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Pathophysiology of Exercise Intolerance and Its Treatment with Exercise-Based Cardiac Rehabilitation in Heart Failure with Preserved Ejection Fraction: A Review

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is the fastest growing form of heart failure in the United States. The cardinal feature of HFpEF is reduced exercise tolerance (peak oxygen uptake, VO_{2peak}) secondary to impaired cardiac, vascular, and skeletal muscle function. There are currently no evidence-based drug therapies to improve clinical outcomes in patients with HFpEF. In contrast, exercise training is a proven effective intervention for improving VO_{2peak}, aerobic endurance, and quality of life in HFpEF patients.This brief review discusses the pathophysiology of exercise intolerance and the role of exercise training to improve VO_{2peak} in clinically stable HFpEF patients. It also discusses the mechanisms responsible for the exercise training-mediated improvements in VO_{2peak} in HFpEF. Finally, it provides evidence-based exercise prescription guidelines for cardiac rehabilitation specialists to assist them with safely implementing exercise-based cardiac rehabilitation programs for HFpEF patients.

Condensed Abstract

Heart failure with preserved ejection fraction (HFpEF) is characterized by severe exercise intolerance. The review provides the pathophysiology underlying exercise intolerance and role of

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exercise training to improve peak oxygen uptake (VO_{2peak}) in HFpEF. It also provides exercise prescription guidelines designed to maximize improvements in VO_{2peak} in patients with HFpEF.

Keywords

cardiorespiratory fitness; cardiac function; vascular function; skeletal muscle function

Heart failure (HF) is a major healthcare problem associated with high morbidity and mortality.[1] Currently, >6 million Americans ≥ 20 yr of age have HF, and its prevalence is expected to increase by 46% by 2030.[1,2] Nearly half of all HF patients have preserved left ventricular ejection fraction (HFpEF) and this phenotype is more common in older individuals, women, and those with a history of hypertension, obesity and anemia.[1,3] Decreased exercise tolerance is a hallmark feature in clinically stable HFpEF patients and is associated with reduced quality of life.[4,5] Given the relationship between cardiorespiratory fitness (i.e. peak oxygen uptake; VO_{2peak}) and survival,[6,7] an important goal of therapy should be to improve HFpEF patients' cardiorespiratory fitness.[8–12]

Currently, exercise training is the only proven effective intervention to improve VO_{2peak}, aerobic endurance, and quality of life in HFpEF patients.[4,10] Several recent meta-analyses have reported that endurance exercise training, performed alone or combined with resistance training, improves VO_{2peak} and 6-min walk test distance by 2.2 mL/kg/min and 33 m, respectively.[4,13,14] Accordingly, understanding the mechanisms responsible for reduced VO_{2peak} and its improvement with exercise training is critical to optimally improve HFpEF patients' functional capacity and quality of life.

In this brief review, the pathophysiology of exercise intolerance and the role of exercise training to improve VO_{2peak} in clinically stable patients with HFpEF is discussed. Further discussion of the mechanisms responsible for the exercise training-mediated increase in VO_{2peak} is provided, along with evidence-based exercise prescription guidelines for clinically stable HFpEF patients participating in an exercise-based cardiac rehabilitation (CR) program.

PATHOPHYSIOLOGY OF EXERCISE INTOLERANCE IN HFPEF

Appreciating the Fick principle for VO_2 is fundamental to understanding the pathophysiology of exercise intolerance in patients with HFpEF. Specifically, the Fick principle dictates that VO_2 = cardiac output (Q) × arterial-venous O_2 content difference (a-vO_2Diff), with Q and the a-vO_2Diff each having their own modulating factors that ultimately drive the highest achievable VO_2 at peak exercise (Figure 1).

Role of Cardiac Function on Exercise Limitations in HFpEF

The reduction in VO_{2peak} observed in patients with HFpEF is due, in part, to a reduction in cardiac function during exercise. Several independent laboratories have demonstrated that peak Q is 30-40% lower in patients with HFpEF compared with control subjects.[15–18] Evidence to date suggests that chronotropic incompetence rather than SV is a fundamental concern for the blunted Q response to peak exercise in patients with HFpEF.[15–17,19–21]

Indeed, significant relationships between Q (independent of major reductions in SV)[15] and HR[19] with VO_{2peak} have previously been reported, even when matched for important co-morbidities,[20] supporting that underlying chronotropic incompetence is a major contributor to reduced Q and subsequent reductions in VO_{2peak} in HFpEF.

Despite the major role that HR plays on the severely reduced peak exercise VO_2 in patients with HFpEF, several impairments in left ventricular function have also been reported (Figure 1). Normally, left ventricular (LV) relaxation is augmented during exercise to compensate for the reduction in filling time in healthy individuals.[22] However, during exercise in patients with HFpEF, increased LV chamber stiffness and impaired (delayed) LV relaxation causes an increased reliance on left atrial contribution to LV filling.[8,23] Further, a functional consequence of marked increases in pulmonary capillary wedge (PCWP) and pulmonary artery pressures is profound dyspnea.[8,24,25] A recent study by Obokata et al. [26] highlighted the important contribution of elevated LV filling pressures to exercise intolerance in HFpEF by showing that increased PCWP during exercise was directly correlated with greater dyspnea and lower VO_{2peak}.[26]

Role of Vascular Function on Exercise Limitations in HFpEF

Impaired vascular function also contributes to reduced exercise tolerance in HFpEF. Hundley et al.[27], using cardiac magnetic resonance imaging, demonstrated that distensibility of the proximal thoracic aorta (a measure of arterial stiffness and a contributor to increase afterload and impaired LV-arterial coupling) was lower in HFpEF versus healthy age-matched controls, and predicted the lower VO_{2peak}. Kitzman et al.[28] extended these findings by showing a significant reduction in distensibility of the carotid artery in patients with HFpEF compared to healthy age-matched controls, which was also associated with a lower VO_{2peak}. Cumulatively, these findings suggest that increases in central arterial stiffness beyond normal aging contribute to the reduction in exercise tolerance in HFpEF.

Emerging evidence also suggests that skeletal muscle hyperemia is blunted in HFpEF; underscoring a fundamental impairment in O_2 delivery to the active limb. Indeed, Lee et al. [29] found that femoral artery blood flow during one-leg kicking exercise was 15-25% lower in HFpEF patients compared to healthy age-matched controls performing similar work rates. Likewise, femoral artery blood flow recovery has been shown to be approximately 25% slower following exercise compared to healthy normal values. [30,31]

The exact mechanism driving differences in skeletal muscle blood flow during exercise in HFpEF remains incompletely understood. Endothelial dysfunction, measured by flow-mediated dilation in a conduit artery, is indeed impaired in HFpEF patients compared to age-matched reference controls.[32,33] However, such group differences are ameliorated when participants are rigorously screened to exclude for the confounding effects of atherosclerosis.[28,34,35] Lee et al. [36] suggest that HFpEF may be associated with microvascular dysfunction, because reactive hyperemia—the magnitude of limb reperfusion immediately following a 5-min arterial cuff occlusion—was reduced in HFpEF compared to controls. However, caution is warranted when interpreting these results, as one cannot partition the role of skeletal muscle-mediated differences in the ischemic stimulus without knowing the extent of tissue desaturation during cuff occlusion between groups.[37] In support

of the microvascular hypothesis; however, Balmain et al.[38] demonstrated marked impairments in acetylcholine-induced cutaneous vasodilation (a measure of microvascular function) using iontophoresis coupled laser Doppler imaging in HFpEF compared to controls.[38] Likewise, Boyes et al.[39] recently reported that priming exercise, a stimulus that may transiently improve microvascular function,[40] increased skeletal muscle tissue oxygenation and conferred a substantial increase in the rate of VO_2 in the exercising muscles of HFpEF patients. Taken together, these data suggest that microvascular dysfunction may be an important therapeutic target; however, more work is clearly needed to fully elucidate the mechanism(s) contributing to impaired O_2 delivery within skeletal muscle in HFpEF. Emerging technologies capable of quantifying skeletal muscle microvascular perfusion and oxygenation should help shed light on these unmet knowledge gaps.[41]

Role of Skeletal Muscle Dysfunction on Exercise Limitations in HFpEF

A growing body of compelling evidence demonstrates that abnormalities in skeletal muscle composition and function play a major role in limiting VO_{2peak} in patients with HFpEF.[42,43] Haykowsky et al.[17] found that the strongest independent predictor of VO_{2peak} in patients with HFpEF was the change in estimated a-vO_2Diff, and this accounted for approximately 50% of the reduction in VO_{2peak} even when major cardiac determinants of VO_{2peak} were included in the multivariate analysis. These findings have since been confirmed by direct measurement of a-vO_2Diff,[16] and support the prevailing hypothesis that impaired diffusive O_2 conductance (transport of O_2 from red blood cell to muscle mitochondria) and/or an inability to sufficiently augment O_2 extraction during maximal exercise may be important contributors to reduced VO_{2peak} found in HFpEF (Figure 1).[44]

Adverse changes in leg muscle mass and volume may directly limit the increase in a-vO_2Diff during exercise in patients with HFpEF. Specifically, it has been shown that both percent total and percent leg lean mass are significantly reduced in patients with HFpEF,[5] and that the intermuscular adipose tissue and intermuscular adipose/skeletal muscle area ratio are markedly increased.[45] Moreover, the increased intermuscular adipose tissue and ratio of intermuscular adipose to skeletal muscle area have both been found to significantly predict a lower VO_{2peak} in HFpEF.[45] This finding is important because intramuscular fat may adversely affect mitochondrial density and biogenesis.[45,46]

Not unlike HFrEF, adverse muscle fiber changes have also been detected in HFpEF. Consistent with a shift to relatively greater glycolytic-dependent metabolism, HFpEF patients have less type I (oxidative) fibers, a lower type I/type II fiber ratio, and a lower capillary/fiber ratio,[47] and this fiber type and capillary interface profile is associated with a lower VO_{2peak}. Moreover, patients with HFpEF have been shown to have a reduction in mitochondrial content, citrate synthase activity, and mitochondrial fusion compared with healthy age-matched controls, which is consistent with a lower maximal oxidative capacity.[46] Mitochondrial fusion is an important cellular process that ensures that mitochondrial quality and function are preserved by constantly fusing two originally distinct mitochondria together.[48,49] This process allows for repair and removal of mitochondria with damaged DNA and creation of new healthy mitochondria via mitochondrial fission (cell division). As such, dysfunction of mitochondrial fusion may lead to accumulation of dysfunctional

organelles within the mitochondrial network, leading to reduced overall oxidative phosphorylation capacity. Indeed, impaired mitochondrial fusion is predictive of a low VO_{2peak} and 6-min walk test distance in patients with HFpEF.[46] Lastly, during dynamic planter flexion exercise with simultaneous phosphorous magnetic resonance spectroscopy, patients with HFpEF demonstrate a more rapid decrease in phosphocreatine and attenuated maximal oxidative capacity compared to healthy age-matched controls,[50,51] which could also be secondary to microvascular impairment. Accordingly, therapies that target microvascular and skeletal muscle function may prove to be most beneficial for patients with HFpEF.

EXERCISE TRAINING AND IMPROVEMENT IN VO_{2PEAK} IN HFPEF

As highlighted in Table 1, only a few studies have examined the role of exercise training to improve VO_{2peak} in clinically stable HFpEF patients. 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 test distance of 2.2 mL/kg/min [4,13,14] and 33 m, respectively, which exceed clinically meaningful changes for HF patients.[11] In accordance with the Fick Principle, the mechanisms underpinning the improvement in VO_{2peak} may be due to central or peripheral factors. Notably, evidence to date suggests that the increased VO_{2peak} observed with exercise training is primarily secondary to non-cardiac peripheral adaptations.[52,53]

Exercise Training and Cardiac Function in HFpEF

Several studies have investigated changes in resting[54–59] and peak exercise cardiac function[52,53] following exercise training (typically employed in CR programs) in HFpEF. The majority of these studies report little to no change in resting LV volumes, systolic or diastolic function after training.[54,56–59] In agreement with these findings, Fujimoto et al.[60] found no improvement in invasively measured LV diastolic compliance after 1 yr of progressive and vigorous endurance training in HFpEF patients. In addition, a recent meta-analysis by Fukuta et al.[4] concluded that the improvements in VO_{2peak} associated with exercise training occurred without significant changes in resting LV systolic or diastolic function in patients with HFpEF.

To date, only two studies have assessed changes in the Fick principle determinants of VO_{2peak} following exercise training in HFpEF.[52,53] Haykowsky et al.[53] reported that 16-wk of moderate-intensity endurance training significantly increased estimated peak a-vO_2Diff with no change in peak Q. Importantly, 84% of the endurance training-mediated increase in VO_{2peak} was due to the change in estimated a-vO_2Diff. Fu et al.[52] confirmed these findings by demonstrating that increases in VO_{2peak} with 12 wk of high-intensity interval training (HIIT) were secondary to increased estimated a-vO_2Diff, with no changes in peak exercise SV or Q. Taken together, the findings suggest that the improvements in VO_{2peak} observed following exercise training in HFpEF appear to be driven by “non-cardiac” peripheral adaptations that may facilitate improved O_2 extraction and utilization by exercising muscles, with little to no change in resting or peak exercise cardiac function.

Exercise Training and Vascular Function in HFpEF

Exercise training-mediated improvements in peak exercise a-vO_2Diff may be the result of improvements in peripheral vascular and/or skeletal muscle adaptations.[52,53] Several studies have investigated the effects of exercise training on peripheral vascular function in patients with HFpEF.[54,56,57] Kitzman et al.[56,57] found that 16-20 wk of moderate-intensity endurance training did not change carotid arterial stiffness, carotid-femoral pulse wave velocity, or brachial artery flow-mediated dilation. Angadi et al.[54] confirmed and extended these findings by showing that 4 wk of either moderate-intensity endurance training or HIIT did not change brachial artery flow-mediated dilation. To our knowledge, no study has evaluated the effect of exercise training on microvascular function. This is an important unaddressed knowledge gap which warrants future investigation.

Exercise Training and Skeletal Muscle Function in HFpEF

Currently, no studies have examined the role of exercise training on skeletal muscle morphology or function. However, given the plethora of skeletal muscle abnormalities that contribute to exercise intolerance in HFpEF,[44,47,50,51] future studies are urgently needed to examine the improvements in skeletal muscle morphology and oxidative metabolism following exercise training in HFpEF.

NOVEL INTERVENTIONS TARGETING EXERCISE INTOLERANCE IN HFPEF

High-intensity interval training

High-intensity interval training (HIIT) consists of brief intermittent bursts of vigorous exercise (85-95% peak HR), interspersed with periods of rest or active recovery. A growing body of evidence shows that HIIT can serve as an effective alternative to traditional endurance-based training, inducing similar or even superior physiological adaptations in both healthy individuals and diseased populations.[61,62] A 2014 systematic review and meta-analysis by Weston et al.[62] demonstrated that HIIT elicits a 9% superior improvement in VO_{2peak} compared to traditional moderate-intensity endurance training when carried out in clinical populations that included patients with coronary artery disease, HF, hypertension, metabolic syndrome, and obesity. To date, only two randomized controlled trials have assessed the effects of HIIT on improvement in VO_{2peak} in HFpEF.[52,54]

Angadi et al.[54] were the first group to compare improvements in VO_{2peak} with HIIT versus traditional moderate-intensity endurance training in patients with HFpEF. Despite a shorter duration 4 wk), HIIT elicited a significant increase in VO_{2peak} (+1.8 mL/kg/min), with no changes observed following moderate-intensity endurance training. Furthermore, the improvements in VO_{2peak} occurred with only modest changes in cardiac function. Fu et al.[52] compared the effects of 12 wk of HIIT on VO_{2peak} and its determinants *versus* a standard of care sedentary control group in patients with HFpEF. HIIT increased VO_{2peak} by 2.5 mL/kg/min, secondary to increases in peak exercise a-vO_2Diff and improved muscle oxygenation of the *vastus lateralis*, with little to no changes in peak exercise cardiac function. Taken together, these short-term HIIT studies suggest that HIIT is an effective stimulus to improve VO_{2peak}; however, the magnitude of improvement (mean change: +2.2 mL/kg/min) is no different to the mean improvement reported following longer duration moderate-intensity

endurance training in patients with HFpEF.[4,13,14] As such, it is still unclear if HIIT is superior to moderate-intensity endurance training for improving VO_{2peak} in the long-term (>3 mo). However, a large multicenter randomized controlled exercise training intervention study (OptimEX-CLIN) is currently ongoing to assess the optimal dose and intensity of exercise training for improvement of VO_{2peak} in patients with HFpEF, including a direct comparison between 12 mo of HIIT versus moderate-intensity endurance training.[63]

Dietary caloric restriction and exercise training

Over 80% of patients with HFpEF are either overweight or obese, and excess adiposity has been shown to adversely affect cardiac, vascular, and skeletal muscle function.[45,64–67] In obese older adults without HF, weight loss via dietary caloric restriction improves LV hypertrophy and diastolic function, cardiorespiratory fitness, glycemic control, blood pressure regulation, body composition, and skeletal muscle function.[68–72] However, current HFpEF management guidelines do not include dietary caloric restriction as a treatment,[73] in part due to observational studies reporting that overweight or moderate obesity may improve survival in patients with HFpEF when compared to those patients who are normal or underweight.[67]

Despite the apparent presence of an obesity paradox in HFpEF, Kitzman and colleagues[56] recently demonstrated that 20 wk of caloric restriction improved VO_{2peak}, body composition, skeletal muscle quality, and quality of life in obese patients with HFpEF. Furthermore, combining caloric restriction with moderate-intensity endurance training created an additive effect for the improvement in VO_{2peak} (+2.5 mL/kg/min), compared to endurance training (+1.2 mL/kg/min) or caloric restriction (+1.3 mL/kg/min) alone. Finally, improvements in VO_{2peak} were also positively associated with improvements in percent lean mass and the change in thigh muscle to intermuscular fat ratio. Further studies are warranted to establish whether the favorable changes in cardiorespiratory fitness and body composition observed with caloric restriction alone or in combination with exercise training result in reduced clinical endpoints (mortality, hospital readmissions) in patients with HFpEF.

EXERCISE TRAINING AND IMPROVEMENT IN QUALITY OF LIFE IN HFPEF

Supervised exercise training not only improves VO_{2peak} and aerobic endurance, but also patient-reported quality of life in clinically stable HFpEF patients.[55,57,58] Indeed, a recent meta-analysis by Fukuta and colleagues[4] reported that endurance exercise training, performed alone or combined with resistance training, improves Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score (an index of patient-reported quality of life) by 9.1 points compared to usual care controls. A closer examination of the individual components that encompass qualify of life in HF according to the MLHFQ and 36-item Short-Form Survey (SF-36) demonstrate that overall improvements in quality of life following exercise training are driven in large part by improvements in physical, but not mental or emotional, dimensions of quality of life in HFpEF.[4] Given the improvements in exercise tolerance and functional capacity that accompany exercise training, it is not surprising that the physical dimensions of quality of life consistently improve in HFpEF.

However, it is currently unclear why there is no change in mental or emotional dimensions in quality of life following exercise training in this patient population.

APPLICATIONS TO PRACTICE

Criteria for Inclusion in Exercise-Based Cardiac Rehabilitation

Supervised exercise-based CR is recommended for all clinically stable patients with HF and New York Heart Association (NYHA) functional class I – III.[74,75] Clinical stability is defined as no change NYHA functional class, no hospitalizations for HF, and no major cardiovascular events, or procedures during the prior 6 wk.[74,75] Once clinically stability is established, the patient should undergo further screening to determine any contraindications to exercise training based on medical history, clinical examination, electrocardiography, echocardiography, and symptom-limited cardiopulmonary exercise test (CPX).[74,75] A full list of contraindications to exercise testing and training for HF patients can be found in Piepoli et al.[75] In particular, CR health care professionals should pay particularly close attention to: large recent weight gain (>1.8 kg over the previous 1-3 d), progressive worsening of exercise tolerance or dyspnea at rest over previous 3-5 d, NYHA functional class IV, supine resting HR >100 bpm, decrease in systolic blood pressure during exercise, significant ischemia or complex ventricular arrhythmia presenting during low-intensity exercise, or presence of pre-existing co-morbidities that may limit exercise tolerance and patient safety.

Cardiac Rehabilitation Exercise Training Guidelines

In clinically stable HFpEF patients who do not meet any of the aforementioned contraindications to exercise training, large muscle mass (cycling, walking) endurance exercise is recommended for 45 to 60 min, 3 to 5 d/wk at a moderate to high-intensity to improve VO_{2peak}.[74,75] Endurance training intensity can be prescribed based on maximal heart rate reserve (HRR), percentage of VO_{2peak}, or rating of perceived exertion (RPE). In patients who have undergone a maximal CPX, the initial training intensity in the first few training sessions is 40-50% of VO_{2peak} and should progressively increase to 70-80% of VO_{2peak} after several weeks of training as training adaptations and improved exercise tolerance occur.[75] Alternatively, if peak HR is measured, the recommended training intensity is 40-70% of HRR, calculated as HRR = 40% to 70% (peak HR − resting HR) + (resting HR).[75] While exercise prescription based on VO_{2peak} or peak HR are preferred, in instances where VO_{2peak} or peak HR are either not measured, are unattainable, or unreliable (e.g. ß-blockade), the training intensity can be prescribed based on the Borg RPE scale (range: 10-14 out of 20).

While the number of studies that have assessed the efficacy and safety of HIIT in HFpEF patients is limited,[52,54] several recent reviews provide guidelines for implementation and monitoring of HIIT in clinical populations.[74,76,77] Based on these guidelines, HIIT should consist of large muscle mass (cycling, walking) high-intensity intervals (10-20 min of high interval time) interspersed with periods of active recovery for a total of 25-35 min of exercise on 3 d/wk. The high-intensity intervals can consist of either short duration intervals (15-60 s of exercise at 80-100 peak power output followed by 15-60 sec periods of active or

passive recovery) or longer-duration intervals (4 min of exercise at 90-95% peak HR followed by 3 min of active recovery at 50-70% peak HR). HFpEF patients should begin an exercise training program with shorter-duration intervals and gradually increase exercise interval duration as exercise tolerance improves. If there is difficulty obtaining a reliable or meaningful exercise-related HR during intervals, the intensity can be determined using RPE (training goal 15-18 out of 20 for high-intensity intervals) to ensure that HFpEF patients are meeting HIIT intensity goals.[77] Furthermore, those implementing and monitoring exercise training should strive to keep HR and RPE within these recommended target zones and increase workload (e.g. speed/incline on treadmill or watts on bike) to account for training adaptations over time.[77] Finally, a brief (3-5 min) light to moderate-intensity warm-up and cool-down is recommended prior to and following each continuous endurance or HIIT session.

As outlined earlier, HFpEF patients exhibit abnormalities in both skeletal muscle quantity and quality, with a reduced percentage of lean mass and greater intramuscular adipose to skeletal muscle area that contribute to poor exercise tolerance and physical function.[43,45,78] As such, resistance training is an effective mode of training to improve muscle strength, quality (composition), and physical function in HF patients.[55,79] The optimal intensity of resistance training is dependent on the patient's training goals. If the goal is improve muscular endurance, lower intensity (30-40% 1-RM, 10-25 repetitions) upper and lower extremity resistance exercises should be performed on 2-3 d/wk.[75] If the goal is to improve muscular strength, the intensity of training should be higher (40-60% 1-RM, 8-15 repetitions) on 2-3 d/wk.[75] However, it should be noted that resistance training studies performed in physically frail elderly individuals[80] and elderly patients with HFrEF[79] suggest that an intensity of 80% of 1-RM may be required to achieve optimal strength gains in elderly populations. To ensure patient safety and appropriate muscular strength progression, a lower intensity should be incorporated initially with gradual increases in intensity over time to prevent skeletal muscle injury and maximize adaptations in skeletal muscle.

Safety of Exercise Training in HFpEF

A recent meta-analysis by Dieberg et al.[13] that included 7 exercise training intervention studies (performed primarily in a CR setting) with 258 HFpEF patients reported no deaths directly attributable to exercise training in 3,744 h of exercise training. This suggests that the risk of a fatal or adverse event occurring during exercise training is very low in a supervised CR setting. Finally, by ensuring that HFpEF patients are clinically stable and free of contraindications to exercise training as outlined in this paper and others,[74,75] CR specialists can greatly limit the risk of adverse events occurring during training.

Future Directions

As outlined in this review, numerous studies have shown that exercise training is a safe and effective non-pharmacological therapy to improve exercise tolerance, aerobic endurance, and quality of life in HFpEF. However, in the absence of data regarding the effect of exercise training on clinical events, Medicare and Medicaid currently do not reimburse for exercise-based CR in patients with HFpEF, despite covering those with HFrEF.[81] As such, future large scale, multicenter exercise-based CR trials are needed to establish the efficacy of

exercise training to improve survival outcomes and rate of hospitalizations in HFpEF. In addition, future research is warranted to establish whether exercise training performed outside of a medically monitored, non-supervised setting is safe and efficacious in patients with HFpEF.

SUMMARY

HFpEF patients exhibit severe exercise intolerance secondary to cardiac, vascular, and skeletal muscle abnormalities. Randomized controlled exercise intervention trials performed to date demonstrate that moderate to high-intensity endurance training alone or combined with resistance training is efficacious for increasing VO_{2peak}, aerobic endurance, and quality of life in patients with HFpEF. Evidence to date suggests that the improvements in VO_{2peak} are secondary to peripheral 'non-cardiac' factors that result in increased O_2 extraction by the exercising muscles. Novel exercise (high-intensity interval training) interventions have also been shown to improve VO_{2peak} in HFpEF. Large muscle mass (cycling, walking) endurance continuous exercise is recommended for 45 to 60 min on 3 to 5 d/wk at a moderate to high intensity (40-70% VO_{2peak}). High-intensity interval training should consist of large muscle mass (cycling, walking) high-intensity (80-100% peak power output, 90-95% peak HR, 15-18 RPE on Borg 20-point Scale) intervals (10-20 min of high interval time) interspersed with periods of active recovery for a total of 25-35 min of exercise training on 3 d/wk. Resistance training can be supplemented to improve muscular strength, quality (composition), and physical function, with intensity being prescribed based on the goals of the patient.

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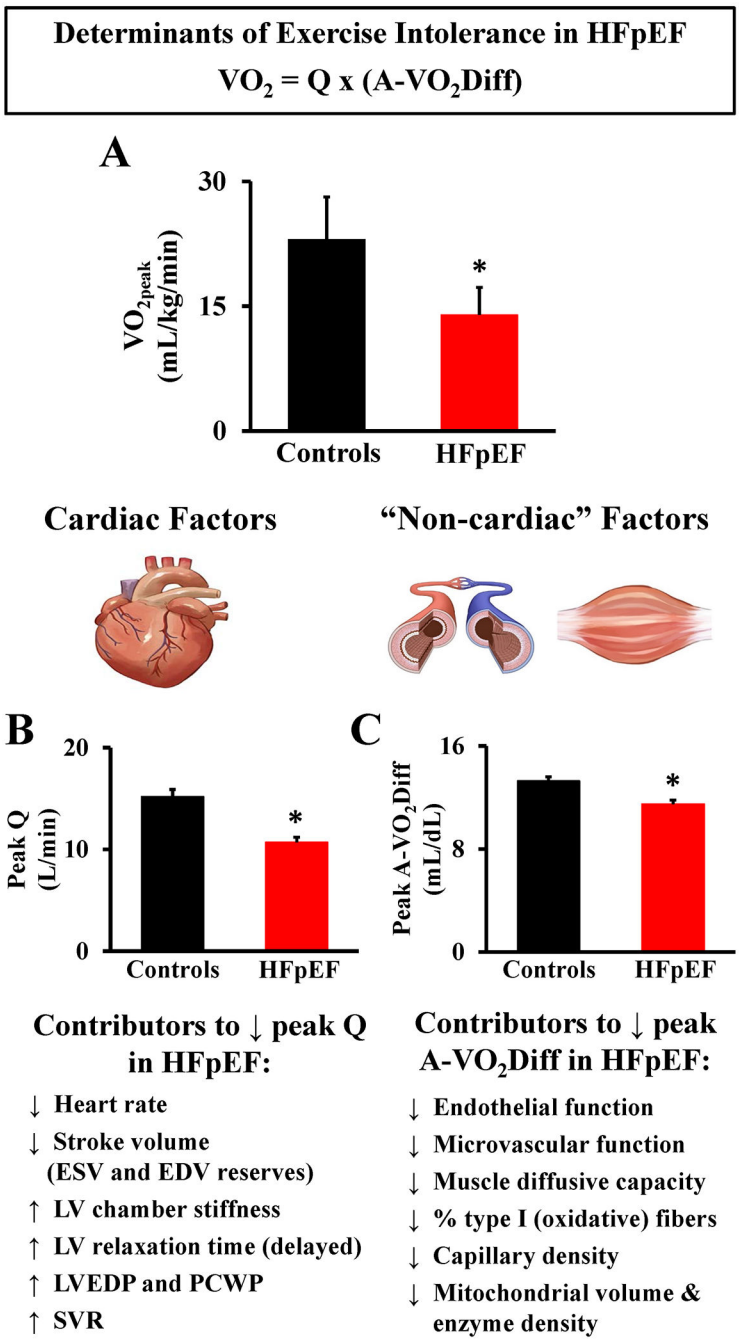

Figure 1.

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/min) during peak aerobic exercise compared to healthy age-matched controls, adapted and pooled (mean ± SD) from published data by Bhella et al. (2011)[50], Dhakal et al. (2015)[16], and Haykowsky et al. (2011)[17]. B. HFpEF patients demonstrate reduced peak exercise cardiac output (Q) (L/min), adapted from published data (mean ± SE) by Dhakal et

al. (2015)[16]. C. HFpEF patients demonstrate reduced peak exercise arteriovenous oxygen difference (a-vO_2Diff) (mL/dL), adapted from published data (mean ± SE) by Dhakal et al. (2015)[16]. 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 <.05) difference between HFpEF and healthy age-matched controls for all figures.

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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)[55]	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)[56]	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)[53]	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)[59]	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)[58]	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)[57]	ET (24)	61*, 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		

Study	Group (n)	EF (%), NHYA class	Male (%)	Age (yr)	Frequency, Intensity, Time, Training Mode	ET Length (wk)	Main Findings
	CON (22)						
Smart et al. (2012)[60]	ET (12)	59, II-III	58	67	3 d/wk 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 = six minute walk-test distance;

Abbreviations: 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.