EXERCISE INTOLERANCE IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

Anisha A. Gupte, Ph.D.a; Dale J. Hamilton, M.D.a,b
aHouston Methodist Research Institute, bHouston Methodist Hospital, Houston, Texas

Abstract

More than 50% of Americans with heart failure have preserved ejection fraction (HFpEF). Exercise intolerance is a hallmark of HFpEF, but the pathophysiology is not well understood. Diverse etiologies and incomplete mechanistic understanding have resulted in ineffective management strategies to improve the outcomes of HFpEF. Traditional therapies that have been beneficial in the treatment of heart failure with reduced ejection fraction (HFrEF), neurohormonal blockade in particular, have not been effective in treating HFpEF. In this review, we address underlying mechanisms of HFpEF and present the rationale supporting exercise as a component of comprehensive management.

Introduction

It is estimated that 8.5 million Americans will have heart failure (HF) by 2030, and that more than 50% of them will have preserved ejection fraction (pEF). Heart failure with preserved ejection fraction (HFpEF) is a result of diastolic dysfunction (DD) that limits ventricular filling and reduces cardiac output. However, the EF in this condition is preserved, e.g., exceeding 45% to 50%, and the hemodynamics result from extensive fibrosis and myocyte stiffening as can be seen with aging and a variety of comorbidities. HFpEF occurs predominantly in elderly female patients. Those with hypertension and symptoms of metabolic syndrome, including central obesity and type 2 diabetes, are particularly at risk, and estrogen deficiency is emerging as a contributing factor.

Morbidity and mortality from HFpEF are equivalent to or greater than that of HF with reduced ejection fraction (HFrEF). Nonetheless, established neurohormonal-based therapies used for treating HFrEF have not provided favorable clinical outcomes for HFpEF, and clinical trials have failed to meet their primary end points. In fact, the lack of successful treatment strategies has made it challenging for clinicians to effectively manage HFpEF. These management challenges result from limited understanding of the underlying pathological mechanisms of HFpEF and its considerable phenotypic heterogeneity. Furthermore, there is a lack of preclinical models for understanding the mechanisms of this disease and identifying potential treatments. Procurement of fresh human heart tissue for metabolic assessment is challenging. Therefore, despite improvements in clinical outcomes with HFrEF, morbidity and mortality from HFpEF has remained the same, and the prevalence is rapidly increasing.

Exercise intolerance is a major symptom of HFpEF and is often used as an end point or outcome measure for therapeutic trials. Because exercise intolerance can be elusive at first, a clinical question about a patient’s ability to carry on a conversation while climbing a flight of stairs can alert the clinician to an emerging problem. The focus of this review is to highlight the role of exercise intolerance and exertional dyspnea in helping clinicians detect HFpEF and to present a mechanistic rationale for including exercise as a component of therapy.

Pathophysiological Mechanisms

The mechanisms underlying diastolic HF—including myocardial and extramyocardial alterations—are not fully understood. From a bioenergetics perspective, the myocardium is energy-deprived. Cardiac-specific alterations occurring in diastolic HF include calcium mishandling resulting from delayed/incomplete sarcoplasmic reticulum calcium release or sequestration and contractile malfunction associated with alterations in titin phosphorylation status. Impairments in myocardial and skeletal muscle energy metabolism, inflammation, and extracellular matrix collagen deposition are leading contenders as pathophysiologic mechanisms. Together, these mechanisms determine the severity and progression of DD. Thus, it would stand to reason that the ideal therapeutic intervention would target altered myocardial bioenergetics, calcium homeostasis, activity of contractile elements, blunt neurohormonal activation, and fibrosis prevention/regression. There have been several disappointing clinical trials using specific medications that target these pathways, but none have demonstrated success. However, exercise is one intervention that is proving to be surprisingly helpful.

Exercise intolerance presents as an early persistent symptom of HFpEF and is a major determinant of reduced quality of life in these patients. In contrast to HFrEF, the mechanisms of decreased exercise capacity in HFpEF are not well understood. Exercise capacity can be calculated during cardiopulmonary exercise testing as the reduction in peak exercise oxygen consumption (VO₂) measured by analyses of expired gas. Aerobic exercise requires efficient delivery of oxygen to muscles, which depends on a number of physiological processes including oxygenation of blood in the lungs, cardiac output (CO), the oxygen-carrying capacity of blood, and the capacity of tissue to extract oxygen from the blood. Normal adults are capable of increasing their VO₂ more than 6-fold during exercise by increasing cardiac stroke volume, heart rate, and the extraction of oxygen from peripheral blood, which patients with HFpEF are unable to achieve (Table 1).

To understand the mechanism of exercise intolerance, Houstis and Lewis analyzed the pathophysiology by applying the Fick principle and segregating the individual variables from the Fick equation as follows: (1) deficiency in the peak heart rate (HR), (2) deficiency in the peak stroke volume (SV), (3) deficiency in the...
peak arteriovenous oxygen difference ($\Delta V_{O2} = \text{difference between the arterial and venous oxygen contents}$), and (4) factors that independently lead to exercise cessation before the Fick variable can reach full reserve potential, for example, inadequate effort and musculoskeletal complaints. This results in the following Fick equation: $\Delta V_{O2} = CO \times (AVO_2) = (HR \times SV) \times (AVO_2)$

In HFpEF, several cardiac and noncardiac mechanisms for reduced aerobic capacity have been speculated. Santos et al. and Abudiai et al. suggested that the major contributor to exercise inability in HFpEF patients is the reduced cardiac output relative to metabolic needs, indicating a cardiac cause. Extensive fibrosis and titin hypophosphorylation is thought to create stiffness in the LV of patients with HFpEF, contributing to the cardiac limitations in exercise capacity. Increased diastolic stiffness prevents the increase in LV end-diastolic volume that normally accompanies exercise, thus patients with HFpEF have a limited ability to use the Frank-Starling mechanism despite greater filling pressures. Augmentation of relaxation velocity fails to occur as heart rate increases during exercise. Therefore, during exercise, diastolic pressure increases, stroke volume fails to increase, and patients with HFpEF experience dyspnea and fatigue.

In contrast, Haykowsly et al. found that while reduced VO$_2$ at peak exercise was associated with reduced cardiac output, the strongest independent predictor of peak VO$_2$ was the change in $\Delta V_{O2}$ difference from rest to peak exercise in HFpEF patients compared to age-matched healthy controls performing exhaustive upright cycling exercise. The impact of $\Delta V_{O2}$ difference suggests that peripheral, noncardiac factors are important contributors to exercise intolerance in HFpEF patients (Figure 1). In support, Dhakal et al. showed that peripheral oxygen extraction was lower in HFpEF compared to controls and HFrEF patients and was the major determinant of reduced exercise capacity. The discrepancies in the above studies can be explained by Little and Borlaug, who observed that although peripheral abnormalities were largely associated with exercise limitations, a cardiac limitation was present and could be the first and foremost underlying cause. It is also likely that common comorbidities associated with HFpEF such as pulmonary disease, obesity, and diabetes may contribute to exercise intolerance independent of the heart. Finally, a common technical problem of submaximal effort due to noncardiac issues can contribute to lower $\Delta V_{O2}$.

In the early 1980s, complete bed rest and avoidance of exercise was thought to be crucial for HF patients. However, this thought has been challenged in recent years, and supervised exercise is now a recommended therapy, especially for patients with HFpEF. Indeed, contrary to the observed exercise intolerance in HFpEF patients, exercise training has been shown to be an effective therapy in the recent Exercise training in Diastolic Heart Failure (Ex-DHF) trial. In this study, 65 patients with HFpEF were randomized to receive supervised exercise in addition to the usual care, while 20 received only the usual care for 3 months. Endurance and resistance exercise resulted in improved VO$_2$ max and diastolic function (reduced E'/e' ratios) and atrial reverse remodeling, with an overall improvement in quality of life scores. The benefits of exercise were not due to changes in blood pressure or body mass index since both parameters remained unchanged in both groups for the duration of the study. Other smaller studies and meta-analyses have also reiterated the benefits of exercise training in HFpEF.

Even with these improvements, the mechanisms underlying the benefits of exercise in patients with HFpEF are still unclear. One speculation is the improvement of myocardial bioenergetics and metabolism with exercise (Figure 2). The process of myocardial relaxation is an energy-consuming process, highly dependent on the ratio of ADP/ATP and levels of ADP and Pi, all of which should be low enough to facilitate ADP to ATP conversion. Production of ATP is dependent on the ability of efficient substrate oxidation. Diastolic relaxation consumes energy since ATP hydrolysis is required for myosin detachment from actin filaments, Ca$^{2+}$ dissociation from troponin C, and sarcoplasmic reticulum Ca$^{2+}$

Table 1. Exercise parameter changes in subject with non-failing heart versus heart failure with preserved ejection fraction. Although both groups have preserved ejection fraction, impaired oxygen delivery and extraction limits exercise capacity in the latter group. EF%: systolic ejection fraction; PCWP: pulmonary capillary wedge pressure; VO$_2$ max: maximum oxygen uptake in mL/kg/min; A-VO$_2$ gradient: difference between arterial and venous blood oxygen concentration.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Failing Heart</td>
<td>HFrEF</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>↑</td>
</tr>
<tr>
<td>EF %</td>
<td>↑</td>
</tr>
<tr>
<td>Stroke Vol</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>↑</td>
</tr>
<tr>
<td>PCWP</td>
<td>NC/↓</td>
</tr>
<tr>
<td>VO$_2$ max</td>
<td>↑</td>
</tr>
<tr>
<td>A-VO$_2$ gradient</td>
<td>↑</td>
</tr>
</tbody>
</table>

![Figure 1](image-url). Mechanism for reduced oxygen uptake and delivery in HFpEF. Ventricular stiffness leads to left ventricular increased diastolic filling pressure and PCWP. This results in increased lung water and alveolar edema that limits oxygen diffusion. In turn, there is decreased oxygen delivery due to the combined effects of reduced cardiac output and arterial oxygen content. Peripheral mechanisms lead to impaired extraction of oxygen in skeletal muscle beds, resulting in decreased exercise capacity. (Figure design by A. Zhang.) HFpEF: heart failure with preserved ejection fraction; PCWP: pulmonary capillary wedge pressure.
reuptake. Thus, diastolic function also depends upon optimal metabolic processes that generate ATP. The commonly associated comorbidities with DD, which include diabetes, hypertrophy secondary to hypertension, and obesity, are all associated with perturbed cardiac metabolism that can reduce the ATP supply required by the relaxing LV.

**Metabolic Adaptation versus Maladaptation**

The myocardium in diastolic HF undergoes major metabolic changes, but not all have been well characterized. Cardiac positron emission tomography (PET) imaging studies have revealed an increase in fatty acid uptake and a decrease in glucose uptake oxidation with increasing severity of DD. This is different from the greater glucose oxidation seen in HFrEF. However, the excess fatty acid oxidation in HFP EF may lead to overburdening of the mitochondria, accumulation of acylcarnitines, and greater oxidative stress. Thus, although fatty acid oxidation is increased, there is not a concomitant increase in ATP generation, thereby creating a net energy deficit. Further, this change is replacing the energy-efficient glucose substrate utilization, which can provide a greater number of ATP molecules per molecule of oxygen consumed. With reduced glucose utilization and incomplete fatty acid oxidation, the myocardium remains energy deprived, and this may underlie the exercise intolerance associated with HFP EF. Enhanced fatty acid uptake and oxidation is followed by mitochondrial uncoupling and production of reactive oxygen species, primarily at the levels of complexes I and III of the mitochondrial respiratory chain. Oxidative stress can trigger fibrosis processes that result in stiffer ventricles and diminished ventricular relaxation.

In a study by Basu et al., type 1 diabetic Akita mice exhibited DD with preserved systolic function associated with increased myocardial fatty acid oxidation rates and greater accumulation of intramyocardial ceramide and diacylglycerol. In addition, insulin treatment reversed these metabolic derangements and alleviated DD. Given that inhibition of fatty acid oxidation appeared to be a promising therapeutic target, several drugs were investigated. For example, perhexiline, an inhibitor of fatty acid oxidation, was shown to correct energy deficiency, DD, and exercise intolerance in patients with hypertrophic cardiomyopathy and dilated cardiomyopathy. However, an emerging view is challenging these treatments by suggesting that reduced glucose uptake and increased fatty acid oxidation is a required metabolic adaptation in the failing heart, and fatty acid oxidation per se should not be blocked. While increased fatty acid oxidation may be adaptive, the incomplete oxidation and resulting intermediates may be maladaptive. Therefore, it is likely more important to improve the bioenergetics mechanism that enables complete and efficient fatty acid oxidation than to reduce the overall amount of fatty acid oxidation or increase excessive glucose oxidation. In fact, Kovacs and colleagues have shown that exercise can improve the efficiency of the mitochondrial machinery in complete fatty acid oxidation that results in efficient energy generation.

**The Role of Estrogen**

In our laboratory, we have identified a mouse model of diastolic HF that stems from pressure overload in estrogen-deficient female mice. Ovariectomized (OVX) female C57Bl6 mice, when treated with L-NAME and angiotensin II, get more severe diastolic HFP EF than their counterparts receiving sham surgery and the same treatments. On the other hand, male mice receiving the same treatments get systolic HF with suppressed ejection fraction. Our preliminary unpublished results show that OVX mice with more severe DD have limited mitochondrial function, greater production of mitochondrial reactive oxygen species, and more morphological aberrations in the myocardium, all of which suggest mitochondrial dysfunction. This model represents the growing problem of HFP EF in elderly, postmenopausal women and can be used to investigate the underlying mechanisms. While we have not yet tested the effects of exercise on these mice, we predict that exercise will reverse the bioenergetics limitations and improve diastolic function.

Exercise has been shown to reverse many metabolic derangements in skeletal muscle, leading to more efficient substrate utilization and improvement of systemic outcomes such as insulin resistance and cardiometabolic fitness. It is likely that exercise benefits in diastolic HF stem from improved bioenergetics in the heart that facilitates efficient fatty acid utilization without the accumulation of acylcarnitines, thereby suppressing mitochondrial oxidative stress and triggers for fibrinogenesis. Exercise may also improve calcium and insulin signaling systemically, which may remove the associated comorbidities that stress the failing heart. As shown in Figure 1, exercise can reverse or counter several pathogenic factors related to HFP EF.

**Conclusion**

While exercise intolerance is a prominent feature of DD, supervised exercise may be beneficial in reversing some of its systemic, structural, and metabolic cardiac derangements (Table 2). Further studies are required to determine which kind of exercise would give the maximum benefits and can be reasonably performed by such patients. Further studies are needed to investigate the mechanisms underlying exercise benefits in patients with HFP EF.
Benefits of Exercise for Individuals with HFpEF

| Improved myocardial substrate delivery and oxidation |
| Improved energetics (ATP/PCr high energy transfer) |
| Improved comorbidity control (Obesity, HTN, MS/DM, lipids) |
| Improved peripheral tissue oxygen delivery |
| Improved exercise capacity |

Table 2. Benefits of exercise for individuals with HFpEF. HFpEF: heart failure with preserved ejection fraction; ATP: adenosine triphosphate; PCr: phosphocreatine; HTN: arterial hypertension; MS/DM: metabolic syndrome/diabetes.

**Key Points:**
- HFpEF is diagnostically and therapeutically challenging.
- Pathophysiological mechanisms of HFpEF remain poorly understood.
- Innovative preclinical and translational research methodologies are needed.
- Exercise limitation serves as both an early symptom and therapeutic end point.
- Exercise is a promising therapy to reverse metabolic derangements in HFpEF.

**Conflict of Interest Disclosure:** The authors have received grant and foundation funding from the American Heart Association, Pat Studdert, Charif Souki, the Stedman-West Foundation, and Elaine and Marvy Finger.

**Keywords:** heart failure with preserved ejection fraction, impaired diastolic function, exercise intolerance, metabolic and bioenergetic factors, exercise therapy, diastolic dysfunction

**References**


