Heart Failure With Preserved Ejection Fraction (Diastolic Dysfunction)

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CME Objective: To review current evidence for the background, prevention, diagnosis, treatment, and practice improvement of heart failure with preserved ejection fraction (diastolic dysfunction).

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Heart failure (HF) is a serious health problem, with an estimated incidence of 660,000 cases per year in the United States, and a prevalence of more than 5 million. HF is the most common discharge diagnosis among patients older than 65 years and the primary cause of readmission within 60 days. As the population ages, HF is expected to become an even greater public health problem.

In contrast to HF patients with a reduced ejection fraction (HFrEF), up to 50% of patients with signs and symptoms of HF have normal or preserved left ventricular ejection fraction (HFpEF), also called diastolic HF (1–2). Although the signs and symptoms of HFpEF and HFrEF are similar, they seem to be clinically distinct syndromes with differing patient demographics and responses to therapy. While recent advances have improved the outcome for patients with HFrEF, they have not been found effective for HFpEF. Consequently, HFpEF creates diagnostic and treatment challenges for clinicians. As the prevalence of HFpEF relative to HFrEF is expected to increase at a rate of about 1% annually, there is an increased need for information with regard to evaluation, diagnosis, and treatment.

### Background

**What is the difference between HFpEF, diastolic dysfunction, and diastolic HF?**

The terms HFpEF, diastolic dysfunction, and diastolic heart failure are often used interchangeably. The American College of Cardiology Foundation and the American Heart Association (ACC/AHA), however, prefer the term HFpEF (4). Most patients with HFpEF have abnormalities in diastolic function—notably a stiffening of the ventricles with resultant impaired diastolic relaxation, filling, and elevated left ventricular (LV) end-diastolic pressure at rest or during stress (5). Multiple non-diastolic abnormalities in cardiovascular function, however, also contribute to the syndrome, including impairment of LV systolic function and functional reserve, chronotrophic incompetence, vascular stiffening and abnormal vasodilatation, pulmonary hypertension, and endothelial dysfunction. In addition, patients with HFpEF are vulnerable to decompensation in the setting of hemodynamic stresses, such as rapid atrial fibrillation, hypertensive crisis, and mitral regurgitation. Diastolic LV dysfunction is not unique to HFpEF because it is almost always present in HFpEF, albeit to a lesser degree. Impaired relaxation is the most commonly found abnormality in milder forms of HFrEF, whereas restrictive diastolic dysfunction is more commonly encountered in patients with lower EFs (6).

**What is the difference between HFpEF and HFrEF?**

Although preserved EF is generally defined as ≥45%–50% (3), no simple binary partition value divides “preserved” and “reduced” systolic function, and there is no consensus about the exact cut-off for preserved EF. Whether HFrEF and HFpEF overlap or are distinct phenotypes is a matter of debate (7). Several lines of evidence suggest that HFpEF is a separate and discrete clinical syndrome (7). Unlike HFrEF, the left ventricle does not dilate in HFpEF. In addition, data from large studies have shown a bimodal distribution of EF in patients with clinical HF. This pattern of clustering of HF patients with preserved EF further lends credibility to the concept that HFpEF is a unique and separate clinical syndrome (8). Moreover, unlike what would be expected if HFpEF and HFrEF were part of the same HF clinical spectrum (7), treatments with proven benefit...
in HFrEF, particularly renin–angiotensin–aldosterone inhibitors, are not effective in HFpEF. Patients with HFpEF tend to be older and female, with a higher frequency of hypertension and lower frequency of coronary artery disease than those with HFrEF (9).

In a study of over 500 Framingham Heart Study participants with new-onset HF, predictors of HFpEF (as opposed to HFrEF) included elevated systolic blood pressure, atrial fibrillation, and female sex (10). Conversely, prior myocardial infarction and left bundle branch block reduced the odds of HFpEF. The median survival (2.1 years) and 5-year mortality rate (74%) was poor in both men and women with HFrEF or HFpEF.

Although currently about equal, the prevalence of HFpEF is rising at about 1% per year relative to HFrEF (1) Notably, unlike HFrEF, outcomes for HFpEF have not improved over the past 2 decades, and the mortality for both is significant. HFpEF is commonly believed to be more benign than HFrEF; however, recent studies have shown that functional decline, hospital readmission rates, and economic costs are similar (11, 12).

**What are the risk factors for HFpEF?**
Risk factors for HF in general include age, hypertension, obesity (13), dyslipidemia (14), and insulin resistance (15). Clinical diabetes mellitus markedly increases the likelihood of HF in patients regardless of the EF (16, 17), particularly in women (18, 19).

Patients with HFpEF tend to be older and more hypertensive and have a higher prevalence of atrial fibrillation than those with HFrEF (9, 20). Prevalence of coronary artery disease is comparatively lower, but coronary artery disease can be the main underlying cause of HFpEF, particularly in men (9).

Overall, women are more likely to develop HFpEF than men, by a 2:1 ratio (21). According to a recent review, this may be because women experience more concentric LV remodeling and less ventricular dilatation in response to arterial hypertension. Also, ventricular and arterial stiffness increase with age more dramatically in women than in men, whereas systolic and diastolic function and functional reserve become more compromised in postmenopausal women than in men of a similar age (21).

In an echocardiographic substudy from the Irbesartan in HFpEF (I-PRESERVE) trial, 745 of 4128 patients had determination of LV volume, mass, left atrial (LA) size, systolic function, and diastolic function (22). LV hypertrophy or concentric remodeling was present in 59%, LA enlargement was present in 66%, and diastolic dysfunction was present in 69% of the patients. Multivariable analyses controlling for 7 clinical variables (including log N-terminal pro-B-type natriuretic peptide [BNP]) indicated that increased LV mass, mass–volume ratio, and LA size were independently associated with increased risk for the primary endpoint (death or cardiovascular hospitalization) and HF events.

**Are any drugs or nonpharmacologic interventions effective for primary prevention of HFpEF?**
Hypertension is a predominant factor in the development and progression of HFpEF. As a result, optimal control of blood pressure is the primary preventive approach. Both systolic and diastolic blood pressure should be lowered in...
accordance with published guidelines, including the most recently published report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (23). Treatment for hyperlipidemia and hyperglycemia can also reduce risk for HFrEF and HFrEF (24, 25). Patients should be encouraged to stop smoking, exercise regularly, and follow a healthy diet, including moderate consumption if they drink alcohol.

Control of hypertension

Many controlled studies have shown that optimal blood pressure control reduces risk for new HF by approximately 50% (26, 27). Several clinical trials have shown that effective reduction in systolic and diastolic blood pressure reduces the risk for HF, even in patients older than 80 years (27, 28). The HOPE trial showed marked reductions in risk for HF even with modest reductions in systolic blood pressure (27).

Treatment should aim to achieve systolic and diastolic blood pressure targets <140/90 mm Hg. In patients with hypertension and diabetes or renal disease, the goal is <130/80 mm Hg (23). The choice of drugs is determined by the concomitant medical problems (e.g., coronary artery disease, diabetes, or renal disease). Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, as single therapies, are not superior to other antihypertensive drug classes for reducing all cardiovascular outcomes (23, 26). Diuretics seem to reduce the incidence of new-onset HFpEF compared with ACE inhibitors and more significantly calcium-channel blockers and alpha-blockers (29).

A study of 910 patients hospitalized with incident HF examined treatment differences for HFpEF and HFrEF (29). Chlorthalidone reduced the risk for HFpEF compared with amlodipine, lisinopril, or doxazosin; the hazard ratios were 0.69 (95% CI, 0.53–0.91; P = 0.009), 0.74 (CI, 0.56–0.97; P = 0.032), and 0.53 (CI, 0.38–0.73; P = 0.001), respectively. Chlorthalidone also reduced the risk for HFrEF compared with amlodipine or doxazosin; the hazard ratios were 0.74 (CI, 0.59 to 0.94; P = 0.013) and 0.61 (CI, 0.47 to 0.79; P = 0.001), respectively. Chlorthalidone was similar to lisinopril with regard to incidence of HFrEF (hazard ratio, 1.07 [CI, 0.82 to 1.40]; P = 0.596). In ALLHAT, with adjudicated outcomes chlorthalidone significantly reduced the occurrence of new-onset hospitalized HFrEF and HFpEF compared with amlodipine and doxazosin.

Other preventive strategies

There is no direct evidence that control of dietary sodium or regular exercise is effective for primary prevention of HF. Compared with elderly athletes, sedentary seniors display reduced ventricular compliance, suggesting that long-term habitual exercise may allow for preservation of diastolic function with aging. However, a 1-year study of exercise training was not found to improve diastolic function in healthy seniors. In patients with hypertension or other vascular disease, however, these efforts may have other health benefits. Patients with diabetes mellitus are at high risk for HF, and glycemic control, in accordance with contemporary guidelines, is important for prevention (25). ACE inhibitors or angiotensin–receptor blockers (ARBs) can prevent end-organ disease in diabetic patients, even in persons without hypertension (30–32). Treatment of hyperlipidemia reduces the likelihood of death and HF in patients with a history of myocardial infarction (26, 33).

Exercise and diet

Weight reduction in obese patients (body mass index >30 kg/m²) should be considered to prevent diabetes, atrial fibrillation, obstructive sleep apnea, and hypertension (3, 4).
Which presenting features help to distinguish HFpEF from HFrEF? Patients with either HFrEF or HFpEF often present with dyspnea, impaired exercise tolerance, orthopnea, and paroxysmal nocturnal dyspnea. Each may have signs suggestive of HF, including tachycardia, elevated neck veins, gallop, inspiratory crackles, displaced apical impulse, hepatomegaly, and dyspnea. However, the prevalence of these various signs and symptoms is not statistically different between patients with HFpEF vs those with HFrEF (34). Similarly, invasive hemodynamic studies have shown that biventricular filling pressures and pulmonary artery pressures are similarly elevated in HFpEF and HFrEF, although cardiac output is somewhat lower in HFrEF. In addition, exercise capacity is impaired in HFpEF and HFrEF.

HFpEF and HFrEF share many risk factors. A history of hypertension and atrial fibrillation may be slightly more prevalent in patients with HFpEF than in those with HFrEF, whereas coronary artery disease is more prevalent in HFrEF (10, 20). Rapid onset of dyspnea in patients who are markedly hypertensive (often termed “flash” pulmonary edema), particularly in elderly women, is more common in HFpEF. Slower-onset HF with a history of coronary disease, particularly in middle-aged men, is more likely to be related to HFrEF (10, 20).

Atrial fibrillation or LV hypertrophy on the electrocardiogram (ECG) is more suggestive of HFpEF. Left bundle branch block or evidence of prior ischemic injury is more suggestive of HFrEF (9, 20).

Which diagnostic tests should the clinician order for patients with suspected HF? Several diagnostic tests are used routinely to confirm or rule out the diagnosis of HF (Table 1).

Electrocardiography
An ECG should be performed in all patients with suspected HF. Although an abnormal ECG has little predictive power for the presence of HF, common abnormal findings in patients with HFpEF include evidence of ventricular hypertrophy, LA abnormality, and atrial fibrillation. Patients with HFrEFA rarely have a normal ECG (3, 4).

Radiography
A chest X-ray is routinely ordered to detect pulmonary vascular congestion and cardiomegaly (3, 4). Radiographic signs of pulmonary congestion, including increased interstitial markings, Kerley “B”
lines, and pleural effusion, frequently indicate pulmonary venous hypertension and elevated LA pressure in a patient with HFpEF. Cardiomegaly in a patient with HFpEF generally reflects ventricular hypertrophy due to longstanding pressure overload as well as atrial and right heart enlargement. These findings may be considered confirmatory, if not diagnostic, of the HF syndrome. The chest X-ray is also important to exclude other diagnoses, such as pneumonia.

**Echocardiography**
Echocardiography is essential for evaluating HFpEF and HFpEF and considered by the ACC/AHA guidelines to be “The single most useful diagnostic test in the evaluation of patients with HF” (4). An echocardiographic evaluation of LV function is essential. An LV EF greater than 45%-50% in a patient with HF is consistent with HFpEF. Echocardiography can also estimate whether ventricular filling pressures are elevated on the basis of the Doppler velocity of bloodflow into the LV during diastole, the pattern of flow through the pulmonary veins into the left atrium, and tissue Doppler velocity (a measure of the relation to increased LA pressure and size. LV wall motion abnormalities may provide evidence of coronary heart disease (20, 34, 35). These may be helpful in evaluating the severity of diastolic dysfunction. Estimated pulmonary arterial systolic pressure is generally elevated in relation to increased LA pressure and size. LV wall motion abnormalities may provide evidence of coronary heart disease (20, 34, 35). If mitral and aortic valve disease, coexist, constrictive pericarditis or infiltrative cardiomyopathy and disorders of the right ventricle are also essential in evaluating the cause of HF because many are treated differently from “garden-variety” HFpEF.

**Laboratory testing**
Essential blood tests include plasma levels of the natriuretic peptides BNP and N-terminal pro-BNP (NT-proBNP), which are useful biomarkers to diagnose elevated diastolic filling pressures in both HFrEF and HFpEF (see below). Other essential studies include complete blood counts to evaluate for anemia, serum electrolytes, creatinine, glucose, liver function, and urinalysis (3, 4). Renal dysfunction and electrolyte disturbances (e.g., in potassium) may often occur with use of diuretics, renin–angiotensin–aldosterone antagonists, and digitalis for treatment of HF.

**What additional tests should clinicians consider for patients with suspected HFpEF?**
Cardiac catheterization is usually done in patients with new-onset HF, particularly if the ECG, echocardiography, or biomarkers (e.g., BNP) suggest coronary heart disease or if HF occurred in relation to chest pain or pressure. The examination usually includes left heart catheterization with measurement of LV end-diastolic pressure (LVEDP) and coronary arteriography. Right heart catheterization is useful for patients in whom echocardiography suggests valvular heart disease, if pulmonary hypertension is not explained by left heart abnormalities, constrictive pericarditis, or the cause of dyspnea is not clear from noninvasive testing. Elevated LVEDP (or its estimation by the pulmonary artery occlusion pressure [PAOP] or “wedge” pressure) in the presence of preserved LVEF is consistent with a diagnosis of HFpEF.

In patients with exertional symptoms not explained by testing performed at rest, early-stage HFpEF may be detected by hemodynamic measurements done during exercise at the time of right heart catheterization. These may reveal exercise-induced elevations in PAOP with secondary elevations in pulmonary artery pressures (37, 38). Further testing is indicated if the cause of LV diastolic dysfunction remains obscure. Specific blood or imaging
tests may be appropriate if conditions causing abnormal myocardial function are considerations, such as radiation-mediated myocardial fibrosis, constrictive pericarditis, sarcoidosis, amyloidosis, the endomyocardial fibrosis/hypereosinophilic syndrome, glycogen storage diseases, or hemochromatosis. Imaging may include myocardial or fat pad tissue computed tomography or magnetic resonance imaging.

**Table 1. Tests for HFP EF**

<table>
<thead>
<tr>
<th>Test</th>
<th>Goal</th>
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<tbody>
<tr>
<td>Echocardiography</td>
<td>Establish the EF (&gt;45%–50%)</td>
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<tr>
<td></td>
<td>Evaluate the LV for signs of coronary heart disease or infiltrative cardiomyopathy</td>
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<td></td>
<td>Assess the presence and severity of diastolic dysfunction</td>
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<tr>
<td></td>
<td>Estimate mean LA or pulmonary capillary wedge pressure from tissue Doppler</td>
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<tr>
<td></td>
<td>Rule out severe left-sided heart valve disease</td>
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<tr>
<td></td>
<td>Rule out constrictive pericarditis</td>
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<tr>
<td></td>
<td>Measure pulmonary artery systolic pressure, which might indicate elevated left-sided pressure</td>
</tr>
<tr>
<td></td>
<td>Measure LA size (a clue to chronically elevated LA pressure)</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Diagnose arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Investigate for evidence of acute ischemia</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Useful for detecting pulmonary vascular congestion and other causes of dyspnea (e.g., interstitial lung disease or pneumonia)</td>
</tr>
<tr>
<td></td>
<td>Assess degree of cardiomegaly</td>
</tr>
<tr>
<td>Plasma levels of the natriuretic peptides (BNP and N-terminal pro-BNP)</td>
<td>Useful for the diagnosis of HFP EF</td>
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<tr>
<td></td>
<td>Increased levels predict higher mortality</td>
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<td></td>
<td>Normal value does not exclude HFP EF in ambulatory patients with exertional dyspnea</td>
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<td></td>
<td>Normal concentration in a patient presenting with ongoing severe dyspnea (e.g., in emergency department or urgent care setting) has good negative predictive value</td>
</tr>
<tr>
<td>Complete blood counts and serum electrolytes</td>
<td>Exclude anemia as a cause of dyspnea or high-output HF</td>
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<td></td>
<td>Serum potassium level must be followed carefully during diuretic therapy</td>
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<tr>
<td>Creatinine, estimation of GFR</td>
<td>Reduced GFR may promote congestion</td>
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<td></td>
<td>Abnormal renal function may be a clue to renovascular disease, especially in patients with peripheral vascular disease</td>
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<tr>
<td></td>
<td>Increased creatinine consistently associated with increased morbidity and mortality</td>
</tr>
<tr>
<td>Glucose and liver function tests, urinary analysis</td>
<td>Evaluate hyperglycemia/diabetes</td>
</tr>
<tr>
<td></td>
<td>Evaluate presence of renal parenchymal disease</td>
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<tr>
<td></td>
<td>Assess presence of hepatic congestion in patients with signs and symptoms of prominent right-sided failure</td>
</tr>
<tr>
<td>Left and right heart catheterization</td>
<td>Assess the presence and severity of coronary disease, especially in patients with sudden presentation of HF or in whom HF symptoms occurred in close relationship to chest pain/pressure</td>
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<tr>
<td></td>
<td>Document elevated diastolic filling pressures</td>
</tr>
<tr>
<td></td>
<td>Identify whether symptoms of dyspnea or pulmonary hypertension as estimated by echocardiography are due to HFP EF or HFr EF by assessing left-sided filling pressures</td>
</tr>
<tr>
<td>Myocardial or fat pad tissue CT or MRI</td>
<td>Evaluate suspected constrictive pericarditis, sarcoidosis, amyloidosis, endomyocardial fibrosis/hypereosinophilic syndrome, glycogen storage diseases, or hemochromatosis</td>
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</table>

**What are the criteria for establishing the diagnosis?**

A diagnosis of HFP EF is usually based on history, physical examination, radiography, BNP levels, and echocardiography. There is no consensus on the criteria for diagnosis.

Four sets of guidelines for the diagnosis of HFP EF have been published (3, 4, 39, 40) (see the Box: Requirements for Diagnosis of HFP EF)

**What is the role of BNP in diagnosis and management?**

Levels of both BNP and NT-proBNP are usually lower in patients with HFP EF than in those
with HFrEF, although they are frequently still elevated. NT-proBNP appears to be superior to BNP for the evaluation of suspected acute HF in patients with preserved EF, because BNP may be falsely negative in up to 20% of patients with HFrEF and does not correlate with symptoms (41-43).

Levels of both NT-proBNP and BNP may be significantly lower in obese patients (32). NT-proBNP at cutoffpoints >450 pg/mL for patients <50 years of age and >900 pg/mL for patients ≥50 years of age are highly sensitive and specific for the diagnosis of acute HF in the emergency department (41-43). Both elevated NT-proBNP and BNP are strong independent predictors of clinical events in patients with HFrEF (43). No consensus exists on use of natriuretic peptide levels to guide medical therapy.

Requirements for Diagnosis of HFrEF

- Presence of signs and/or symptoms of HF
- Preserved systolic LV function (EF ≥45%–50%)
- Evidence of diastolic LV dysfunction, elevated LV filling pressures, or surrogate markers of diastolic LV dysfunction (e.g., LV hypertrophy, LA enlargement, atrial fibrillation, or elevated plasma natriuretic peptides)

HFrEF = heart failure with a normal or preserved left ventricular ejection fraction; LV = left ventricular.

Diagnosis... The signs and symptoms of HFrEF include impaired exercise tolerance, orthopnea, dyspnea, and signs suggestive of HF (e.g., tachycardia, elevated neck veins, gallop, and inspiratory crackles). History may include hypertension and atrial fibrillation. HFrEF is usually readily diagnosed on the basis of history, physical examination, radiography, BNP levels, and echocardiography. Although there is no consensus on the criteria for diagnosing HFrEF, 4 sets of guidelines require the presence of signs and/or symptoms of HF; preserved systolic LV function (EF ≥45%–50%); and evidence of diastolic LV dysfunction, elevated LV filling pressures, or surrogate markers of diastolic LV dysfunction (e.g., LV hypertrophy, LA enlargement, atrial fibrillation, or elevated plasma natriuretic peptides).

CLINICAL BOTTOM LINE

How should HFrEF be treated?

Management of HFrEF focuses on relieving symptoms of pulmonary congestion and peripheral edema by ameliorating the hemodynamic perturbations that cause increased wall stress. This involves controlling heart rate in patients with rapid atrial fibrillation and decreasing afterload and preload by treating hypertension and volume overload. Another goal is to reduce mortality, but this has been elusive (44-46).

Reducing preload

Reducing LV preload with diuretics and vasodilators is a mainstay of therapy to relieve congestive symptoms, including dyspnea and peripheral edema. However, aggressive reduction in preload may cause hypotension in hypertensive and normotensive patients and volume status assessment (also see below) is essential. Control of hypertension in euvolemic patients with vasodilators alone may be appropriate.

Acute HFrEF

Vasodilators are first-line therapy in most patients with acute HFrEF. Intravenous nitrates in combination with furosemide can improve cardiac output and reduce the symptoms of HF. Randomized, controlled trials have shown that titration to the highest hemodynamically tolerable dose of nitrates together with low-dose furosemide is superior to high-dose diuretic treatment alone (37). Nitroglycerin relieves the symptoms of acute pulmonary edema by reducing preload and is often the vasodilatory agent of choice in patients with underlying ischemic heart disease. Nitroglycerin should be administered to ensure the fastest onset of action, preferably intravenously. The initial infusion rate of 10 µg/min may be increased to 300 µg/min to achieve desired effects. The dose should not be increased when the systolic arterial pressure decreases below 90 mm Hg. It can also be administered orally or by inhalation (glyceryl trinitrate spray 400 µg [2 puffs] every 5–10 min) or...
buccally (isosorbide dinitrate 1 or 3 mg) while blood pressure is being monitored. Buccal absorption, however, may be erratic.

While vasodilators are established treatments for decompensated HF, a recent study found that compared with patients with HFrEF, those with HFrpEF have greater reduction in blood pressure and less improvement in forward stroke volume with intravenous nitrates. In addition, patients with HFrpEF were 4 times more likely to have a drop in stroke volume in response to vasodilator therapy than patients with HFrEF, despite the presence of very high LV filling pressures. Because vasodilators reduce afterload, the reduction in stroke volume was almost certainly due to reduction in LV diastolic volumes. These phenomena are related to ventricular–arterial stiffening in HFrpEF—there are more dramatic changes in blood pressure with altered cardiac load, and because of an increase in diastolic LV stiffness, a higher pressure is often required to maintain an adequate LV preload volume. Thus, caution is required when administering parenteral vasodilators to patients with acute HFrpEF in the absence of significant hypertension, in addition to other patient groups who are reliant on high filling pressure for adequate preload (such as aortic stenosis and hypertrophic cardiomyopathy).

Loop diuretics (furosemide, bumetanide, torsemide) are the most widely used diuretics to treat HFrpEF. The dose should be titrated according to the diuretic response and relief of congestive symptoms. Administration of a loading dose followed by continuous infusion of furosemide has not been shown to be more effective than bolus intravenous dosing alone (38). A combination of diuretics may result in fewer secondary adverse effects than higher doses of a single drug. Thiazides and spironolactone can be used in conjunction with loop diuretics to achieve a more robust diuretic response while using lower doses of loop diuretics overall. The diuretic doses for patients with mild congestion and new-onset HFrpEF are generally much lower than those for patients with chronic HFrpEF or in patients with renal dysfunction. Note that diuretic use needs to be adjusted in the setting of a decreased glomerular filtration rate. As noted above, many patients with acute HFrpEF are not markedly hypervolemic. Indeed, elevated filling pressures or preload does not always correspond to increased volume, and patients with HFrpEF often have normal or low LV end-diastolic volumes. Aggressive diuresis is to be avoided in such patients because it may cause significant hypotension.

Management of acute HFrpEF may also require heart rate control, particularly in patients with rapid atrial fibrillation (discussed below).

Long-term treatment of hypertension
Hypertension can worsen myocardial stiffness and relaxation properties through its immediate effects of increasing afterload and wall stress. Acute rises in wall stress worsen myocardial relaxation properties and raise filling pressures leading to congestive symptoms. It also contributes to the long-term deleterious effects of myocardial hypertrophy or remodeling through neurohormonal activation, including the renin–angiotensin–aldosterone system. Blood pressure control per se has been shown in 2 studies to improve early diastolic tissue velocity in patients with hypertension but no clinical HF.

The choice of antihypertensive agent is dictated by the specific circumstances of the patient (e.g., diabetes, coronary artery disease), and no individual class of agent has been shown to be clearly superior to another in HFrpEF (4, 47). ALLHAT suggests that thiazide diuretics reduce overall incidence of HF and should be considered first if there are no other comorbid conditions (48).

45. Meta-analysis: Global Group in Chronic Heart Failure. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J. 2012;33:1750-7. [PMID: 21821849]
Neurohormonal blockade to reduce or reverse adverse remodeling has been a target of therapy in both HFpEF and HFrEF. Conceptually, a reduction in LV mass would be beneficial in HFpEF by addressing underlying pathophysiologic abnormalities. ARBs have been shown to cause the greatest reduction in LV mass index compared with other antihypertensive agents (49). However, clinical trials have not shown a clear mortality benefit of ARBs over other antihypertensive agents, although ARBs do seem to reduce hospitalization for HF (44, 50).

Thus, the selection of antihypertensive medication is dependent on comorbid conditions. For example, in the setting of coronary atherosclerosis or atrial fibrillation, a beta-blocker may be more desirable.

**Rate and rhythm control**

Atrial fibrillation is particularly troublesome for patients with HFpEF. Rapid heart rates shorten diastolic filling time and result in loss of atrial contribution to LV filling in late diastole.

In patients with atrial fibrillation and HFpEF, restoration of a normal heart rate and maintenance of sinus rhythm may improve symptoms but not clearly outcomes (3, 47). Whether a rate control strategy is superior to a rhythm control strategy is unknown (51–53).

In most cases of atrial fibrillation in HFpEF, rate control is a reasonable initial strategy and is achieved with atioventricular nodal blocking agents, such as nondihydropyridine calcium–channel blockers (diltiazem or verapamil) and beta-blockers. Criteria for rate control varies with age but usually involves achieving ventricular rates between 60 and 80 beats/min at rest and 90 and 115 beats/min during moderate exercise (4, 47, 51–54).

A rhythm control strategy may be preferred for patients in whom rate control has not been achieved or symptoms persist despite adequate rate control. In addition, immediate electrical cardioversion is recommended for patients with new-onset atrial fibrillation and myocardial ischemia, symptomatic hypotension, or symptoms of pulmonary congestion or rapid ventricular response that cannot be promptly controlled by appropriate pharmacologic measures (3, 4, 47).

Whether a rate control or rhythm control strategy is adopted, anticoagulation is still recommended—data from AFFIRM and RACE show equivalent thromboembolic risk with either strategy (51, 52). In general, patients with HFpEF frequently have multiple risk factors for thromboembolism.

Pulmonary vein isolation and atrial fibrillation ablations are promising techniques to reduce the occurrence of atrial fibrillation in patients with HF (55). However, data on outcomes in patients with HFpEF are limited.

**When should inotropic agents be considered?**

Inotropic agents are not indicated in management of HFpEF. They increase inotropy, can increase heart rate, and have no lusitropic effects. Studies on digoxin have not shown a significantly positive result in HFpEF (54).

**How does drug therapy for HFpEF differ from that of HFrEF?**

Many of the same drugs are used for the treatment of HFrEF and HFpEF. However, the evidence differs. Several randomized clinical trials show improvement in mortality and morbidity for HFrEF with such therapies as ACE inhibitors, ARBs, beta-blockers, and aldosterone antagonists, but no clinical studies to date have shown similar outcomes in HFpEF. Drug therapy for HFpEF focuses on symptom...
relief, blood pressure control, and heart rate control.

**Are any novel drug therapies being investigated for HFrEF?**
Spirinolactone is a proven therapy for HFrEF and is under investigation for HFpEF in the TOPCAT study (56). Phosphodiesterase-5 inhibition with sildenafil was shown in a small study in patients with HFpEF and pulmonary hypertension to reduce pulmonary arterial pressure, improve right ventricular systolic function, reduce right atrial pressure, and improve quality of life measures compared with placebo (57). A larger, multicenter randomized trial sponsored by the National Heart, Lung, and Blood Institute called the RELAX trial has completed enrollment and is studying the efficacy of sildenafil in HFpEF (58) (Table 2) (20).

**What triggers decompensation?**
Precipitating factors in decompensated HF are similar in HFpEF and HFrEF and include dietary indiscretion, use of nonsteroidal anti-inflammatory drugs, and medication nonadherence. Other factors include dysrhythmias, particularly atrial fibrillation, ischemia or infarction, hypertension, worsening renal function or valvular cardiac disease, alcohol abuse, and infection.

**What is the role of diet and monitoring weight?**
Patients should weigh themselves daily and note any unexpected weight gain of, for example, 2 kg (4.4 pounds) over 3 days, although smaller changes may warrant prompt action and close attention in others. Patients should know what to do if weight gain, an increase in edema, or other symptoms of HF occur. Instructions may include promptly calling their health care provider or instituting a predefined plan, such as a transient increase in diuretic dosage with careful attention and communication with the health care team. It is important for patients to understand the risks for volume depletion with excessive diuretic use.

Sodium restriction is recommended in symptomatic HF to prevent fluid retention. Although no specific guidelines exist for HFpEF, because many patients have concomitant comorbid conditions the U.S. Department of Agriculture and Health and Human Services recommend that persons with hypertension, chronic renal insufficiency, diabetes, or age older than 51 years or those of African descent to limit sodium intake to 1.5 g/day (59).

### Table 2. Management Principles for Patients With HFrEF*

<table>
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<tr>
<th>Goal</th>
<th>Treatment</th>
<th>Commonly Used Doses</th>
</tr>
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<tbody>
<tr>
<td>Reduce pulmonary or systemic venous congestion</td>
<td>Salt restriction, Diuretics, ACE inhibitors, Angiotensin II-blockers, Diuretics</td>
<td>Furosemide, 10–120 mg/d, Lisinopril, 10–40 mg/d, Losartan, 50–100 mg/d</td>
</tr>
<tr>
<td>Maintain sinus rhythm</td>
<td>Cardioversion of atrial fibrillation</td>
<td>Metoprolol, 25–100 mg/d, Verapamil, 180–360 mg/d</td>
</tr>
<tr>
<td>Prevent tachycardia; promote bradycardia</td>
<td>β-blockers, calcium-channel blockers</td>
<td>Metoprolol, 25–100 mg/d, Verapamil, 180–360 mg/d</td>
</tr>
<tr>
<td>Treat and prevent myocardial ischemia</td>
<td>Nitrates, β-blockers, calcium-channel blockers</td>
<td>Isosorbide dinitrate, 30–180 mg/d, Metoprolol, 25–200 mg/d, Diltiazem, 90–360 mg/d</td>
</tr>
<tr>
<td>Control hypertension and promote regression of hypertrophy</td>
<td>Antihypertensive agent</td>
<td>Per JNC 7 guidelines</td>
</tr>
<tr>
<td>Attenuate neurohormonal activation</td>
<td>β-blockers, ACE inhibitors</td>
<td>See above</td>
</tr>
<tr>
<td>Prevent fibrosis and promote regression of fibrosis</td>
<td>Spironolactone, ACE inhibitors or ARBs</td>
<td>25–75 mg/d, See above</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; HFrEF = heart failure with reduced ejection fraction; JNC 7 = The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

*The treatments listed for the first 4 goals are those generally used in clinical practice. ACE inhibitors, ARBs, and spironolactone inhibit the renin–angiotensin–aldosterone system and thus have a theoretical benefit, but more data are required to show that they reduce the risk for HF. The list of medications is not comprehensive; rather, it includes examples that are in common clinical use or have been included in studies of pathophysiologic mechanisms in diastolic dysfunction or HF or were included in larger trials that generally were not designed to assess outcomes in diastolic HF. Candesartan is the only agent studied in a randomized, controlled trial involving patients with diastolic HF. Adapted from reference 20.
Patients should be educated about the salt content of common foods and limit foods with over 150 mg of sodium/serving.

Fluid restriction of 1.5–2 L/day may be considered in patients with severe symptoms of HF, especially those with hyponatremia. Routine fluid restriction in all patients with mild to moderate symptoms does not seem to confer clinical benefit.

What should clinicians advise patients with HFpEF about exercise? Regular, moderate daily activity is recommended for all patients with HF. Exercise, especially aerobic exercise, may improve cardiovascular performance, lower blood pressure, prevent or reverse deconditioning, and increase energy levels while also reducing the symptoms of HF (60). Recent evidence also suggests that cardiac structure and filling pressure may be increased with exercise.

How should clinicians assess the response to therapy for HFpEF? Response to therapy is based on alleviation of symptoms, improvement in functional capacity, and decreased hospitalizations for decompensated HFpEF. Other treatment targets include optimal blood pressure control, and adequate heart rate control in patients with atrial fibrillation.

Because there is no proven or agreed-on therapeutic strategy for HFpEF, medications should be changed or added on the basis of inadequate response to therapy, suboptimum control of blood pressure, and poor heart rate control in patients with atrial fibrillation.

What is the prognosis of HFpEF? Patients with HFpEF may have a lower risk for death than patients with HFrEF, although data conflict and some studies suggest equal risk (61–64). Nearly half of HFpEF patients die owing to noncardiovascular diseases, and there has been a temporal trend for higher noncardiovascular mortality in HFpEF in the most recent decade (9). Annual death rate is estimated to be about 5% based on the I-PRESERVE HFpEF trial.

Of 4128 patients with HFpEF (EF >45%) enrolled in the I-PRESERVE trial, 445 patients in the irbesartan group and 436 in the placebo group died during the mean follow-up period of 49.5 months. The cause of death was cardiovascular in 60% (including 26% sudden death, 14% HF, 5% myocardial infarction, and 9% stroke), noncardiovascular in 30%, and unknown/not classified in 10% (46).

Risk factors for mortality in HFpEF are largely similar to HFrEF and include increasing age, higher natriuretic peptide levels, coronary artery disease, peripheral vascular disease, diabetes mellitus, chronic renal insufficiency, higher New York Heart Association class, lower EF, male gender, and a restrictive filling pattern on Doppler echocardiography (65–68). Low and very high body mass index are also associated with increased risk for death in HFpEF.

How should patients with HFpEF be followed? To prevent exacerbation of HF, clinicians should educate patients to recognize the signs of fluid retention, such as weight gain, leg swelling, and abdominal fullness. They should provide patients with guidelines for using a flexible diuretic regimen and telephone access to health care providers for further guidance on management. They should also emphasize the importance of a low-salt diet and compliance with their medical regimen, including antihypertensive therapy.

The frequency of follow-up visits depends on the relative stability of the patient. Patients should ideally be seen within 7 days of hospital discharge for decompensated HF. Well-compensated patients could be seen every 4 to 6 months.
When should patients with HFpEF be hospitalized?

Hemodynamically unstable patients or patients with acute respiratory failure/distress should be hospitalized. Significant comorbid conditions, such as acute renal failure, dysrhythmias, evidence of ischemia, severe electrolyte disturbances, concomitant infections, poor compliance, or unreliable follow-up, should prompt the clinician to strongly consider inpatient therapy. Clinicians should also consider hospitalization in patients whose condition worsens despite outpatient therapy (see the Box: Considerations for Hospitalizing Patients With HFpEF).

When should clinicians consider consulting a cardiologist?

Consultation with a cardiologist should be considered when the diagnosis of HFpEF is uncertain or the cause is unclear. Other reasons include that the patient remains symptomatic despite treatment or requires frequent hospitalization for decompensated HFpEF. Consultation may also be needed when other comorbid cardiac conditions, such as coronary artery disease or dysrhythmia, complicate management.

When should clinicians consider placing an intracardiac device?

In the absence of symptomatic bradyarrhythmias and need for the secondary prevention for sudden cardiac death, there are no indications for a pacemaker or an intracardiac defibrillator for management of HFpEF itself. However, biventricular pacing is currently being studied (69).

Treatment...

Management of HFpEF is aimed at treating the triggers of HF decompensation and at relieving acute pulmonary congestion and intravascular and interstitial volume excess. Treatment targets include alleviation of symptoms, improvement in functional capacity, and decreased hospitalizations as well as optimal blood pressure control and adequate heart rate control in patients with atrial fibrillation. To prevent exacerbation HF, clinicians should educate patients to recognize the signs of fluid retention and to use a flexible diuretic regimen if needed. Education should emphasize the importance of a low-salt diet and compliance with their medical regimen, including antihypertensive therapy. Cardiologist consultation is warranted when the diagnosis of HFpEF is uncertain, the cause is unclear, or the patient remains symptomatic despite treatment. Patients whose condition worsens or who develop complications may need to be hospitalized.

CLINICAL BOTTOM LINE

What do professional organizations recommend with regard to the care of patients with HFpEF?

There are no “evidence-based” therapeutic guidelines for HFpEF. Although several professional societies have published guidelines on management, only 2 have addressed HFpEF (3, 54). The ACC/AHA guidelines emphasize blood pressure control, diuretics to relieve congestion, ischemia relief, and heart rate control in rapid atrial fibrillation, but there have been few if any randomized, controlled trials to guide therapy (3, 47).

These recommendations include diuretics to reduce fluid overload and ACE inhibitors or ARBs to treat hypertension and to promote regression of LV hypertrophy. Treatment recommendations include beta-blockers or rate-lowering calcium-channel blockers to slow heart rate in atrial fibrillation and assign a class IIb indication to these agents in the absence of...

Considerations for Hospitalizing Patients With HFpEF

- Respiratory failure secondary to pulmonary edema
- Moderate to severe volume overload
- Atrial fibrillation with rapid ventricular response
- Severe hypotension or hypotension
- Need for close monitoring during therapy (e.g., of renal function, electrolytes)


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uncontrolled hypertension or ischemic heart disease (4, 47).

**What other resources are available on the Internet to help clinicians manage patients with HFpEF?**

The Heart Failure Society of America (www.hfsa.org/publications.asp) has a comprehensive list of resources for the clinician caring for HF patients.

**What measures do stakeholders use to evaluate the quality of care for patients with HFpEF?**

The Deficit Reduction Act of 2005 mandated that the Secretary of Health and Human Services make outcome and efficiency measures publicly available under the Hospital Inpatient Quality Reporting Program. The Centers for Medicare & Medicaid Services has developed 3 risk-standardized, 30-day readmission measures for patients with acute myocardial infarction, HF, and pneumonia.

The readmission measures for these three conditions are in addition to those already reported on Hospital Compare (www.hospitalcompare.hhs.gov).
THINGS YOU SHOULD KNOW ABOUT HEART FAILURE WITH PRESERVED EJECTION FRACTION
(DIASTOLIC DYSFUNCTION)

What is diastolic dysfunction?
• Heart failure is when the heart is unable to pump blood effectively.
• In some patients, this results from processes that make it harder for the heart to relax or fill between beats (diastolic dysfunction).
• Unlike in other patients with heart failure, a measurement of how well the heart beats, the ejection fraction, is normal.

What are risk factors for diastolic dysfunction?
• Older than 45 years.
• High blood pressure.
• Aortic stenosis (narrowing of the aortic heart valve).
• Atherosclerosis (clogged arteries).
• Diabetes.
• More common in women.
• Cardiac catheterization, in which a thin tube is inserted into the heart, may be warranted to learn more about its functioning.
• Blood tests may be done.

What are the symptoms?
• Shortness of breath.
• Irregular or abnormal heart beat.
• Fatigue.
• Light-headedness or fainting.

How is it diagnosed?
• Your doctor will ask you questions about your health and conduct a careful physical examination.
• He or she may order an imaging test called an echocardiography (a sonogram of the heart); this is often combined with a stress test to show how blood is flowing in the heart during exercise.
• Cardiac catheterization or surgery to fix problems, such as narrowed or obstructed blood vessels.

How is it treated?
• Smoking cessation, physical activity, and dietary changes.
• Treatment for conditions that can stiffen the left ventricle (high blood pressure, high cholesterol, diabetes).
• Medications may include:
  • Beta-blockers to slow the heart rate.
  • Calcium-channel blockers to reduce ventricular stiffness.
  • Angiotensin-converting enzyme (ACE) inhibitors.
  • Diuretics to reduce fluid accumulation.

For More Information

Information on heart failure and chronic mitral regurgitation from the National Institutes of Health MedlinePlus.

http://familydoctor.org/online/famdocen/home/common/heartdisease/risk/292.html
Information on assessing your risk for heart disease and on ways to lower high blood pressure from the American Academy of Family Physicians.

www.heart.org/HEARTORG/Conditions/HeartFailure/HeartFailureTools/Resources/Patient-Information-Sheets-Heart-Failure_UCM_306377_Article.jsp
Patient resources about heart failure, including questions to ask your doctor, from the American Heart Association.
1. A 42-year-old man is hospitalized for progressively worsening dyspnea on exertion for 6 months, now occurring with minimal activities. He has had frequent episodes of dyspnea at rest, progressive fatigue, leg edema, and a 9.1-kg (20.0-lb) weight gain over the past 4 weeks. He reports symptoms of 3-pillow orthopnea and nocturnal dyspnea but does not have chest pain, palpitations, syncope, or cough. There is no family history of sudden cardiac death. He has no other medical problems. His medications are metoprolol, disopyramide, and furosemide.

On physical examination, temperature is normal, blood pressure is 100/50 mm Hg, pulse is 48/min, and respiration rate is 28/min. Jugular venous distention is noted, with brisk carotid upstrokes. Estimated central venous pressure is 10 cm H2O. Cardiac examination reveals an S3 gallop at the apex and a grade 3/6 midsystolic murmur along the lower left sternal border that accentuates with a Valsalva maneuver and diminishes with a hand-grip maneuver. Pulmonary examination discloses dullness to percussion in the posterior lung fields at the bases, crackles in the basilar posterior lung fields, and no wheezing. The lower extremities show 3+ edema. Laboratory studies reveal hemoglobin, 13.5 g/L; leukocyte count, 8.3 × 10^9 cells/L, with normal differential; creatinine, 167.9 µmol/L (2.2 mg/dL); blood urea nitrogen, 17.9 mmol/L; albumin, 40 g/L; iron normal ferritin normal thyroid-stimulating hormone, 2.5 mIU/L; B-type natriuretic peptide, 2045 ng/L; and 12-lead electrocardiogram shows sinus bradycardia, left atrial enlargement, and left ventricular hypertrophy. Echocardiogram shows hyperdynamic left ventricular systolic function, a left ventricular ejection fraction of 80%, asymmetric septal hypertrophy, left ventricular dynamic outflow obstruction with a peak gradient of 144 mm Hg, left ventricular diastolic dysfunction, and left atrial enlargement. Septal thickness is 26 mm. Chest radiograph discloses no infiltrates, an enlarged cardiac silhouette, and small pleural effusions.

Which of the following is the most appropriate treatment?
A. Carvedilol
B. Implantable cardioverter-defibrillator
C. Permanent pacemaker
D. Surgical septal myectomy

2. A 40-year-old woman is evaluated for 2 months of progressive dyspnea on exertion, orthopnea, and lower extremity edema. She has no other medical problems and takes no medications, including over-the-counter drugs, and she does not use illicit drugs. She does not smoke cigarettes and rarely drinks alcohol. There is no family history of heart disease.

On physical examination, she is afebrile. Blood pressure is 120/80 mm Hg and pulse is 80/min. Estimated central venous pressure is 8 cm H2O. The lungs are clear. Cardiac examination reveals a regular rhythm, an S3, and no murmurs. There is mild ankle edema. Chest radiograph shows mild vascular congestion.

Electrocardiogram shows normal sinus rhythm. Initial laboratory evaluation reveals a normal hemoglobin level and a normal metabolic profile, including thyroid studies.

Which of the following is the most appropriate initial diagnostic test?
A. B-type natriuretic peptide level
B. Echocardiography
C. Radionuclide ventriculography
D. Stress test

3. A 60-year-old woman is evaluated for follow-up after hospitalization 2 weeks ago for pulmonary edema and volume overload that readily resolved with intravenous diuretics. She is currently feeling well without edema or shortness of breath. A stress echocardiogram done in the hospital was negative for ischemia and showed an ejection fraction of 60% and no significant valvular abnormalities. She has a history of hypertension, hyperlipidemia, and chronic atrial fibrillation. She takes metoprolol (75 mg twice daily), hydrochlorothiazide, warfarin, aspirin, and pravastatin.

On physical examination, she is afebrile. Blood pressure is 150/90 mm Hg, and pulse is 50/min. Jugular veins are not distended, and the lungs are clear. Cardiac examination shows an irregularly irregular rhythm, with variable intensity of the S1, and no murmurs. There is no edema.

Which of the following is the most appropriate adjustment to her treatment?
A. Add candesartan
B. Add digoxin
C. Change hydrochlorothiazide to furosemide
D. Increase metoprolol dosage