Heart failure with preserved ejection fraction (HFpEF) is a complex clinical condition. Initially called diastolic heart failure, it soon became clear that this condition is more than the opposite side of systolic heart failure. It is increasingly prevalent and lethal. Currently, HFpEF represents more than 50% of heart failure cases and shares a 90-day mortality and readmission rate similar to heart failure with reduced ejection fraction. Heart failure with preserved ejection fraction is best considered to be a systemic disease. From a cardiovascular standpoint, it is not just a stiff ventricle. A stiff ventricle combined with a stiff arterial and venous system account for the clinical manifestations of flash pulmonary edema and the marked changes in renal function or systemic blood pressure with minor changes in fluid volume status. No effective pharmacologic treatments are available for patients with HFpEF, but an approach to the musculoskeletal system has merit: the functional limitations and exercise intolerance that patients experience are largely due to abnormalities of peripheral vascular function and skeletal muscle dysfunction. Regular exercise training has strong objective evidence to support its use to improve quality of life and functional capacity for patients with HFpEF. This clinical review summarizes the current evidence on the pathophysiologic aspects, diagnosis, and management of HFpEF.

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Until the past 50 years, heart failure was synonymous with left ventricular (LV) systolic dysfunction. Presbycardia (previously known as senile heart disease) was described in 1966 as a condition of certain elderly individuals. It was characterized by decreased elasticity of the heart and mild fibrotic changes of the valves. It was considered to be a rare cause of heart failure by itself but was presumed to decrease the adaptive reserve of the heart. Patients with presbycardia were thought to be more likely to develop heart failure in the setting of increased myocardial demands by conditions including fever, anemia, and excess fluid administration. In retrospect, presbycardia may have been the first description of what we now call heart failure with preserved ejection fraction (HFpEF).

With the subsequent development of echocardiography and then Doppler echocardiography, physicians had a tool to investigate the systolic and diastolic components of myocardial contractile function. Epidemiologic studies now indicate that this condition is far from rare and, in fact, may be the most prevalent form of heart failure. In this clinical review, we summarize the current evidence on the pathophysiologic process, diagnosis, and management of HFpEF.
Preclinical diastolic dysfunction (PDD, or diastolic dysfunction with normal LV ejection fraction and no signs or symptoms of heart failure), may be a predecessor to HFpEF. Patients who have structural heart disease without signs or symptoms of heart failure would be considered to have stage B heart failure according to the American College of Cardiology’s Classification of Heart Failure.

Preclinical diastolic dysfunction is prevalent in up to 30% of the elderly adult population and is associated with a profound increase in all-cause mortality. Patients with diabetes mellitus and PDD may be especially prone to progression to overt heart failure. The incidence of HFpEF at 5 years among diabetic patients with PDD is close to 37%, compared with about 17% among patients without PDD.
Hypertrophy and interstitial fibrosis, and functional changes, including incomplete relaxation of myocardial strips and increased myocardial stiffness.

It is now recognized that the LV is a helical-shaped chamber that twists during systole, wringing blood out with each heartbeat, much like when wringing out a dish towel. The heart then untwists to cause ventricular suction during early diastole. Tan et al. offered a contrasting model, one based on an application of newer imaging modalities. They demonstrated abnormalities of both systolic and diastolic ventricular function involving torsion, untwisting of the LV in diastole, and reduced longitudinal motion. They concluded that the abnormalities of HFpEF involved more than delayed cardiomyocyte relaxation and increased LV stiffness and included LV ar-

Table 1.
Comparison of Patients With HFpEF and HFrEF*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HFpEF</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection Fraction</td>
<td>≥50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Left Ventricular Remodeling</td>
<td>Concentric</td>
<td>Eccentric</td>
</tr>
<tr>
<td>More common in... Women (62%)</td>
<td>Men (60%)</td>
<td></td>
</tr>
<tr>
<td>Age (mean [SD]), y</td>
<td>Older (73.9 [13.2])</td>
<td>Younger (69.8 [14.4])</td>
</tr>
<tr>
<td>Prevalence of Hospitalizations</td>
<td>Increasing</td>
<td>Decreasing</td>
</tr>
<tr>
<td>Associated Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>↑ (77%)</td>
<td>↓ (69%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>↑ (45%)</td>
<td>↓ (40%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>↑ (41.4%)</td>
<td>↓ (35.5%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>↓ (50%)</td>
<td>↑ (59%)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>↓ (24%)</td>
<td>↑ (36%)</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>↓ (3%)</td>
<td>↑ (11%)</td>
</tr>
<tr>
<td>30-d Hospital Readmission Rate</td>
<td>↓ (25%)</td>
<td>↑ (64%)</td>
</tr>
<tr>
<td>Proven Therapies to Decrease Mortality</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Arrows indicate increased or decreased prevalence in the given area; parenthetical percentages indicate the rate of the given comorbidity among patients.

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Pathophysiologic Process
Too often, physicians have taken the expedient view that HFpEF can be explained by a ventricle that is too stiff to allow adequate filling for the next heartbeat. Although an abnormality in LV relaxation corresponds to diastolic dysfunction, HFpEF is more complex than that, and the pathophysiologic mechanisms are the subject of vigorous study.

Because the predominant symptom in patients with HFpEF is breathlessness due to elevated LV diastolic pressure, Zile et al. emphasized abnormalities in active relaxation and passive stiffness. Initial research focused on the extracellular matrix and on the cardiomyocyte itself. Studies on myocardial tissue showed specific alterations in myocardial structure, including cardiomyocyte hypertrophy and interstitial fibrosis, and functional changes, including incomplete relaxation of myocardial strips and increased myocardial stiffness.

It is now recognized that the LV is a helical-shaped chamber that twists during systole, wringing blood out with each heartbeat, much like when wringing out a dish towel. The heart then untwists to cause ventricular suction during early diastole. Tan et al. offered a contrasting model, one based on an application of newer imaging modalities. They demonstrated abnormalities of both systolic and diastolic ventricular function involving torsion, untwisting of the LV in diastole, and reduced longitudinal motion. They concluded that the abnormalities of HFpEF involved more than delayed cardiomyocyte relaxation and increased LV stiffness and included LV ar-
have the typical heart failure signs of ankle edema and neck vein elevation. The standard approach is to start with the medical history, physical examination, electrocardiography, and chest radiography. If heart failure is suspected, 2-dimensional Doppler echocardiography is the next step.

The European Society of Cardiology calls for 3 conditions to be satisfied for the diagnosis of HFpEF:

- signs or symptoms of heart failure
- normal or only mildly abnormal LV systolic function
- evidence of diastolic LV dysfunction

A 2014 article updated the 2007 European Society of Cardiology guideline in terms of evidence for diastolic dysfunction while maintaining the clinical orientation of the original approach. The decision tree starts with a measure of the relaxation velocity of the LV in early diastole (a tissue Doppler recording of the velocity of the LV at the mitral annulus, abbreviated to e’) and asks if LV diastolic dysfunction is present. If not, other considerations would be raised, such as primary mitral valve regurgitation, constrictive pericarditis, dyspnea as an anginal equivalent, and noncardiac dyspnea.

The stepwise approach then moves to a measure of LV filling pressure (the tissue Doppler index, which is the ratio of the mitral early diastolic blood flow velocity to the mitral annular relaxation velocity, abbreviated to E/e’). If this criterion is fulfilled, the diagnosis is established. A small number of patients will meet these 2 criteria.

If these parameters are borderline or the filling pressure is not elevated, the next step is to assess other Doppler/echocardiographic parameters and clinical features, such as response to exercise, pulmonary arterial...
pressure, left atrial size (expressed as left atrial volume index), brain natriuretic peptide (BNP) levels, and the presence of atrial fibrillation (Figure 1). If 2 or more of these additional findings are met, the diagnosis of HFpEF is established. If none is present, the diagnosis is excluded. Cardiac catheterization can be used to measure LV end-diastolic pressure directly in situations where the diagnosis remains uncertain. Although not supported by large-scale research, several centers have implemented right-sided heart catheterization, at times with fluid challenges, to better establish the diagnosis of HFpEF.

The echocardiographic parameters described here are typically measured in a standard echocardiographic study. However, the interpreting physician may not put these findings into the context of an evaluation for HFpEF unless requested by the ordering physician. For example, a patient may not meet the criteria for HFpEF on the basis of tissue Doppler echocardiographic characteristics alone. In that case, the diagnosis may be made if the patient has some of the other features that contribute to the diagnosis, such as atrial fibrillation, elevated BNP level, pulmonary hypertension, or increased left atrial volume index. Heart failure with preserved ejection fraction is a clinical diagnosis.

One challenge of the assessment of echocardiographic markers is whether the changes of delayed relaxation are just part of normal aging or if they represent HFpEF. An increase in left atrial volume or pulmonary hypertension would indicate that these resting findings are pathological and not just a sign of aging. Because patients with HFpEF may be very symptomatic with activity, an exercise test with repeated measures of diastolic function can be helpful.

**Impact of Exercise on HFpEF**

Six randomized controlled trials have assessed the impact of exercise training on aerobic fitness and QOL exclusively in patients with HFpEF. Although there were small variations in training periods and exercise mo-

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**No effective medications exist for HFpEF, but an approach to the musculoskeletal system has merit.**

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**Treatment**

Unlike systolic heart failure, for which multiple effective medications are available, the pharmacologic treatment of HFpEF is disappointing. No agents have been shown to improve survival or to enhance quality of life (QOL), exercise tolerance, or diastolic function. Several agents are in investigational trials, including sildenafil (RELAX Trial) and LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (PARAMOUNT Trial). In each case, the preliminary information shows no benefit of treatment at this point. The TOPCAT Trial, an investigation of aldosterone antagonists published in early 2014, demonstrated no efficacy of spironolactone.

The mainstay of medical treatment should be prevention for persons at risk for HFpEF and control of blood pressure, heart rate, and fluid status in patients with established disease. For those patients with concomitant medical problems that are associated with HFpEF, management of the underlying condition, such as obstructive sleep apnea, is reasonable, although there are no outcomes data to support this approach. In patients with type 2 diabetes mellitus, elevated serum triglyceride levels are associated with myocardial steatosis, which in turn causes diastolic dysfunction. Prolonged caloric restriction reduces myocardial triglyceride content and improves diastolic heart function.

The target value for dietary sodium restriction has not been defined in trials, but clinical experience indicates that it should be the same as patients with HFrEF: start with a goal of less than 2000 mg of salt per day and proceed to more stringent levels if required by the patient response. Data suggest that dietary sodium restriction improves LV diastolic function in hypertensive patients with HFpEF.
dality, overall the outcomes showed benefits of exercise training (Table 2). The exercise programs used low- to moderate-intensity walking or cycling and occasionally resistance training, either in a home-based setting or as part of a standard outpatient cardiac rehabilitation exercise program. Typically, the patient exercised for 30 minutes at an intensity based on a previous exercise stress test. The duration of exercise was 3 times per week for 12 to 24 weeks. The fitness outcomes were measured by a 6-minute walk distance or exercise oxygen consumption (VO$_2$) measured at maximum exercise (peak VO$_2$). The QOL measurements focused on the physical and mental domains. Other parameters assessed included echocardiographic measures of diastolic function and neurohormones such as BNP and norepinephrine.

As shown in Table 2, patients who underwent exercise training demonstrated improved exercise capacity. When peak exercise capacity was measured, the magnitude of improvement was above the threshold of a 10% improvement, which represents a clinically significant increase. The improvement in QOL was more likely to reflect the physical than the mental domain. Some trials showed improvement in diastolic function after exercise training. None showed a change in neurohormonal markers. Exercise training has not been evaluated in terms of hospital readmission rates or mortality.

Peak VO$_2$ is the criterion standard to measure peak exercise capacity. Because it involves cardiopulmonary stress testing with metabolic gas analysis, its use is reserved for research studies and in-depth evaluation of patients with heart failure, especially in terms of evaluation for cardiac transplantation. Peak VO$_2$ consumption reflects the stroke volume multiplied by the peripheral oxygen utilization. This calculation allows an estimate of the relative improvement with exercise training that can be attributed to improved myocardial pump performance and that is due to enhanced efficiency at the skeletal muscle level.

The available data suggest that impaired oxidative metabolism in skeletal musculature, which is caused...
Exercise Training Prescription

Recommendations

The consensus document of the Heart Failure Association and European Association for Cardiovascular Prevention and Rehabilitation provides guidance for medical providers. After exercise training, Haykowsky et al demonstrated that just 16% of the improvement in exercise capacity takes place at the myocardial level; the remaining 84% is attributed to changes at the skeletal muscle level. Therefore, adaptation of skeletal muscle to the pathophysiologic process of HFpEF may be one in which improved functionality is achieved by exercise training–driven efficiency in perfusion, oxygen transfer from the erythrocyte to skeletal muscle, and use of oxygen at the level of the mitochondrial complex within skeletal musculature.

Table 2.
Summary of Randomized Controlled Trials of the Benefits of Exercise Training in Patients With HFpEF

<table>
<thead>
<tr>
<th>Trial</th>
<th>Group, n</th>
<th>Exercise Training</th>
<th>Control</th>
<th>Intensity</th>
<th>Length of Training Program, wk</th>
<th>Major Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smart</td>
<td>12</td>
<td>13</td>
<td>60%-70% peak VO\textsubscript{2}</td>
<td>16</td>
<td>↑ Peak exercise capacity ↔ QOL</td>
<td></td>
</tr>
<tr>
<td>Alves</td>
<td>20</td>
<td>22</td>
<td>70%-75% maximal heart rate for 3-5 min (5-7 intervals)</td>
<td>24</td>
<td>↑ Peak metabolic equivalents ↑ Rest LV ejection fraction ↓ Left atrial pressure ↓ LV stiffness</td>
<td></td>
</tr>
<tr>
<td>Haykowski</td>
<td>22</td>
<td>18</td>
<td>40%-70% heart rate reserve</td>
<td>16</td>
<td>↑ Peak exercise capacity ↑ Peak heart rate</td>
<td></td>
</tr>
<tr>
<td>Edelmann</td>
<td>44</td>
<td>20</td>
<td>50%-70% maximal heart rate; 60%-65% peak VO\textsubscript{2}; 1 repetition max</td>
<td>12</td>
<td>↑ Peak exercise capacity ↑ 6-min walk distance ↑ Self-reported physical function</td>
<td></td>
</tr>
<tr>
<td>Kitzman</td>
<td>24</td>
<td>22</td>
<td>40%-70% heart rate reserve</td>
<td>16</td>
<td>↑ Peak exercise capacity ↑ 6-min walk distance ↑ Physical QOL</td>
<td></td>
</tr>
<tr>
<td>Gary</td>
<td>15</td>
<td>13</td>
<td>40%-60% maximal heart rate</td>
<td>12</td>
<td>↑ 6-min walk distance ↑ Physical QOL</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; QOL, quality of life; VO\textsubscript{2}, exercise oxygen consumption.
exertion that would be “somewhat hard.” Two to 3 weekly sessions of strength training should be considered with an intensity goal of 40% to 60% maximal strength. In elderly patients with multiple comorbidities, slow, goal-oriented up-titration of duration and intensity may maximize benefits. The patient should be in stable, compensated heart failure before beginning exercise training. If there is concern about the stability of the patient, the initial exercise training should take place in a supervised environment with direct monitoring during exercise and with gradual transition to home-based maintenance exercise regimens.

Prevention
Because there is no useful pharmacologic treatment for HFrEF, prevention represents a practical approach. Recognizing the importance of prevention, the American College of Cardiology presented a new classification of the stages of heart failure in 2001. One of the important aspects was the introduction of Stage A Heart Failure (risk factors but no definite heart disease) and Stage B Heart Failure (definite structural cardiac changes but no symptoms).

Although the mechanism whereby exercise might lower the incidence of heart failure is not fully understood, there is evidence to suggest that higher levels of exercise might have a direct effect on cardiac structure and function, because patients with higher levels of exercise across a lifetime have more compliant LVs than sedentary, age-matched controls. A recent report from the Cooper Center Longitudinal Study describes the cross-sectional association between cardiorespiratory fitness and echocardiographic measures of cardiac structure and function. This study of 1678 men and 1247 women demonstrated that (1) low fitness was associated with smaller heart size and a pattern of concentric LV remodeling and diastolic dysfunction and that (2) higher fitness was associated with lower prevalence of diastolic dysfunction, less adverse LV remodeling, and lower LV filling pressures (reduced E/e' ratio). In the accompanying editorial, Borlaug described a scenario in which fitness, stiffness, and age interact to lead to heart failure. He proposed that exercise training might halt or even reverse diastolic dysfunction (Figure 2).

Summary
Heart failure with preserved ejection fraction is now the most common form of heart failure. It is a complex disorder where patients have a stiff LV and a stiff arterial and venous system. Typically, these patients are older, are female, and have multiple comorbidities, including obesity, hypertension, renal disease, diabetes mellitus, and obstructive airway disease.

The clinical presentation is usually with symptoms of breathlessness and fatigue; physical signs of heart failure are less common. Patients often have labile hypertension, flash pulmonary edema, or deterioration in renal function with minor decreases in fluid volume. There are no specific medications for HFpEF itself, but management is directed to the comorbid conditions. Here the maxim is “go low and go slow,” because adverse effects are common.

**Take-Home Points**

**Diagnosis**

Unexplained dyspnea may be suspected in the typical patient with heart failure with preserved ejection fraction (HFrEF), because these patients often lack the usual physical signs of heart failure such as ankle edema and neck vein elevation.

The diagnosis of HFrEF is established with a composite of findings including abnormal left ventricular relaxation on echocardiography or Doppler echocardiography and other clinical features such as left atrial enlargement, pulmonary arterial hypertension, atrial fibrillation, and elevated brain natriuretic peptide.

**Interventions**

The primary care physician can implement an exercise program for the patient with HFrEF, either by a referral to a local cardiac rehabilitation program, or by setting up a home-based program of walking or other aerobic exercise.

The basic aspects of a home-based exercise program are aerobic exercise performed 3 times per week, in sessions of at least 20 minutes, at low to moderate intensity.
The musculoskeletal system plays a large role in HFpEF. Many of the symptoms are due to abnormalities of peripheral vascular function and skeletal muscle dysfunction. Because of vasodilation failure with activity, patients may become very symptomatic with modest exertion. Short-term, low- to moderate-intensity aerobic exercise training promotes clinically significant increases in functional capacity and QOL scores—improvements that are attributed to skeletal muscle and not the pump itself. Long-term fitness is associated with a lower prevalence of diastolic dysfunction, less adverse LV remodeling, and lower LV filling pressures.

References


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