Role of Physical Training in Heart Failure with Preserved Ejection Fraction

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Abstract About 50 % or more of heart failure (HF) patients living in the community have preserved left ventricular ejection fraction (HFpEF), and the proportion is higher among women and the very elderly. A cardinal feature of HFpEF is reduced aerobic capacity, measured objectively as peak exercise pulmonary oxygen uptake (peak VO_2), that results in decreased quality of life. Specifically, peak VO_2 of HFpEF patients is 30–70 % lower than age-, sex-, and comorbidity-matched control patients without HF. The mechanisms for the reduced peak VO_2 are due to cardiovascular and skeletal muscle dysfunction that results in reduced oxygen delivery to and/or utilization by the active muscles. Currently, four randomized controlled exercise intervention trials have been performed in HFpEF patients. These studies have consistently demonstrated that 3–6 months of aerobic training performed alone or in combination with strength training is a safe and effective therapy to increase aerobic capacity and endurance and quality of life in HFpEF patients. Despite these benefits, the physiologic mechanisms underpinning the improvement in peak exercise performance have not been studied; therefore, future studies are required to determine the role of physical

training to reverse the impaired cardiovascular and skeletal muscle function in HFpEF patients.

Keywords Heart failure and preserved ejection fraction · Aerobic capacity · Physical training · Exercise · Pathophysiology · Nonpharmacologic therapy

Introduction

Heart failure with preserved ejection fraction (HFpEF) occurs in about 50 % or more of heart failure (HF) patients in the community, and the proportion is higher among women and the very elderly [1–3]. A cardinal feature of HFpEF is reduced aerobic capacity, measured objectively as peak exercise pulmonary oxygen uptake (peak VO_2) [4, 5, 6, 7, 8, 9], that results in decreased quality of life (Fig. 1) [9]. Although many studies have examined the pathophysiology of exercise intolerance in HF and reduced ejection fraction (HFrEF) [10–18], much less is known regarding the underlying determinants of the marked exercise intolerance in HFpEF [19, 20]. This review will provide an overview of the physiologic mechanisms underpinning the reduced aerobic capacity in HFpEF patients and the role of physical training to improve peak VO_2 and quality of life (QOL) in this group.

Decreased Aerobic Capacity in HFpEF

The paucity of studies performed to date have shown that peak VO_2 is 30–70 % lower in HFpEF patients compared to age-, sex-, and comorbidity-matched control patients (Fig. 1) [4, 5, 6, 7, 8, 9, 14]. Of greater concern, aerobic capacity of HFpEF patients is below the threshold range

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Fig. 1 Aerobic capacity in heart failure and preserved ejection fraction (HFpEF) and control patients (Con) matched for age, sex, or comorbidities without heart failure. *Peak VO₂* peak oxygen uptake; *Hyp* hypertensive age-matched control patients

required for full and independent living, and as a result, many of these patients are at increased risk for functional dependence (Fig. 1) [4, 5, 6, 7, 8, 9, 14, 21, 22]. The underlying mechanisms for the reduced aerobic capacity may be due to cardiovascular and skeletal muscle dysfunction and concomitant reduction in oxygen delivery to and/or utilization by the active muscles (Table 1).

To date, seven studies have examined the pathophysiology of peak exercise intolerance in HFpEF [4, 5, 6, 7, 8, 14, 23]. The early study by Kitzman et al. [4], using invasive hemodynamic and radionuclide angiography assessments during incremental cycle exercise, found that the reduced aerobic capacity in HFpEF patients was primarily due to lower cardiac output (CO) and, to a lesser extent, to a lower arterial venous oxygen difference (A-VO₂DIFF; Table 1). In turn, the lower CO was secondary to a blunted heart rate (HR) and stroke volume (SV) reserve. The blunted SV was due to an inability to utilize the Frank-Starling mechanism as the 2.6-fold increase in pulmonary capillary wedge pressure from rest to peak exercise occurred without a change in end-diastolic volume (EDV). Although the mechanism for the reduced A-VO₂DIFF was not studied, it is likely due, in part, to skeletal muscle hypoperfusion because Katz et al. [14] found that peak exercise femoral venous oxygen content was nearly twofold lower in HFpEF patients compared to age-matched control patients (Table 1). Thus, a consequence of impaired peak and reserve CO is that there is increased capillary transit time and greater oxygen extraction by the active muscles [14].

In a follow-up study from the Kitzman laboratory, Haykowsky et al. [7] confirmed that the reduced aerobic capacity in HFpEF patients versus healthy control patients was the result of both a decreased peak CO and A-VO₂DIFF. Moreover, multivariate analysis revealed that the change

from rest to peak exercise in A-VO₂DIFF was the strongest independent predictor of peak VO₂ [7]. In contrast to the original Kitzman et al. [4] study, the reduced peak VO₂ was not due to a failure of the left ventricle (LV) to dilate as the absolute change in EDV from rest to peak exercise was not significantly different between HFpEF patients and control patients. This discrepancy is due to the different types of patients studied in the two studies. In particular, the original Kitzman et al. [4] study included HF patients (amyloid or hypertrophic cardiomyopathy) who have limited use of the Frank-Starling mechanism during exercise [24], while these patients were excluded in the Haykowsky et al. [7] study.

A series of studies by Borlaug et al. [5, 6] compared cardiovascular reserve function in HFpEF patients and age-, sex-, and comorbidity-matched control patients. The major finding of both studies was that the decreased peak VO₂ in HFpEF patients was due to impaired inotropic, chronotropic, and vasodilator reserve. Similar to Haykowsky et al. [7], EDV reserve was not different between HFpEF patients and control patients [5, 6]. In a similar study design, Ennezat et al. [23] found that the reduced CO reserve in HFpEF patients versus hypertensive control patients was secondary to blunted inotropic and vasodilator reserve.

A recent study by Bhella et al. [8] examined the acute hemodynamic responses during incremental cycle exercise in elderly HFpEF patients versus age-matched healthy control patients. The major finding was that the decreased aerobic capacity in HFpEF patients was solely due to a lower A-VO₂DIFF as peak exercise SV, stroke work, CO, and cardiac power output were not significantly different between groups. Further, preliminary analysis (two HFpEF patients and two control patients), using ³¹Phosphate magnetic

Table 1 Mechanisms responsible for the decreased peak exercise pulmonary oxygen uptake in HFpEF patients

	Kitzman et al. [4] HFpEF vs AC	Katz et al. [14] HFpEF vs AC	Borlaug et al. [5] HFpEF vs ACC	Ennezat et al. [23] HFpEF vs HYP	Borlaug et al. [6•] HFpEF vs AC HFpEF vs HYP		Haykowsky et al. [7•] HFpEF vs AC	Bhella et al. [8•] HFpEF vs AC
VO ₂	↓	↓	↓	ND	↓	↓	↓	↓
Peak								
CO								
Peak	↓	ND					↓	↔
Reserve			↓	↓	↓	↓	↓	
HR								
Peak	↓	↓	↓				↓	↓
Reserve			↓	↔	↓	↓	↓	
SV		ND			ND	ND		
Peak	↓						↔	↔
Reserve			↔	↓			↔	
EDV								
Peak	↓	ND					↓	ND
Reserve			↔	↔	↔	↔	↔	
ESV								
Peak	↔	ND	ND				↔	ND
Reserve				↓	↓	↓	↓	
EF								
Peak	↔	ND					↔	ND
Reserve			↓	↓	↓	↓	↔	
SVR								
Peak	ND	ND					↔	ND
Reserve			↓	↓	↓	↓	↔	
A-VO ₂								
DIFF								
Peak	↓	ND	ND	ND	ND	ND	↓	↓
Reserve		ND					↓	
FVO ₂ C								
Peak	ND	↓	ND	ND	ND	ND	ND	ND

HFpEF heart failure and preserved ejection fraction; AC age-matched control; ACC Age-sex and co-morbidity matched controls; HYP hypertensive age-matched controls; VO₂ peak pulmonary oxygen uptake; ↓ lower in HFpEF vs comparison group; ND no data; CO cardiac output; ↔ no difference between HFpEF and comparison group; HR heart rate; SV stroke volume; EDV end-diastolic volume; ESV end-systolic volume; EF ejection fraction; SVR systemic vascular resistance A-VO₂DIFF arterial-venous oxygen difference; FVO₂C femoral vein oxygen content

resonance spectroscopy during and after performing static leg lifts, revealed impaired skeletal muscle oxidative metabolism in HFpEF patients. Notably, the finding of this study that peak cycle exercise CO is not significantly different between HFpEF patients and age-matched healthy control patients reinforces the finding by Haykowsky et al. [7•] that peripheral “non-cardiac” factors play a greater role in limiting exercise performance in HFpEF.

In summary, the severe and marked exercise intolerance in HFpEF patients versus age-, sex-, and comorbidity-matched control patients without HF is due to decreased CO and/or A-VO₂DIFF that results in a lower oxygen delivery to and/or utilization by the active muscles (Table 1).

Physical Training in Patients with HFpEF

Currently, four randomized controlled exercise intervention trials have assessed the role of physical training on aerobic capacity or aerobic endurance (distance walked in 6 min [6MWD]) and QOL in HFpEF patients [25, 26•, 27•, 28]. In the first published randomized trial, Gary et al. [25] compared the effects of a 12-week combined walking (light to moderate intensity) and HF-management education program versus an HF-management education program alone on aerobic endurance and QOL in 28 older elderly women with HFpEF (Table 2). The investigators reported that the 12-week

Table 2 Randomized controlled exercise intervention trials in HFpEF patients

Study	Group (n)	Age, y	EF, %	Mode	Frequency, d/wk	Intensity	Duration, min	Length of program, wks	Main findings
Gary et al. [25]	ET (15) CNT (13)	67 69	54 57	Walk	3	40 %–60 %	30	12	↑ 6MWD, QOL
Kitzman et al. [26••]	ET (24) CNT (22)	70 69	61 60	Walk/cycle	3	40 %–70 % HRR	60	16	↑ peak VO ₂ , ventilation threshold, 6MWD, and physical QOL
Edelmann et al. [27••]	ET (44) CNT (20)	64 65	67 66	Cycle + RT (UE/LE)	2–3 2	HR 50 %–70 % peak VO ₂ 60 %–65 % 1RM	20–40 15 REPS	12 Wks 5–12	↑ peak VO ₂ , 6MWD, physical function, ↓ rest LAV, E/e', and procollagen type I
Alves et al. [28]	ET (20) CNT (11)	63* 62	56* 55	Cycle/ treadmill	3	5–7 intervals (3- to 5-min duration) at 70 %–75 % HR _{max} with 1 min active recovery at 45 %–55 % HR _{max}	15–35	24	↑ peak MET, ↑ rest LVEF, E/A ratio, ↓ DT

HFpEF heart failure and preserved ejection fraction; EF ejection fraction; ET exercise training; CNT control; ↑ increased; 6MWD distance walked in 6 min; QOL quality of life; HRR heart rate reserve; peak VO₂ peak oxygen uptake; RT resistance training; UE upper extremity; LE lower extremity; HR heart rate; 1RM one-repetition maximum; REPS repetitions; ↓ decreased; LAV left atrial volume; HR_{max} maximal heart rate; MET metabolic rate; LVEF left ventricular ejection fraction; E/A early to late mitral inflow velocity; DT deceleration time; E/e' early transmitral inflow velocity to early diastolic mitral annulus velocity ratio

* Mean of whole group

walking and education program improved aerobic endurance and QOL compared to control patients.

In the first medically supervised, single-center, randomized, controlled, single-blind exercise trial in HFpEF, Kitzman et al. [26••] compared 16 weeks of endurance exercise training with attention control on aerobic capacity and endurance, LV morphology and function, biomarkers, and QOL in 46 elderly patients with HFpEF. The major new finding was that endurance training increased peak VO₂, ventilation threshold, 6MWD, and improved physical QOL without altering LV morphology or neuroendocrine function (Table 2). Importantly, the improvement in aerobic capacity was clinically meaningful because baseline peak VO₂ in patients randomly assigned to endurance training was below the minimal VO₂ value required for full and independent living and was above this value after 16 weeks of endurance training.

Edelmann et al. [27••], in a multicenter trial of exercise training in HFpEF, evaluated the effects of 12 weeks of endurance training with supplemental strength training (initiated in week 5 of the program) with a usual care control on aerobic capacity and endurance, LV systolic and diastolic function, biomarkers, and QOL in 64 HFpEF patients. The authors reported that combined training was associated with a significant increase in peak VO₂, aerobic endurance, and self-reported physical dimension of QOL (Table 2). Combined training also significantly decreased resting left atrial volume and early transmitral inflow velocity to early diastolic mitral annulus velocity (E/e') ratio and procollagen

type 1 levels. Finally, the improvement in peak VO₂ was inversely related to the change in resting E/e' ratio and suggests that favorable changes in rest diastolic function may result in increased aerobic capacity [27••].

Lastly, Alves et al. [28] recently reported that 6 months of moderate-intensity aerobic interval training significantly increased estimated metabolic equivalents during peak treadmill exercise and improved resting LV ejection fraction and diastolic function in HFpEF with no change in the usual care control group (Table 2). Despite the small sample size, this study reported improvements in resting LV systolic and diastolic function after physical training in HFpEF (Table 2) [28].

In summary, the few randomized controlled exercise intervention trials performed to date in HFpEF consistently demonstrate that endurance training performed alone or in combination with strength training is a safe and effective intervention to increase aerobic capacity (16 %) and endurance (13 %) and improves QOL (Table 2). Moreover, two recent studies have shown that combined moderate-intensity continuous aerobic and strength training or moderate-intensity interval training can improve resting diastolic function in HFpEF patients.

Safety of Physical Training in HFpEF

The safety of exercise training was reported in the four randomized exercise intervention trials discussed above.

Gary et al. [25] reported no adverse events during a 12-week partially supervised (full supervision during the first week followed by weekly supervision) walking program performed in local shopping malls, grocery stores, or gymnasiums. Also, no adverse events occurred with exercise testing or endurance training in the 16-week single-center trial by Kitzman and associates [26••]. Similarly, no serious adverse events occurred in HFpEF patients who participated in the multicenter exercise intervention trial by Edelmann et al. [27••]. Of note, nine (20 %) of the combined aerobic and strength-trained patients reported mild musculoskeletal discomfort during exercise. Finally, Alves et al. [28] reported no adverse events during exercise testing or moderate-intensity aerobic interval training in HFpEF patients. Taken together, the studies performed to date suggest that well-screened HFpEF patients can safely perform physical training in a partially supervised or supervised setting.

Exercise Prescription Recommendations for HFpEF Patients

A supervised maximal exercise test with monitoring for ischemia should be performed before HFpEF patients beginning a physical training program. The exercise training program for clinically stable HFpEF patients should consist of continuous large muscle mass endurance exercise (ie, walking, treadmill, cycling, combined arm and leg ergometry) performed at an intensity between 40 % and 80 % peak VO_2 (40–70 % heart rate reserve or Borg rate of perceived exertion between 10 and 14 out of 20) for 20–60 min per session, 3–5 days per week [29]. The intensity and duration of exercise may need to be lower and gradually progressed (ie, “start low and go slow”) for severely debilitated elderly HFpEF patients. In addition, supplemental strength training should be considered, ranging from 40 % to 60 % of maximal strength for 1 set, 2–3 days per week [29]. The exercise program should be initiated in a supervised setting with direct supervision and monitoring. Depending on individual progress and safety during monitored exercise, patients usually should be able to be transitioned to a home exercise maintenance training program.

Conclusions and Future Considerations

Individuals with HFpEF have severe and marked exercise intolerance that is due, in part, to impaired cardiovascular and skeletal muscle function that results in decreased oxygen delivery or utilization by the active muscles. The few randomized controlled exercise intervention trials performed to date show that physical training (aerobic training alone or combined with strength training) is a safe and effective intervention to increase aerobic capacity and endurance and self-

reported QOL in HFpEF patients. The underlying mechanisms for the improvement in aerobic capacity remain unknown; therefore, future studies are required to determine if regular physical training can reverse the impaired cardiovascular and skeletal muscle that occurs in HFpEF patients. Finally, future trials are required to determine if newer training modalities (ie, high-intensity aerobic interval exercise [30] or isolated muscle mass training [31]) are effective forms of training to improve aerobic capacity in HFpEF patients [20].

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