REVIEW

Clinical Considerations and Exercise Responses of Patients with Heart Failure and Preserved Ejection Fraction: What Have We Learned in 20 Years?

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately 50% of all heart failure (HF) cases and is the fastest growing form of HF in the United States. The cornerstone symptom of clinically stable HFpEF is severe exercise intolerance (defined as reduced peak exercise oxygen uptake, VO_{2peak}) secondary to central and peripheral abnormalities that result in reduced oxygen delivery to and/or use by exercising skeletal muscle. To date, pharmacotherapy has not been shown to improve VO_{2peak}, quality of life, and survival in patients with HFpEF. In contrast, exercise training is currently the only efficacious treatment strategy to improve VO_{2peak}, aerobic endurance, and quality of life in patients with HFpEF. In this updated review, we discuss the specific central and peripheral mechanisms that are responsible for the impaired exercise responses as well as the role of exercise training to improve VO_{2peak} in clinically stable patients with HFpEF. We also discuss the central and peripheral adaptations that contribute to the exercise training-mediated improvement in VO_{2peak} in HFpEF. Finally, we provide clinical exercise physiologists with evidence-based exercise prescription guidelines to assist with the safe implementation of exercise-based cardiac rehabilitation programs in clinically stable patients with HFpEF. *Journal of Clinical Exercise Physiology*. 2020;9(1):17–28.

Keywords: exercise intolerance, pathophysiology, peak exercise oxygen uptake, exercise training, cardiac rehabilitation

INTRODUCTION

Heart failure (HF) is a major healthcare burden and is associated with high morbidity and mortality (1,2). Recent estimates indicate that over 6 million Americans 20 years of age or older currently have HF (1), which represents an increase of more than 1 million cases over the past 20 years (3,4). Perhaps of greater concern is that the prevalence of HF is expected to increase by 46% by 2030, with projected healthcare costs exceeding $70 billion annually (1,2). While thought to be a "needle in the haystack" over two decades ago, it is now widely accepted that ~50% of HF patients have HF with preserved ejection fraction (HFpEF), with this phenotype being more common in older individuals, women, and those with a history of hypertension, obesity, and anemia (5–7).

The hallmark symptom in clinically stable HFpEF patients is reduced exercise tolerance (8–11). Specifically, peak aerobic power (VO_{2peak}) is ~35% lower in patients with HFpEF compared to age-matched healthy controls, as a result of central and peripheral abnormalities that reduce oxygen delivery to and/or oxygen use by active skeletal muscles (10,12–14). A consequence of this reduction in

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VO_{2peak} is that basic (getting dressed) and instrumental (grocery shopping, meal preparation, housework) activities of daily living require near-maximal effort (15,16), which greatly diminishes quality of life in these patients (17,18). Given the relationship between VO_{2peak} and survival (19,20), a major goal of therapy is to improve cardiorespiratory fitness in patients with HFpEF (21–23).

In this updated review, we discuss the clinical research performed over the past 20 years that has greatly improved our understanding of the pathophysiology of exercise intolerance in clinically stable patients with HFpEF. We also discuss the central and peripheral adaptations that contribute to the improvement in VO_{2peak} that accompanies exercise training in HFpEF. Finally, we provide clinical exercise physiologists with evidence-based exercise prescription guidelines to assist with the safe implementation of exercise-based cardiac rehabilitation programs in clinically stable patients with HFpEF.

Pathophysiology of HFpEF

In 1923, Henderson (24) astutely observed that, "If an old man's heart relaxes slowly, his capacity for physical exertion is thus limited, even though the systolic contractions were still like those of youth." This early description of what we now commonly call "HFpEF" had not been widely accepted as "real" HF until the turn of the century in 2000. In the early 1990s, Kitzman and colleagues published a paper (11) that stimulated over 30 years of investigations, focusing on understanding the pathophysiology of HFpEF, and examining the role of exercise training (and other lifestyle changes) in these patients. While it took more than three decades of research, it is now widely accepted that HFpEF and HFrEF represent two distinct HF "phenotypes." Although HFpEF and HFrEF will often exhibit similar symptoms—including exercise intolerance, dyspnea, and pulmonary and/or peripheral edema—there are a number of clinical features that may differentiate between these phenotypes (21). Generally, echocardiography, magnetic resonance imaging, or invasive hemodynamic testing is required to clearly distinguish HFpEF from HFrEF (21).

Whereas left ventricular (LV) systolic dysfunction can be considered a defect in the ability of myofibrils to shorten against a load, resulting in a reduced ventricular ejection, LV diastolic dysfunction results from an increased resistance to LV ventricular filling, leading to an inappropriate upward shift of the end-diastolic pressure volume relationship (25). Patients with HFrEF present with elevated end-diastolic and end-systolic volumes, resulting in a reduced ejection (≤35%) fraction, whereas the patient with HFpEF will have reduced end-diastolic and end-systolic volumes with a resultant normal or greater than normal ejection fraction (≥50%–70%). Diastolic dysfunction can be caused by a) inappropriate LV relaxation, secondary to abnormalities in intracellular calcium, and/or b) increases in LV stiffness secondary to concentric hypertrophy (26). The former is usually associated with LV hypertrophy, hypertension, and myocardial ischemia, whereas the latter is seen with aortic stenosis,

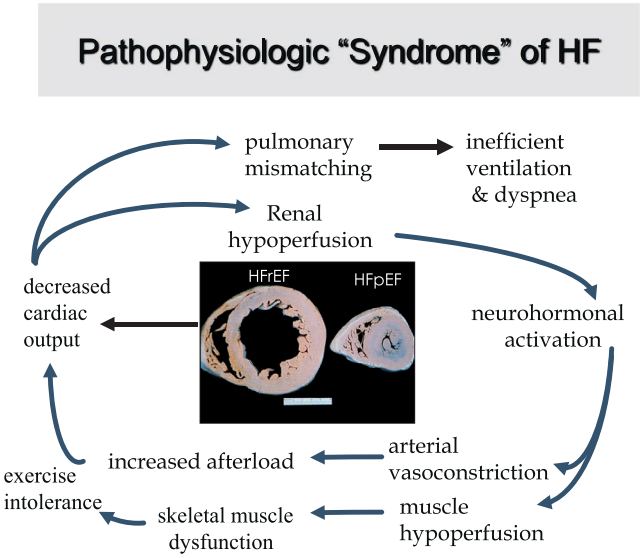

FIGURE 1. Pathophysiologic syndrome of heart failure (HF) begins with either/both left ventricular systolic or diastolic dysfunction that results in a reduced cardiac output during exertion. Reduced blood supply to the lungs and kidneys results in symptoms and activation of a variety of neurohormones that further decrease perfusion of skeletal muscle. Reduced skeletal muscle blood flow results in structural and functional alterations that cause decreased exercise capacity and fatigue.

hypertension, hypertrophic cardiomyopathy, and a variety of infiltrative disease disorders (27). Moreover, age-related changes may predispose the heart to diastolic dysfunction and symptoms of HF. Age-related changes to the heart include the following: (a) an increase in LV wall thickness, (b) a sigmoid-shaped septum, (c) a reduction of the base-to-apex dimension shortening, (d) a decrease in LV cavity size, and (e) left atrial dilation (28). Furthermore, the aging heart has a decreased rate of LV filling, an increased myocardial interstitial fibrosis, and a prolonged LV relaxation (28).

A patient with LV systolic and/or diastolic dysfunction will likely produce an insufficient cardiac output response to exertion, leading to a variety of complex and interrelated pathophysiologic alterations in the pulmonary and renal systems resulting in abnormal neurohormonal responses in addition to abnormal vascular and skeletal muscle structure and function (5,21). These compensatory physiological mechanisms, although designed to preserve vital body functions, ultimately result in the HF "syndrome" (see Figure 1) noted in both the HFrEF and HFpEF phenotypes (3).

Determinants of Exercise Intolerance in HFpEF

Kitzman and colleagues (11) were the first to perform invasive cardiopulmonary exercise testing in patients (n = 7) who presented with HF symptoms and normal LV ejection fraction. Compared to normal subjects, what we now term HFpEF patients demonstrated severe exercise intolerance with a 47% reduction in VO_{2peak} (11.6 ± 4.0 versus 22.7 ± 6.1 $mL \cdot kg^{-1} \cdot min^{-1}$) that was primarily due to a 41% reduction in peak cardiac index (4.2 ± 1.4 versus 7.1 ± 1.1 $L \cdot min^{-1} \cdot m^{-2}$). HFpEF patients' peak LV stroke volume indexes (34 ± 9

versus 46 ± 7 mL·m^{-2}) and end-diastolic volume indexes (56 ± 14 versus 68 ± 12 mL·m^{-2}) were also significantly reduced compared to the normal subjects. In contrast, peak LV ejection fraction, end-systolic volume index, and arteriovenous oxygen content difference were not significantly different. Also, pulmonary capillary wedge pressure (PCWP; an index of left ventricular filling pressure) was markedly increased at peak exercise in HFpEF patients compared with normal subjects (25.7 ± 9.1 versus 7.1 ± 4.4 mm Hg). The increased LV filling pressure observed during exercise was not accompanied by an increased end-diastolic volume as noted in normal subjects, indicating a limitation to LV filling. This early study clearly demonstrated for the first time that abnormalities in LV diastolic function could limit a patient's ability to augment stroke volume (SV) by means of the Frank-Starling mechanism, resulting in severe exercise intolerance.

To fully understand the pathophysiology of exercise intolerance, we must consider the Fick Principle of VO_2 (VO_2 = cardiac output (Q) × arteriovenous oxygen content difference (a-vO_2Diff). In accordance with this principle, a reduction in peak exercise VO_2 could be the result of impaired Q (cardiac abnormalities) and/or impaired a-vO_2Diff (vascular and skeletal muscle abnormalities), which results in impaired O_2 delivery to and uptake/use by exercising skeletal muscle. In the past 20 years, numerous studies have been performed to further improve our understanding of the cardiac, vascular, and skeletal muscle mechanisms that underlie exercise intolerance in patients with HFpEF (8–10,12,29–42). A detailed discussion of these mechanisms is presented in the subsequent sections of this review.

Impairments in Cardiac Function

Our exercise physiology laboratory (10) and several others (12,29) have observed that peak cardiac output is 30% to 40% lower in patients with HFpEF compared with normal subjects. Specifically, chronotropic incompetence (i.e., HR at peak exercise ≤80% of age predicted), rather than SV, appears to be the largest contributor to the blunted Q response to peak exercise observed in patients with HFpEF (8–10,12,29,43). Furthermore, a significant positive association exists between Q (independent of SV) (29) and HR (8) with VO_{2peak}, even when important comorbidities are considered (9). Finally, our lab (44) has demonstrated that change in HR accounts for ~20% to 25% of the increase in VO_2 observed during maximal exercise in older HFpEF patients.

While chronotropic incompetence appears to be a major factor in the blunted cardiac output response to exercise in patients with HFpEF, several abnormalities in LV function have also contribute significantly to reduced peak exercise VO_2 (Figure 2). In healthy individuals, LV relaxation is increased during peak exercise to account for a reduction in LV filling time (45). However, during peak exercise in patients with HFpEF, the LV is unable to augment relaxation which, coupled with impaired passive filling, creates an overreliance on the left atrial contribution to LV filling

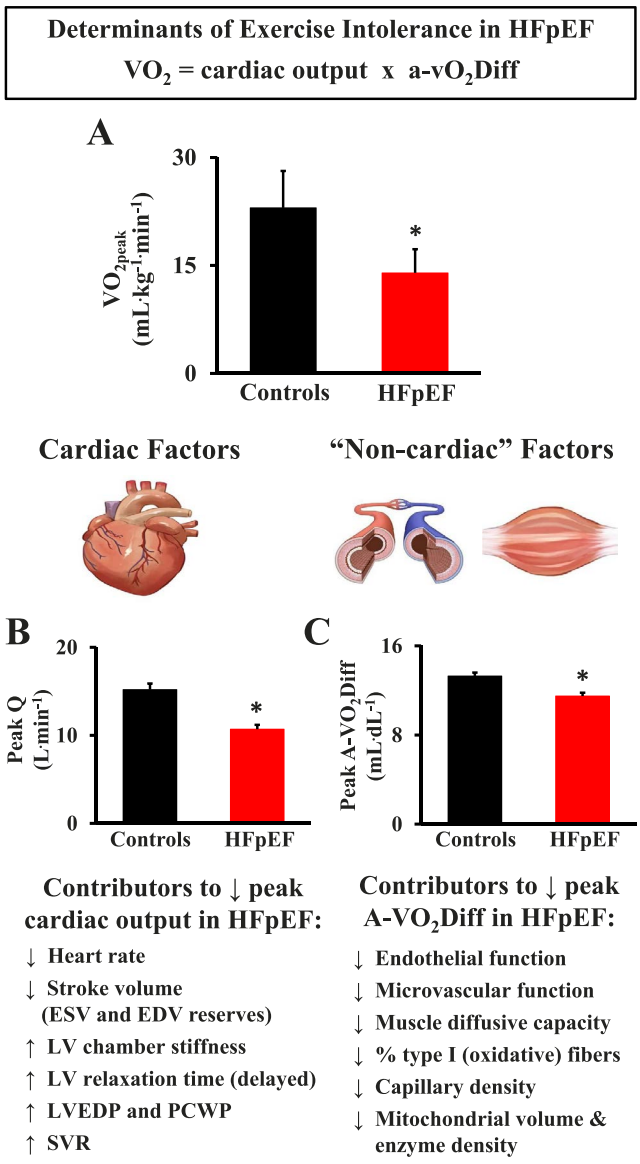

FIGURE 2. Magnitude and pathophysiology of exercise intolerance in patients with heart failure and preserved ejection fraction (HFpEF). A. HFpEF patients demonstrate severe exercise intolerance, measured objectively as a ~40% reduction in peak oxygen uptake (VO_{2peak}) (mL·kg^{-1}·min^{-1}) during peak aerobic exercise compared to healthy age-matched controls, adapted and pooled (mean ± SD) from published data by Bhella et al. (2011), Dhakal et al. (2015), and Haykowsky et al. (2011). B. HFpEF patients demonstrate reduced peak exercise cardiac output (L·min^{-1}), adapted from published data (mean ± SE) by Dhakal et al. (2015). C. HFpEF patients demonstrate reduced peak exercise arteriovenous oxygen difference (a-vO_2Diff) (mL·dL^{-1}), adapted from published data (mean ± SE) by Dhakal et al. (2015). EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricle; LVEDP = left ventricle end-diastolic pressure; SVR = systemic vascular resistance; PCWP = pulmonary capillary wedge pressure. * indicates significant ($P < 0.05$) difference between HFpEF and healthy age-matched controls for all figures. Figure reprinted with permission from Tucker et al. (46).

(31,46). These impairments in diastolic function create large increases in LV end-diastolic pressure resulting in severe dyspnea upon exertion in patients with HFpEF (21,47). Indeed, a recent study by Obokata and colleagues (32) further demonstrated the important contribution of increased LV filling pressures to poor exercise tolerance in HFpEF by showing that increased exercise PCWP was directly correlated with higher exercise dyspnea and lower VO_{2peak}.

Vascular Impairments

While early studies in the 1990s of HFpEF patients focused primarily on cardiac dysfunction, it has become apparent that impaired vascular function also contributes to reduced exercise tolerance. Using cardiac magnetic resonance imaging, our group (37) reported that the distensibility of the proximal thoracic aorta (a measure of arterial stiffness and a contributor to increase afterload and impaired LV-arterial coupling) was significantly reduced in HFpEF patients compared to healthy age-matched controls and was also predictive of poor exercise tolerance (lower VO_{2peak}). We extended these findings by demonstrating that carotid arterial distensibility (measured by high-resolution ultrasound) was significantly lower in patients with HFpEF compared to healthy age-matched controls and directly related to a reduced VO_{2peak} (38). Taken together, the findings from these studies (37,38) suggest that increases in arterial stiffness, beyond normal aging, directly contribute to exercise intolerance in patients with HFpEF.

Recent evidence also suggests that these patients have an impaired ability to sufficiently augment skeletal muscle blood flow in response to exercise, which results in compromised oxygen delivery to the active muscles. Indeed, Lee and colleagues (41) reported that femoral artery blood flow was 15% to 25% lower during submaximal unilateral kicking exercise in HFpEF compared to healthy age-matched controls. These findings suggest that impaired vasodilation in exercising skeletal muscle may play a key role in reduced convective oxygen delivery to the muscle, greatly contributing to exercise intolerance in this patient population. However, the specific mechanisms responsible for the blunted skeletal muscle blood flow responses to exercise in HFpEF remain incompletely understood.

In accordance with the principles of vascular biology and blood flow hemodynamics, impaired skeletal muscle blood flow can be the result of macrovascular and/or microvascular abnormalities. In those with HFpEF, several studies have shown that large conduit endothelial function is impaired relative to age-matched individuals (40,48,49). However, these differences in large conduit endothelial function appear to be ameliorated when patients with HFpEF are rigorously screened to exclude for the confounding effects of atherosclerosis (36,50). In contrast, multiple studies demonstrate the presence of microvascular dysfunction in patients with HFpEF (33,40). This was first demonstrated by Balmain et al. (33), who found marked impairments in acetylcholine-induced cutaneous vasodilation (a measure of microvascular function) using iontophoresis coupled laser Doppler imaging in HFpEF compared to age-matched controls with coronary heart disease but no evidence of HF. In agreement with these findings, Lee et al. (40) recently reported that reactive hyperemia following a 5-min arterial cuff occlusion (an indirect measure of microvascular function) was significantly reduced in HFpEF compared to healthy age- and sex-matched controls. Cumulatively, these data suggest that microvascular dysfunction may be an important contributor to exercise intolerance in HFpEF. However, more research is needed to fully elucidate the mechanism(s) contributing to impaired oxygen delivery within exercising skeletal muscle during in HFpEF.

Skeletal Muscle Dysfunction

In recent years, our lab at Wake Forest University (Winston-Salem, North Carolina) has completed multiple studies demonstrating that abnormalities in skeletal muscle composition and function play a major role in limiting VO_{2peak} in patients with HFpEF (10,18,39,42,51). We first reported that the strongest independent predictor of VO_{2peak} in patients with HFpEF was the change in estimated a-vO_2Diff, which accounted for ~50% of the reduction in VO_{2peak} even when adjusting for major cardiac determinants of VO_{2peak} (10). These initial findings have since been confirmed by direct measurement of a-vO_2Diff during peak exercise in patients with HFpEF (12,35). This supports the prevailing hypothesis that impaired muscle diffusive oxygen conductance (transport of oxygen from red blood cell to muscle mitochondria) and/or an inability to sufficiently augment O_2 extraction during peak exercise appear to important contributors to reduced VO_{2peak} in HFpEF (Figure 2).

Adverse changes in both leg muscle quantity and quality may directly limit the increase in a-vO_2Diff during peak exercise in patients with HFpEF. Using dual-energy x-ray absorptiometry (DXA) and peak exercise testing, our group (18) reported that older HFpEF patients have significantly reduced percent total and leg lean mass as well as reduced peak VO_2 indexed to lean body mass when compared to healthy age-matched individuals. More recently, we (51,52) demonstrated that patients with HFpEF have significantly increased intermuscular adipose tissue (fat between muscle) and ratio of intermuscular adipose to skeletal muscle area, with both of these deleterious morphological changes being independent predictors of reduced VO_{2peak}. Taken together, these findings suggest that both losses in lean body mass and reductions in the quality of skeletal muscle contribute to reductions in VO_{2peak}. Furthermore, increased intramuscular fat may also adversely affect skeletal muscle mitochondrial density and function (39,42).

Multiple histological and metabolic skeletal muscle abnormalities are reported in HFpEF patients (30,39,42,53). Our lab (39) demonstrated that patients with HFpEF exhibit a shift in skeletal muscle fiber type distribution toward a greater percentage of glycolytic (type II) fibers, with a subsequent decrease in the percentage of type I (aerobic) fibers, type I/type II fiber ratio, and capillary-to-fiber ratio versus healthy age-matched controls. In addition, this fiber type and

capillary interface profile is associated with a reduced VO_{2peak}. Subsequent work performed by our group (42) extended these findings by showing that skeletal muscle oxidative capacity, mitochondrial content, and mitochondrial fusion were all abnormal in older patients with HFpEF. Furthermore, each of these skeletal muscle histological abnormalities was significantly associated with a reduction in VO_{2peak} and 6-min walk distance. Taken together, these findings suggest that a fiber-type shift from aerobic to glycolytic fibers together with reduced mitochondrial function contributes to impaired aerobic metabolism during exercise in HFpEF. An elegant recent study performed by Weiss and colleagues (53) demonstrated that HFpEF patients display severe exercise intolerance and a marked reduction in leg muscle aerobic metabolism (measured by 31P magnetic resonance spectroscopy) during small muscle mass exercise compared to healthy individuals. Overall, impaired skeletal muscle aerobic metabolism appears to be a major contributor to reduced exercise tolerance in HFpEF. Accordingly, skeletal muscle may serve as an important treatment target for exercise therapies aimed at improving exercise tolerance in patients with HFpEF (46,54).

Improvement in VO_{2peak} with Exercise Training in HFpEF

At the time of the original review article two decades ago, there were no available guidelines/recommendations for prescribing exercise training in HFpEF patients. Thus, at that time, we replicated the current exercise prescription recommendations for patients with HFrEF and the approaches used in traditional cardiac rehabilitation programs. Our original exercise training (ET) intervention (55) was 16 weeks of endurance exercise training with 60-min exercise sessions completed on 3 d per week. After 10 min of light exercise and stretching, patients exercised an equal length of time on a cycle ergometer (Schwinn Airdyne) and walked in a gymnasium. Patients gradually increased the duration on each modality to a maximum of 20 min per session. To ensure "specificity" of the training protocol during maximal cycle ergometer testing, each patient performed a portion of the training session on a cycle ergometer. It took most patients several weeks before they would obtain the desired duration even at the lowest bicycle workload setting. Consequently, the goal was to increase each patient's total work output (by increasing distance walked and cycled) weekly by 5%. Throughout the training sessions, we attempted to keep the exercise intensity between 50% to 70% of peak VO_2 by monitoring heart rate and rating of perceived exertion (RPE). In older HFpEF patients, as with most clinical patients, exercise prescription is as much of an "art" as it is a "science." Indeed, some older HFpEF patients tolerated a rapid progression with favorable results, whereas others had to progress more slowly. Inevitably, there will always be some trial and error involved when implementing exercise training in HFpEF patients. Since resistance training was not recommended in HFrEF patients in the late 1990s, we did not include this mode of training in our early clinical trials.

In the 1999 review (3), our "unpublished preliminary" data appeared to suggest that HFpEF patients randomized to exercise training were able to increase peak VO_2 by 24% (12.5 to 15.6 $mL \cdot kg^{-1} \cdot min^{-1}$) in 16 weeks. In contrast, there was no change from baseline to follow-up in the peak VO_2 of the HFpEF patients randomized to the attention control (i.e., no exercise training) group. Furthermore, our original review (3) stated that the "increase in peak VO_2 in the exercise training group was associated with a small increase in peak exercise heart rate but without any change in SV or end-diastolic volume." Consequently, it was cautiously concluded that "exercise-induced improvements in functional capacity in HFpEF patients are not due to central hemodynamic changes but rather to peripheral adaptations" (3).

Table 1 includes the limited number of studies (including three conducted in our lab) (55–57) that have examined the role of exercise training to improve in clinically stable HFpEF patients over the past 20 years. Meta-analyses of exercise (endurance alone or combined with resistance exercise) training versus sedentary usual care have reported a mean increase in VO_{2peak} and 6-min walk distance of 2.2 $mL \cdot kg^{-1} \cdot min^{-1}$ (17,58,59) and 33 m, respectively, which exceeds the threshold to be classified as clinically meaningful in patients with HFpEF (23). The predominant evidence to date suggests that increases in VO_{2peak} observed following exercise training in HFpEF are primarily due to noncardiac, peripheral adaptations (60,61). Thus, evidence to date supports my initial conclusions from 20 years ago (3).

Cardiac Adaptations to Exercise Training in HFpEF

Over the last two decades, multiple studies have assessed changes in resting (55–57,62–64) and peak exercise cardiac function (60,61) following exercise training in HFpEF. Most of these studies report little to no change in resting LV volumes, systolic or diastolic function (measured with noninvasive techniques such echocardiography and magnetic resonance imaging) posttraining (55–57,62,63). In contrast, Edelmann et al. (64) demonstrated that 12 weeks of combined endurance and supplemental resistance exercise training (Table 1) resulted in a significant reduction in resting left atrial volume index and the ratio of early mitral inflow velocity and mitral annular early diastolic velocity (E/e′) (a surrogate measure of LV filling pressure) (64). Furthermore, the increase in VO_{2peak} was inversely associated with the improvement in E/e′. Although these findings suggest that exercise training may reduce LV filling pressure and thus improve diastolic function, Fujimoto and colleagues (65) reported that 1 year of high-intensity endurance exercise training did not alter invasively measured LV diastolic compliance in older HFpEF patients including during cardiac (un)loading maneuvers. In agreement with this finding, a recent meta-analysis by Fukuta et al. (17) showed that the increase in VO_{2peak} associated with exercise training occurred with no significant changes in resting LV systolic or diastolic function in HFpEF. Finally, while endurance exercise

TABLE 1. Randomized controlled exercise intervention trials in heart failure patients with preserved ejection fraction (HFpEF).

Study	Group (n)	EF (%), NHYA Class	Male (%)	Age (yr)	Frequency, Intensity, Time, Training Mode	ET Length (wk)	Main Findings
Angadi et al. (2015)[62]	HIIT (9)	65, II-III	89	69	3 d/wk 4 × 4 min intervals at 85%–90% HR_{peak} with 3 min active recovery at 50% HR_{peak} between intervals 25 min total exercise time (16 min HIIT) Treadmill	4	↑ VO_{2peak}; ↓ E, DD grade; ↔ VO_2 at VT, LAVI, A, E/A, DT, e′ (septal), E/e′, IVRT, EF, BAFMD
	MICT (6)	66, II-III	67	72	3 d/wk 60%–70% HR_{peak} 30 min Treadmill		↔ VO_{2peak}, VO_2 at VT, LAVI, E, A, E/A, DT, e′ (septal), E/e′, IVRT, DD grade, EF, BAFMD
Edelmann et al. (2011)[63]	ET (44)	67, II-III	45	64	2–3 d/wk cycle + 2 d/wk RT (wk 5–12) 50%–70% VO_{2peak} cycle, 15 reps at 60%–65% 1RM RT 20–40 min Cycle + RT	12	↑ VO_{2peak}, VO_2 at VT, 6MWD, QoL, NYHA class, e′; ↓ E/e′, LAVI, procollagen type I; ↔ LVEF, LVMI, NT-proBNP
	CON (20)	66, II-III	40	65			
Fu et al. (2016)[54]	ET (30)	58, II-III	67	61	3 d/wk 5 × 3 min intervals at 80% VO_{2peak} with 3 min active recovery at 40% VO_{2peak} between intervals 30 min Cycle	12	↑ VO_{2peak}, arteriovenous oxygen difference, leg muscle oxygenation; ↓ Ve/VCO_2, E/e′; ↔ LVEF, LVIDd, LVIDs, peak SVI, CI, HR
	CON (30)	57, II-III	60	63			
Kitzman et al. (2010)[57]	ET (24)	61, II-III	17	70	3 d/wk 40%–70% HRR 60 min Treadmill/cycle	16	↑ VO_{2peak}, VO_2 at VT, 6MWD, physical QoL; ↔ rest E, A, DT, IVRT, LV EDV, ESV, EF, LVM, LVM/volume, norepinephrine, BNP
	CON (22)	60, II-III	9	69			
Kitzman et al. (2013)[59]	ET (24)	58, II-III	28	70	3 d/wk 40%–70% HRR 60 min Treadmill/cycle/arm ergometer	16	↑ VO_{2peak}, VO_2 at VT, peak HR, 6MWD, physical QoL; ↔ carotid arterial stiffness, BAFMD, rest E, A, DT, IVRT, LV EDV, ESV, EF
	CON (30)	56, II-III	20	70			
Kitzman et al. (2016)[58]	ET (24)	61[a], II-III	19[a]	67[a]	3 d/wk 40%–70% HRR 60 min Treadmill	20	Main Effect for ET: ↑ VO_{2peak}, 6MWD; ↓ peak DBP, NYHA class, body weight, fat mass; ↔ rest E, E/A, E/e′, LVM, EDV, EF, LAD, arterial stiffness
	CR (24)				–400 kcal/d CR		Main effect for CR: ↑ VO_{2peak}, 6MWD, rest E/A, leg muscle quality, QoL; ↓ peak DBP, NYHA class, body weight, lean mass, fat mass (abdominal visceral and subcutaneous, thigh subcutaneous), rest LVM, h/R
	CR + ET (24)				–350 kcal/d CR + ET		
	CON (22)						
Smart et al. (2012)[64]	ET (12)	59, II-III	58	67	3 d/week 60%–70% VO_{2peak} 30 min Cycle	16	↑ VO_{2peak}; ↓ Ve/VCO_2 slope; ↔ peak HR, rest E, A, E/A, S, E/e′, DT, strain, strain rate, LVEF, CO
	CON (13)	57, II-III	46	62			

↑ = increase; ↓ = decrease; ↔ = no change; 1RM = one repetition maximum; 6MWD = 6-min walk distance; A = atrial filling velocity; CI = cardiac index; CO = cardiac output; CR = caloric restriction; DBP = diastolic blood pressure; DD = diastolic dysfunction grade; DT = deceleration time; E = early filling velocity; e′ = early diastolic velocity of the mitral annulus; E/A = early to atrial filling velocity ratio; E/e′ = early mitral inflow velocity to early diastolic mitral annulus ratio; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; ET = exercise training; HIIT = high-intensity interval training; h/R = relative wall thickness; HR = heart rate; HR_{peak} = peak heart rate; HRR = heart rate reserve; IVRT = isovolumic relaxation time; LAD = left atrial diameter; LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LVIDd = left ventricular internal diameter in diastole; LVIDs = left ventricular internal diameter in systole; LVM = left ventricular mass; LVMI = left ventricular mass index; MICT = moderate-intensity continuous training; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; QoL = quality of life; Reps = repetitions; RT = resistance training exercise; S = systolic annular velocity; SV = stroke volume; SVI = stroke volume index; VT = ventilatory threshold; VO_{2peak} = peak oxygen uptake
[a]indicates whole group mean

training has been shown to decrease the prevalence of chronotropic incompetence and improve HR responses to exercise in patients with HFrEF (44), it is less well established if this same effect is present in HFpEF. Some studies performed in our lab (55,57,61) have shown a small (yet significant) increase in peak exercise HR following 16 weeks of endurance exercise training; however, this increase in peak exercise HR did not result in an increase in peak exercise cardiac output in patients with HFpEF (61).

To date, only two studies have measured changes in the Fick principle determinants of VO_{2peak} following exercise training in patients with HFpEF (60,61). Our lab (61) was the first to show that 16 weeks of moderate-intensity endurance training (Table 1) significantly increased estimated peak exercise a-vO_2Diff with no change in peak exercise cardiac output measured by 2D echocardiography. Moreover, 84% of the exercise training-mediated increase in VO_{2peak} was due to the change in estimated peak exercise a-vO_2Diff. Fu et al. (60) confirmed these findings by showing that the increase in VO_{2peak} following 12 weeks of high-intensity interval training (HIIT) was secondary to increases in estimated peak exercise a-vO_2Diff in HFpEF. In contrast, peak exercise HR, SV index and cardiac index (measured by bioelectrical impedance) were unchanged following exercise training. Taken together, these two studies (60,61) suggest that the increases in VO_{2peak} following moderate- or high-intensity endurance exercise training appear to be primarily driven by noncardiac peripheral adaptations that result in increased oxygen extraction by the active muscles.

Vascular and Skeletal Muscle Adaptations to Exercise Training in HFpEF

Exercise training-mediated increases in peak exercise a-vO_2Diff may be the result of improvements in peripheral vascular and/or skeletal muscle adaptations. Several investigators have examined the effects of exercise training on peripheral vascular function in patients with HFpEF (56,57,62). Our lab (56,57) has shown that 16 to 20 weeks of moderate-intensity endurance exercise training does not change carotid arterial stiffness, carotid-femoral pulse wave velocity (arterial stiffness), or vascular endothelial function (measured by brachial artery flow-mediated dilation) in HFpEF patients. Our findings were confirmed and extended by Angadi et al. (62) who found that 4 weeks of either moderate-intensity endurance training or HIIT did not change vascular endothelial function (measured by brachial artery flow-mediated dilation) in older patients with HFpEF. Taken together, the few studies performed to date suggest that the benefits of exercise training on VO_{2peak} do not appear to be related to improvements in central or peripheral vascular function in clinically stable HFpEF patients. However, no study to date has examined the effect of exercise training on microvascular function in HFpEF. As such, future studies are needed to address this important knowledge gap in the literature.

Further, no study to date, has investigated the effects of exercise training on changes in skeletal muscle fiber type, oxidative metabolism, or capillary density. Given the plethora of skeletal muscle abnormalities that underlie exercise intolerance in patients with HFpEF (18,39,42,51,53,54), future studies are urgently warranted to assess the role of exercise training to improve skeletal muscle morphology and oxidative capacity in this patient population.

Role of Exercise Training Intensity on Improvement in VO_{2peak} in HFpEF

HIIT is characterized by brief (30 to 240 s) intermittent bursts of vigorous (85% to 95% peak HR) aerobic exercise, interspersed with periods of rest or active recovery. HIIT has been shown to be a safe and effective alternative to traditional endurance-based exercise training for inducing similar (or even superior) physiological adaptations in both healthy and clinical populations (66–68). These superior physiological adaptations may yield superior HIIT-mediated improvements in VO_{2peak}. Indeed, Weston et al. (67) published a systematic review and meta-analysis in 2014 showing that HIIT elicits a significantly greater improvement in VO_{2peak} compared to traditional moderate-intensity endurance training in clinical populations that included patients with coronary artery disease, HF, hypertension, metabolic syndrome, and obesity. To date, only two randomized controlled exercise trials have examined the effects of HIIT to improve VO_{2peak} in HFpEF (60,62).

Angadi and colleagues (62) were the first research group to investigate the efficacy of HIIT to improve VO_{2peak} in in older patients with HFpEF. Despite the short duration of the intervention (4 weeks), HIIT resulted in a significant increase in VO_{2peak} (1.8 $mL \cdot kg^{-1} \cdot min^{-1}$) compared to no change with traditional moderate-intensity endurance training. Moreover, the increase in VO_{2peak} following HIIT occurred despite only modest changes in cardiac function. Fu et al. (60) assessed the effects of 12 weeks of HIIT on VO_{2peak} and its determinants compared with a sedentary, standard of care control group in patients with HFpEF. Similar to the findings by Angadi et al. (62), the authors reported that HIIT increased VO_{2peak} by 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$, secondary to increased estimated peak exercise a-vO_2Diff and enhanced muscle oxygenation of the vastus lateralis (measured by near-infrared spectroscopy), with no change in estimated peak exercise cardiac function (measured by bioelectrical impedance). Taken together, short-term HIIT appears to be an effective training stimulus to increase VO_{2peak} in HFpEF. However, the magnitude of increase in VO_{2peak} (mean change: 2.2 $mL \cdot kg^{-1} \cdot min^{-1}$) (60,62) is similar to that reported following longer duration traditional moderate-intensity endurance training in patients with HFpEF (17). Furthermore, it is currently unknown if HIIT is superior to traditional moderate-intensity endurance training for improving VO_{2peak} in studies lasting longer than 3 months. To address this research question, a large, multicenter, randomized controlled exercise training intervention trial (OptimEx-CLIN study) is currently underway to assess the optimal dose and intensity of exercise (12 months of HIIT versus traditional moderate-intensity endurance training versus sedentary control) to increase VO_{2peak} in patients with HFpEF (69).

TABLE 2. Exercise training guidelines in clinically stable patients with heart failure and preserved ejection fraction (HFpEF).

	Frequency	Intensity	Time	Type
Aerobic/Endurance Exercise				
Moderate-intensity continuous endurance	3–5 d/wk	50%–70% VO_{2peak}, 40%–70% HRR, RPE of 10–14	45–60 min	Walking, cycling
High-intensity interval training (HIIT)	3 d/wk	Intervals: 85%–95% peak HR, 80%–95% PPO, RPE 15 – 18	25–35 min (10–20 min of interval "on time")	Walking, cycling
Resistance Exercise (supplemental)				
If goal is to ↑ muscular endurance	2–3 d/wk	30%–40% 1RM, 10–25 reps		Upper and lower body resistance exercises
If goal is to ↑ muscular strength	2–3 d/wk	40%–60% 1RM, 8–15 reps		

Abbreviations: ↑ = increase; 1RM = 1 repetition maximum; HR = heart rate; HRR = heart rate reserve; PPO = peak power output; reps = repetitions; RPE = rating of perceived exertion (Borg 20-point scale); VO_{2peak} = peak exercise oxygen uptake

Exercise Training Guidelines and Prescription in HFpEF

Indications and Contraindications to Exercise Training in HFpEF

To ensure patient safety, supervised exercise training should only be performed in clinically stable patients with HF and New York Heart Association (NYHA) functional class I–III (15,70). For a patient with HF to be deemed clinically stable, they should meet the following criteria: no recent change of NYHA functional class, no hospitalizations for HF, and no major cardiovascular events or procedures during the past 6 weeks (15,70). If the HF patient meets these criteria and is classified as clinically stable by the clinical exercise physiologist and/or physician, the patient should undergo further screening to check for the presence of other contraindications to exercise training based on medical history, clinical examination, electrocardiography, echocardiography, and symptom-limited cardiopulmonary exercise test (15,46,70). A full list of contraindications to exercise testing and training for HF patients can be found in an excellent review published by Piepoli and colleagues (70). In particular, clinical exercise physiologists should pay close attention to the following contraindications to exercise in HF: (a) shortness of breath at rest or progressive worsening of exercise tolerance over the past 3 to 5 d, (b) large recent weight gain (>1.8 kg increase over the previous 1 to 3 d), (c) NYHA functional class IV, (d) supine resting HR >100 $b \cdot min^{-1}$, (e) decrease in systolic blood pressure during exercise, (f) significant ischemia or complex ventricular arrhythmia presenting during low-intensity exercise, or (g) presence of pre-existing comorbidities that may limit exercise tolerance and patient safety (46,70).

Exercise Training Guidelines Specific to the HFpEF Patient

Currently no guidelines exist that provide specific guidance for exercise training in clinically stable patients with HFpEF. Therefore, the exercise training prescription guidelines presented in Table 2 are based on the limited number of exercise interventions studies performed to date and our cumulative experience training HFpEF patients over the last two decades. For aerobic/endurance exercise, training intensity is prescribed using either a percentage of VO_{2peak}, heart rate reserve (HRR), or rating of perceived exertion (RPE). For HFpEF patients who successfully undergo a peak exercise test, it is recommended that initial endurance training intensity start low (40% to 50% VO_{2peak}) and gradually increase to 60% to 70% of VO_{2peak} after several weeks of training as training adaptations and improved exercise tolerance occur (15,70). In our exercise intervention studies (55–57,61), we preferred to use HRR for prescription of exercise intensity in HFpEF, with 40% to 70% of HRR being selected as the intensity to elicit improvements in VO_{2peak}. For situations in which VO_{2peak} or peak HR is not measured, is unattainable, or is altered due to the effects of β-blockade therapy, exercise training intensity can be prescribed using the Borg 20-point RPE scale.

As mentioned earlier in this review, the number of studies using HIIT in HFpEF patients is limited. Therefore, the exercise training recommendations for HIIT presented in Table 2 are based on these limited studies and several recent reviews published in other clinical populations including HFrEF and coronary artery disease (15,67,70,71). Based on these guidelines, HIIT should consist of large muscle mass (walking, cycling) high-intensity intervals (10 to 20 min of interval "on time") separated by periods of passive or active recovery for a total exercise time in each session of 25 to 35 min. High-intensity intervals should consist of either short (15 to 60 s of exercise at 80% to 95% of peak power output) or long duration (4 min of exercise at 85% to 95% peak HR) intervals with 30-s to 3-min periods of passive or active recovery between each interval. It is recommended that patients with HFpEF begin with shorter duration intervals and progressively increase interval length as exercise intolerance improves. While the use of HR to track exercise intensity is preferred, it often may be difficult to obtain an accurate and reliable HR during intervals (e.g., patient has atrial fibrillation). In these instances, RPE can be used to assess whether HFpEF patients are achieving HIIT intensity goals (Goal RPE of 15 to 18 during intervals). Finally, it is recommended that each HIIT session begin with a short (3 to

5 min) light to moderate-intensity warm-up and end with the same length and intensity cooldown.

Given the many skeletal muscle abnormalities present in patients with HFpEF (34,39,42,51–54), resistance exercise may be an effective mode of training to improve muscle strength, quality (composition), and physical function. Indeed, several exercise intervention trials have shown that resistance training performed alone (72–74) or in combination with endurance exercise training (72,75) improves VO_{2peak} and functional capacity in patients with HFrEF. As outlined by Piepoli et al. (70) and Haykowsky et al. (15), the optimal intensity of resistance training is contingent upon the training goals of the patient. If the patient's goal is to increase muscular endurance, select lower intensity (30% to 40% 1RM, 10 to 25 repetitions) upper- and lower-body resistance exercises and perform them on 2 to 3 d per week (15,46,70). If the patient's goal is to increase muscular strength, select a higher intensity (40% to 60% 1RM, 8 to 15 repetitions) upper-, and lower-body resistance exercises and perform them on 2 to 3 d per week (15,46,70). It is recommended that patients start at a lower intensity and gradually increase the intensity (weight lifted) over time to prevent skeletal muscle injury and maximize training adaptations.

Compliance and Safety of Exercise Training in HFpEF

Our 20+ years of cumulative experience (4 exercise-based randomized controlled trials in >200 HFpEF patients) has demonstrated to us that these patients can tolerate, benefit from, and enjoy exercise training. Compliance with exercise sessions in our lab is ~90% and there have been no significant adverse events. Indeed, our safety data is in agreement with the meta-analysis by Dieberg and colleagues (58) who reported no deaths directly attributable to exercise training in 3,744 h of exercise training from the 7 exercise training intervention studies performed to date. Taken together, these findings suggest that the risk of a fatal or adverse event occurring during exercise training in clinically stable HFpEF patient is minimal when exercise training is performed in a supervised cardiac rehabilitation setting.

Future Directions

In contrast to what was known 20 years ago, studies from several independent laboratories have shown that endurance exercise training is a safe and effective nonpharmacological therapy that improves exercise tolerance and quality of life in those with HFpEF. However, cardiac rehabilitation is currently not covered by Medicare and Medicaid in these patients, despite covering those services for those with HFrEF (7). This is due to insufficient data on the long-term efficacy of exercise training to reduce mortality in HFpEF patients. As such, large scale, multicenter exercise-based cardiac rehabilitation trials are needed to establish the efficacy and safety of exercise training to improve major clinical endpoints (survival and rate of hospitalization) in patients with HFpEF. Finally, future research is also needed to determine whether home-based and/or nonsupervised exercise training is safe and effective in patients with HFpEF.

CONCLUSION

Since we published our first review (3) in this journal two decades ago, we have learned a great deal about HFpEF patients that can be of value to the clinical exercise physiologists who work with this patient population. Importantly, we have learned that severe exercise intolerance in HFpEF patients is the result of cardiac, vascular, and skeletal muscle abnormalities. In addition, multiple randomized controlled exercise intervention trials show that moderate to high-intensity endurance training performed alone or combined with supplementary resistance training is safe and effective for improving VO_{2peak}, functional capacity (6-min walk distance), and quality of life in patients with HFpEF. Most of the evidence to date suggests that the exercise-training mediated increase in VO_{2peak} is largely the result of peripheral "noncardiac" adaptations that result in improved oxygen extraction and utilization by exercising skeletal muscle (increased peak exercise a-vO_2Diff). While there are currently no official exercise training guidelines in HFpEF, we provide exercise training recommendations based on the studies performed to date and our 20+ years of experience in training these patients. Clinically stable HFpEF patients are encouraged to perform large muscle mass (walking, cycling) endurance exercise for 45 to 60 min on 3 to 5 d per week at a moderate to high intensity (40% to 70% VO_{2peak}). High-intensity interval training appears to be safe and effective for improving VO_{2peak} in patients with HFpEF. If incorporated into the exercise training program, HIIT should consist of large muscle mass (walking, cycling) high-intensity (85% to 95% peak HR) intervals (10 to 20 min of interval "on time") interspersed with periods of active recovery for a total of 25 to 35 min of exercise per training session on 3 d per week. Resistance training may also be supplemented to improve muscular strength, endurance, and composition, with intensity (percentage of 1RM) prescribed based on patient goals.

Acknowledgments: More than two decades ago (May 1999) I published "Clinical Considerations and Exercise Responses of Patients with Heart Failure and Primary Left Ventricular Diastolic Dysfunction" in in an early edition of the predecessor journal to Journal of Clinical Exercise Physiology titled Clinical Exercise Physiology (3). At that time, my colleagues (primarily Dr. Dalane Kitzman) and I at Wake Forest University were just finishing our first randomized controlled trial of exercise training in HF patients with isolated diastolic dysfunction (now called HFpEF). Subsequently, over the past two decades we have continued to perform several more exercise training and caloric restriction studies in this patient population. I am indeed honored that the Editor-in-Chief of the Journal of Clinical Exercise Physiology, Dr. Jonathan Ehrman, asked if I would "revisit" this topic and revise this paper after accumulating over 20 years of research and clinical exercise experience with HFpEF patients. Thus, this manuscript is an update of what we, and other investigators from around the world, have learned about the clinical considerations and exercise responses of HFpEF patients. I have asked two of my esteemed collaborators, Drs. Mark Haykowsky and Wesley Tucker, to coauthor this paper with me; they have also performed important studies and analyses that have increased our understanding of HFpEF and how these patients respond to acute exercise and adapt to exercise training over time. I must also recognize the brilliant leadership of Dr. Dalane Kitzman because without his tireless efforts much of the research presented in this paper would not be available.

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