Heart Failure With Preserved Ejection Fraction

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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.

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.[1] 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.

Epidemiologic Factors

The prevalence of HFpEF has increased over the past few decades. In western populations, HFpEF now accounts for up to 54% of all patients with clinical heart failure.[2] Whereas hospitalization for patients with heart failure with reduced ejection fraction (HFrEF) has declined over the past few years, that of patients with HFpEF is on the rise and requires longer lengths of stay.[3] Although patients with HFpEF have a lower 30-day hospital readmission rate compared with patients with HFrEF (25% vs 64%, respectively), no difference is observed in 30-day and 1-year all-cause mortality rates (*Table 1*).[4] The annual mortality rate of patients with HFpEF is close to 8%, with a 5-year mortality rate close to 50% among patients older than 70 years.[5]

Heart failure with preserved ejection fraction is a heterogeneous entity, and most patients do not have a specific cause. Instead, patients are more likely to be female and of advanced age and to have a constellation of comorbid conditions, such as diabetes mellitus, hypertension, obesity, renal disease, obstructive lung disease, and LV hypertrophy.[6,7] Women have higher rates of ventricular and arterial stiffness as they age, resulting in more concentric myocardial remodeling and less dilatation than men.[8,9] Obesity also seems to influence women's LV shape more than that of men, with greater LV mass and relative wall thickness. In patients with HFpEF, more than 75% have a clinically significant history of hypertension.[7]

Although women have a higher prevalence of HFpEF, the risk of death is much greater in men regardless of whether they have preserved or reduced ejection fraction.[10] Thirty percent of patients with HFpEF die of noncardiac causes compared with 17% of patients with systolic heart failure. This comparison emphasizes the role of comorbidities in mortality rates.[11]

This condition is an important cause of or factor in exertional dyspnea. When coupled with advanced parenchymal lung disease, dyspnea is often greatly magnified. Pulmonary hypertension is highly predictive of overall increased mortality in patients with HFpEF.[12]

KEY POINTS

Heart failure with preserved ejection fraction (HFpEF) is considered a systemic disease. Approximately 30% of patients with HFpEF die of comorbid conditions rather than heart disease.

In ventricular aterial coupling, a stiff ventricle is coupled with arterial stiffness, which is amplified by hypertension, diabetes mellitus, and kidney disease.

Women are especially prone to increased myocardial and arterial stiffness with aging, and these effects are most prominent with exercise.

The peripheral vascular system and skeletal muscle play a much larger role in the pathophysiologic aspects of HFpEF and in its improvement with exercise training than does the cardiac pump function itself.

The musculoskeletal system plays a major role in HFpEF. Exercise training has an immediate, direct action to reverse adverse changes in peripheral vascular and skeletal muscle function. Lifelong fitness is associated with less diastolic dysfunction in the general population.

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.[13] Preclinical diastolic dysfunction is prevalent in up to 30% of the

HFpEF is now the most common form of heart failure. It is increasingly prevalent and it is lethal.

elderly adult population and is associated with a profound increase in all-cause mortality.[14] 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.[15]

Table 1.
Comparison of Patients With HFpEF and HFrEF[a]

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

[a] 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[16] 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.[17]

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[18] 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-

chitecture and basic LV mechanics that involve the elastic properties of the LV, which are especially prominent with exercise.

Paulus and Tschope[19] have proposed a new paradigm that suggests that comorbidities such as obesity, diabetes mellitus, and chronic obstructive pulmonary disease lead to a systemic proinflammatory state that induces coronary microvascular endothelial inflammation. This inflammation and resultant oxidative stress cause stiff cardiomyocytes and interstitial fibrosis, which characterize the myocardial dysfunction and ventricular remodeling of HFpEF. Although hypertension is commonly thought to cause HFpEF by afterload excess, this model changes the emphasis to inflammation.

The pathophysiologic process of HFpEF is incompletely understood, in part because there are few animal models. The most comprehensive view incorporates cardiac structural and functional alterations and systemic and pulmonary vascular abnormalities, which, when coupled with extracardiac causes of volume overload (eg, kidney disease), can lead to signs and symptoms of heart failure.[11]

An understanding of the vascular abnormalities is helpful to understand the clinical characteristics of these patients.[18] Arterial stiffness increases as a consequence of aging and is amplified by hypertension, diabetes mellitus, and kidney disease. With an increase in arterial stiffness, the ejected pressure wave is reflected back to the heart, thus altering systolic pressure load and diastolic function and increasing hydraulic work and myocardial oxygen consumption. These effects lead to impaired LV reserve function, labile systemic blood pressures, diminished coronary flow reserve, and increased diastolic filling pressures with resultant breathlessness.

Diagnostic Studies

Patients with HFpEF typically have symptoms of breathlessness and fatigue with exertion. They may not 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.

Echocardiographic findings considered with clinical features can establish the diagnosis of HFpEF.

The European Society of Cardiology calls for 3 conditions to be satisfied for the diagnosis of HFpEF[20]:

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

A 2014 article[21] 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.

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.[22] The TOPCAT Trial, an investigation of aldosterone antagonists published in early 2014, demonstrated no efficacy of spironolactone.[23]

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.[24]

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

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

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response. Data suggest that dietary sodium restriction improves LV diastolic function in hypertensive patients with HFpEF.[25]

Impact of Exercise on HFpEF

Six randomized controlled trials[26-31] 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-

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.[27,29-31] The improvement in QOL was more likely to reflect the physical than the mental domain. Some trials[26,27] showed improvement in diastolic function after exercise training. None showed a change in neurohumoral 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 stoke 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.

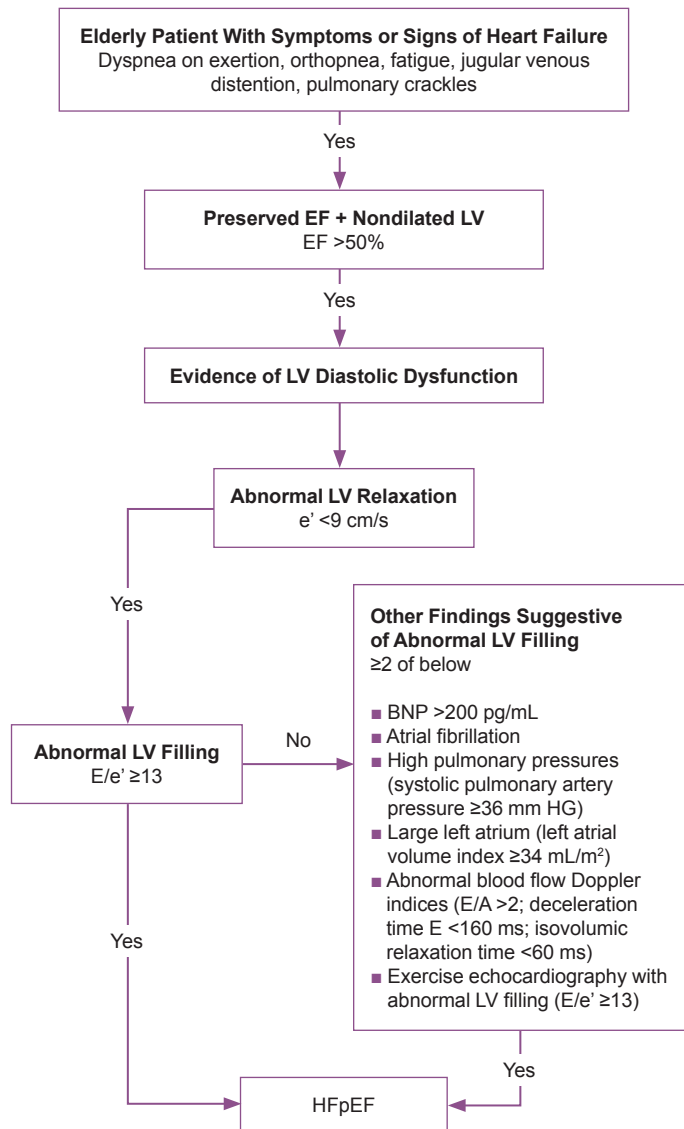The available data suggest that impaired oxidative metabolism in skeletal musculature,[32,33] which is caused

Figure 1.

Step-by-step diagnosis of heart failure with preserved ejection fraction (HFpEF).[20,21] Shortness of breath without objective signs of pulmonary congestion is a common early symptom of HFpEF. Interpreting this symptom is especially challenging in elderly patients. Signs or symptoms of heart failure (HF) is the first obligatory criterion in the diagnosis of HFpEF. A nondilated left ventricle (LV) with preserved ejection fraction (EF) is the second required criterion for the diagnosis of HFpEF. Presence of echocardiographic evidence of diastolic dysfunction with both LV relaxation and filling abnormalities is the third required criterion. Abnormal LV relaxation can be a silent echocardiographic finding, whereas abnormal LV filling is associated with symptoms of HF. *Abbreviations:* A, late mitral valve blood flow Doppler velocity; e', early mitral valve tissue Doppler lengthening velocity; E, early mitral valve blood flow Doppler velocity; BNP, brain natriuretic peptide.

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

Trial	Group, n		Intensity	Length of Training Program, wk	Major Conclusions
	Exercise Training	Control			
Smart[31]	12	13	60%-70% peak VO$_2$	16	↑ Peak exercise capacity ↔ QOL
Alves[26]	20	22	70%-75% maximal heart rate for 3-5 min (5-7 intervals)	24	↑ Peak metabolic equivalents ↑ Rest LV ejection fraction ↓ Left atrial pressure ↓ LV stiffness
Haykowski[29]	22	18	40%-70% heart rate reserve	16	↑ Peak exercise capacity ↑ Peak heart rate
Edelmann[27]	44	20	50%-70% maximal heart rate; 60%-65% peak VO$_2$; 1 repetition max	12	↑ Peak exercise capacity ↑ 6-min walk distance ↑ Self-reported physical function
Kitzman[30]	24	22	40%-70% heart rate reserve	16	↑ Peak exercise capacity ↑ 6-min walk distance ↑ Physical QOL
Gary[28]	15	13	40%-60% maximal heart rate	12	↑ 6-min walk distance ↑ Physical QOL

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; QOL, quality of life; VO$_2$, exercise oxygen comsumption.

by greater intramuscular fat content and decreased supply to or utilization of oxygen to the working muscle, is perhaps the major contributor to the decreased functional capacity experienced by patients with HFpEF.[29,34-36] After exercise training, Haykowsky et al[29] 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.[35]

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.[37] Candidates should be evaluated for cardiac ischemia by means of an appropriate stress testing protocol before initiating an exercise training program. Once stable disease is confirmed, patients with HFpEF should initiate 3 to 5 weekly sessions of continuous large muscle group endurance activities (ie, walking, cycling, and upper and lower extremity ergometry), performed for periods of 20 to 60 minutes. Intensity targets should likely be set at a rate of perceived

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 HFpEF, 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.[13] 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.[38,39] A recent report from the Cooper Center Longitudinal Study[40] 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[41] described

a scenario in which fatness, 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 (HFpEF), because these patients often lack the usual physical signs of heart failure such as ankle edema and neck vein elevation.

The diagnosis of HFpEF 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 HFpEF, 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.
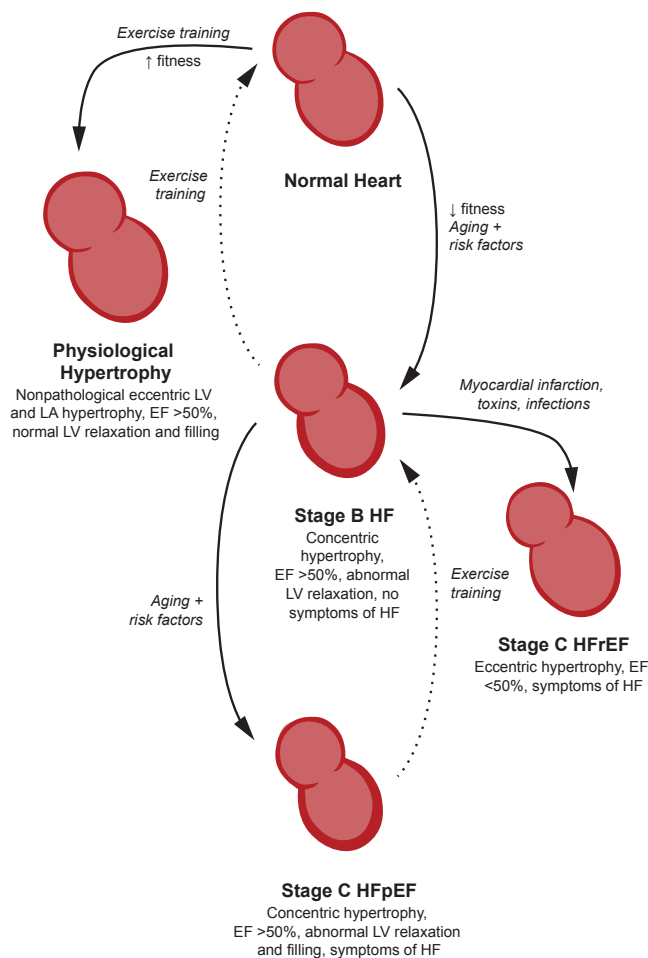
Figure 2.
Progression of heart failure. A healthy heart, when subjected to risk factors of obesity, diabetes mellitus, chronic hypertension, and a sedentary lifestyle, undergoes pathological remodeling leading to a smaller left ventricle (LV) chamber size, thickened LV, and dilated atrium. In stage B heart failure (HF), there is echocardiographic evidence of diastolic dysfunction without signs or symptoms of HF. Further exposure to these risk factors along with aging leads to stage C heart failure with preserved ejection fraction (HFpEF). Here, there are signs or symptoms of HF with further LV hypertrophy. Stage B HF could also progress to stage C heart failure with reduced ejection fraction (HFrEF) when there is concomitant obstructive coronary artery disease or exposure to toxic or infectious insults. A normal heart exposed to rigorous exercise training with an overall increase in fitness level leads to nonpathological left arterial and LV hypertrophy, preserved ejection fraction (EF), and no echocardiographic signs of filling or relaxation abnormalities. Reprinted from *JACC: Heart Failure*, vol 2, Borlaug BA, Fatness, fitness, stiffness, and age: how does it lead to heart failure [editorial]? pages 238-246, copyright 2014, with permission from Elsevier.[41]

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.

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