemorrhagic and thrombotic strokes; skin infections; pump thrombosis; and gastrointestinal bleeding, which is usually associated with small bowel arteriovenous malformations. Despite these complications, LVADs have been associated with survival of more than 10 years in some patients.

Management of Posttransplant Patients

Most patients who undergo heart transplantation quickly recover physical activity and have normal quality of life, with a mean survival of more than 11 years. The most frequent complication within the first year after transplant is infection. Cytomegalovirus (CMV) infection is common, and patients at moderate risk (CMV-positive donor/CMV-positive recipient) and high risk (CMV-positive donor/CMV-negative recipient) often receive antiviral prophylaxis for 6 months. Incidence of rejection is highest in the first 6 months after transplantation. Because most patients with rejection are asymptomatic, regularly scheduled endomyocardial biopsies are often performed to detect rejection for the first few years after transplant. Severe rejection is characterized by signs of acute heart failure and atrial arrhythmias (typically atrial flutter) or conduction abnormalities. Early complications related to immunosuppressive therapy include hypertension (more than 90% of patients) and diabetes (15%-20% of patients). Long-term complications after transplantation include CAD and an increased incidence of malignancies, including skin cancer (common) and B-cell lymphoma related to immunosuppressive therapy (less common).

When new drugs are added to a transplant patient's medication regimen, careful attention is essential to avoid drug-drug interactions. Cyclosporine and tacrolimus, two agents commonly used for immunosuppression, are metabolized by the CYP3A4 system. Many drugs increase or decrease the metabolism of cyclosporine and tacrolimus, and conversely, these agents may alter the metabolism of other drugs. An extensive list of drugs that can interact through the CYP3A4 isoenzyme can be found at medicine.iupui.edu/clinpharm/ddis.

- Patients with severe heart failure symptoms despite maximal medical therapy are candidates for advanced treatment, including placement of a left ventricular assist device and heart transplantation.
- Cardiac transplantation is the gold standard therapy for patients with end-stage heart failure.
- Endomyocardial biopsy should be routinely performed after heart transplantation to diagnose rejection.

Specific Cardiomyopathies

For a discussion of hypertrophic cardiomyopathy and restrictive cardiomyopathy, refer to Myocardial Disease. Peripartum

cardiomyopathy is discussed in Pregnancy and Cardiovascular Disease.

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy, also known as stress cardiomyopathy or apical ballooning syndrome, is a clinical syndrome associated with reduced ejection fraction, elevated cardiac enzyme levels, and signs of ischemia on electrocardiography. It typically occurs in older women and is usually precipitated by a stressful physical or emotional event, such as the death of a loved one, sudden surprise, or other acute stressors. The exact mechanism of takotsubo cardiomyopathy is unknown, but the condition is postulated to result from a reversible toxic effect of very high catecholamine levels on the myocardium. On cardiac imaging, wall motion abnormalities that do not follow a coronary artery territory (typically, apical dyskinesia or ballooning) are often found with preservation of basal wall motion. Because these acute events often resemble an acute coronary syndrome, emergent coronary angiography is often performed and demonstrates nonobstructive CAD. Treatment is largely supportive and is similar to that for other heart failure syndromes (diuretics, ACE inhibitors, β -blockers). Most patients will recover cardiac function over the course of a few weeks to months. As with other forms of new-onset heart failure, repeat echocardiography should be performed in 3 to 6 months to evaluate recovery. If a patient has recovery of function, it is unclear for how long medical therapy should be continued, but most clinicians continue therapy for at least 1 year.

Acute Myocarditis

Myocarditis is a clinical syndrome of acute-onset heart failure. Causes include viral, bacterial, or other infections; toxins; and immunologic syndromes. The classic form is viral in origin and is usually preceded by a typical upper respiratory tract infection caused by adenovirus, echovirus, or coxsackievirus. Although the pathogenesis is not completely understood, it is thought that acute viral infection causes early destruction of the myocytes, followed by an immune response that causes further destruction.

Clinically, patients may be asymptomatic or have a viral prodrome with fever, myalgia, and muscle soreness. Patients may also present with acute heart failure symptoms. Echocardiography is useful to assess for other causes of heart failure. Definitive diagnosis may require cardiac magnetic resonance imaging or endomyocardial biopsy. Anti-inflammatory agents are not of benefit in the treatment of acute myocarditis. Standard therapy for heart failure is recommended. Prognosis depends on the clinical presentation.

Giant Cell Myocarditis

Giant cell myocarditis is an acute and frequently fatal form of myocarditis that typically occurs in younger persons. It is often rapidly progressive and can cause both left and right ventricular dysfunction. Giant cell myocarditis is also associated with

an increased incidence of high-grade atrioventricular block and ventricular arrhythmias. Unlike in acute myocarditis, aggressive immunosuppressive therapy has some benefit and should be initiated in these patients. For this reason, patients with acute heart failure unresponsive to usual care or with accompanying arrhythmias should undergo endomyocardial biopsy for diagnosis. Initial biopsy findings may be negative because of the patchy nature of the inflammation. Patients with giant cell myocarditis often require percutaneous or surgical ventricular support until they recover or need heart transplantation or LVAD placement. If giant cell myocarditis is suspected, prompt transfer to a hospital equipped with mechanical support should be considered because patients can progress from feeling well to moribund within hours.

Tachycardia-Mediated Cardiomyopathy

Tachycardia-mediated cardiomyopathy has been associated with both supraventricular and ventricular arrhythmias. Reversible causes of tachycardia, such as hyperthyroidism, should be ruled out. Importantly, heart rate control improves left ventricular function in these patients. The primary treatments are medications, such as β -blockers, and catheter-directed ablation. In patients with atrial fibrillation associated with rapid ventricular response, there is no evidence that converting to sinus rhythm is more efficacious than controlling the heart rate. In patients with ventricular arrhythmias or frequent premature ventricular contractions, cardiomyopathy is generally thought to develop when the burden of premature ventricular contractions is more than 10,000/day; ablation, especially if the premature ventricular contractions are unifocal, should be considered.

Arrhythmias

Introduction

Arrhythmias are traditionally categorized as supraventricular or ventricular based upon simple electrocardiographic (ECG) findings. Supraventricular arrhythmias originate from the atrium or atrioventricular (AV) node and are characterized by normal-appearing QRS complexes unless complicated by an aberrant ventricular condition. Ventricular arrhythmias originate below the AV node and are characterized by abnormal-appearing and prolonged QRS complexes. Disruptions in rhythm and rate occur in seven basic patterns: early beats, bigeminal beats, grouped beats, pauses, bradycardia, tachycardia, and chaotic rhythms. This section provides an approach to bradycardia and tachycardia and discusses the diagnosis and management of specific rhythm disorders.

Approach to Bradycardia

Clinical Presentation and Evaluation

Bradycardia (heart rate <60 /min) may be asymptomatic or associated with symptoms of lightheadedness, syncope, exertional

intolerance, dyspnea, and fatigue. It can result from disease in the sinus node, AV node, or His-Purkinje system, or from dysfunction of the autonomic system.

Diagnostic evaluation consists of a thorough history, physical examination, focused laboratory testing (electrolyte levels, thyroid function testing), and resting 12-lead ECG. It is important to identify severe or unstable conduction abnormalities that require urgent intervention. The evaluation should also include investigation for extrinsic and reversible causes of bradycardia, including ischemia, myocarditis, endocarditis, hypothyroidism, electrolyte disturbances, and medication use (especially β -blockers and digoxin). Clues from the history and physical examination may suggest Lyme disease, elevated intracranial pressure, or typhoid as other potential causes of bradycardia. Additional testing may include exercise treadmill testing to assess chronotropic competence and ambulatory ECG monitoring (see Diagnostic Testing in Cardiology).

Sinus Bradycardia

Sinus bradycardia is defined as the presence of sinus rhythm with a heart rate below 60/min. Sinus bradycardia may be appropriate in trained athletes and during sleep. Inappropriate or pathologic sinus bradycardia is most commonly caused by sinus node dysfunction due to age-related myocardial fibrosis. Less commonly, sinus node dysfunction may result from right coronary ischemia; intracranial hypertension; postoperative scarring or fibrosis from cardiothoracic surgery; or infiltrative or inflammatory disorders, such as sarcoidosis. The most common extrinsic cause is medication use.

Atrioventricular Block

AV block may be classified as first degree, second degree, or third degree. First-degree AV block is defined by a delay in AV conduction (PR interval >200 ms). In large cohort studies, first-degree AV block has been associated with an increased risk for atrial fibrillation and all-cause mortality.

In second-degree AV block, only some P waves conduct to the ventricles. Mobitz type 1 second-degree (Wenckebach) AV block is characterized electrocardiographically by a PR interval that progressively prolongs until a beat is dropped (Figure 10). Mobitz type 2 second-degree AV block is typified by ECG findings of grouped beating and progressive shortening of the RR intervals (Figure 11). The PR interval does not lengthen in Mobitz type 2 before nonconducted atrial beats. When 2:1 block is present, the Mobitz type cannot be determined. Mobitz type 2 AV block usually occurs below the AV node and has a higher risk for progression to complete heart block.

In third-degree AV block, also termed complete heart block, no P waves conduct to the ventricles. AV dissociation is observed on the ECG (Figure 12).

Treatment

In patients with symptomatic bradycardia and hemodynamic distress, atropine should be administered. If atropine is

