Exercise intolerance in heart failure with preserved ejection fraction: more than a heart problem

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Abstract

Heart failure (HF) with preserved ejection fraction (HFpEF) is the predominant form of HF in older adults, and is increasing in prevalence as the overall population ages. Although the long-term mortality in HFpEF is similar to HF with reduced EF (HFrEF), guideline based medications that improve survival in HFrEF have not been successful in reducing mortality in HFpEF patients. This syndrome was historically considered to be caused exclusively by left ventricular (LV) diastolic dysfunction. However, recent data from multiple sources indicating that even in well-characterized, symptomatic HFpEF, many patients do not have echo-Doppler indexes of diastolic dysfunction that differ greatly from that expected based on age and comorbidities. These findings suggested that abnormalities of intrinsic diastolic function may not always be present during or completely explain the occurrence of HFpEF. In acknowledgement of these considerations, as well as data supporting a broader paradigm for HFpEF pathophysiology and outcomes, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) HF management guideline takes a practical, approach to HFpEF. It states that the diagnosis of HFpEF is based on: (1) typical symptoms and signs of HF; (2) normal or near normal LVEF; and (3) no other obvious factors to account for the apparent HF symptoms, including significant valvular abnormalities.

Substantial attention has focused on defining the central versus peripheral mechanisms underlying the reduced functional capacity and symptoms among patients with HF. Numerous prior studies have investigated the physiological mechanisms underlying the reduced exercise intolerance in patients with HFrEF; however much less is known regarding its mechanisms in patients with HFpEF. In this review, we will summarize the current understanding of the pathophysiology of exercise intolerance and how peripheral limitations, including skeletal muscle, contribute to exercise intolerance in HFpEF patients.
2 Epidemiology of HFpEF

HFpEF is the most common form of HF in older adults. The annual incidence of HF in both men and women doubles with every decade increase in age after age 65, and the prevalence of HF increases from less than 0.5% in the age group of 20–39 years to more than 10% in those 80 years of age and older. Elderly persons have a substantial risk for death after a diagnosis of HF, and a normal LVEF does not ensure a favorable outcome, (Figure 1). Although the adjusted mortality risk was greatest in participants with HFrEF, only a minority of community-based elderly persons were in this category. Outcomes following hospitalization for decompensated HFpEF are quite poor, with over 1/3 of patients dead or rehospitalized within 60–90 days of discharge.

Figure 1. Survival of patients in the cardiovascular health study. Control: nested case controls without heart failure; DHF: heart failure with a normal ejection fraction; Ass LVD: reduced ejection fraction with no symptoms of heart failure; SHF: systolic heart failure. Modified from: Gottdiener, et al.

3 Pathophysiology of exercise intolerance

The primary chronic symptom in patients with HFpEF, even when well compensated, is severe exercise intolerance, which can be measured objectively as decreased peak oxygen consumed during maximal effort exercise (peak VO2), and is a strong determinant of prognosis and reduced quality of life. Importantly, the finding of increased peak A-VO2 Diff indicates that after exercise training there was an improvement in either diffusive oxygen transport via improved peripheral vascular, microvascular function and/or skeletal muscle adaptations that increase diffusive oxygen transport and/or improvements in oxygen extraction by skeletal muscle. Accordingly, impaired skeletal muscle O2 extraction may be an important factor limiting exercise tolerance in HFpEF.

4 Impaired arterial function

In healthy older adults, the 11-fold increase in blood flow to the active muscles during peak cycle exercise is caused by sympathetic-mediated redistribution of blood from non-exercising regions to the working muscles coupled with metabolic-mediated vasodilation in the exercising muscles. Normal aging is associated with significant alterations in peripheral arterial blood flow responses at rest and

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after a variety of stressors, including exercise. Changes in central and peripheral arterial function may result in inefficient distribution of CO to the active muscles and contribute to exercise intolerance in patients with HFpEF.

Conduit artery (aorta and large artery) stiffening occurs as part of the normal aging process which can be accentuated by many of the diseases associated with HFpEF. Both aortic distensibility and carotid artery distensibility are severely reduced in elderly HFpEF patients and correlate with their degree of exercise intolerance and objectively measured peak exercise VO2. Puntawangkoon, et al. found that post-exercise submaximal exercise leg blood flow was reduced in older HF patients versus healthy controls. They also indicated that older HF patients have reduced leg blood flow with exercise beyond that which is associated with normal aging.

Impaired peripheral arterial endothelial function may result in impaired exercise blood flow reserve in patients with HFpEF. Using phase-contrast magnetic resonance imaging (superficial femoral artery), Hundley, et al. showed that resting and flow-mediated increases in leg blood flow in elderly HFpEF patients are not significantly impaired and are similar to those of age-matched healthy subjects. Haykowsky, et al. using high resolution brachial artery ultrasound to assess flow-mediated dilation and healthy age matched controls, found no reduction in endothelial function in HFpEF patients who were free of clinically significant coronary, cerebrovascular, and peripheral arterial disease. Similarly, in elderly HFpEF patients, 16 weeks of endurance exercise training improved peak VO2 without altering endothelial function or arterial stiffness. In a recent pilot study, four weeks of exercise training in HFpEF patients significantly improved VO2 without affecting endothelial function assessed by brachial artery flow-mediated dilation. This suggests that large vessel endothelial dysfunction may not be an inherent feature of HFpEF. An important feature of these studies was exclusion of patients with any evidence of clinical atherosclerosis, which is known to independently reduce endothelial function.

However, flow-mediated vasodilation in large conduit arteries (e.g., femoral) may differ from that observed in the microvasculature. Microvascular endothelial dysfunction as measured by digital artery tonometry was impaired in HFpEF compared with controls and correlated with reduced exercise capacity and greater symptoms. Similarly in another study microvascular endothelial dysfunction was an independent predictor of poorer prognosis, mainly readmission, in patients with HFpEF. A consequence of the blunted microvascular reserve is that it may be associated with decreased diffusive oxygen transport to the active muscle, which would reduce exercise tolerance. Recently in an autopsy-based study, Mohammed et al. reported reduced microvascular density in HFpEF patients which was independent of coronary artery disease and hypertension and in adjusted analyses appeared to account for the increased fibrosis. Their findings suggest that co-morbidities other than hypertension may perpetuate microvascular rarefaction. Advanced age and common HFpEF comorbidities such as obesity, systemic hypertension and diabetes mellitus have been shown to be associated with coronary microvascular dysfunction. This supports an over-arching hypothesis for HFpEF pathogenesis as originally proposed by Paulus: a systemic pro-inflammatory state that results in systemic arterial and microvascular dysfunction. Indeed peripheral endothelial dysfunction might impair matching of perfusion to regional demand in skeletal muscle microcirculation.

5 Role of skeletal muscle in exercise intolerance

After delivery of O2 to skeletal muscle, O2 utilization is dependent on the pathway consisting of skeletal muscle tissue microcirculatory O2 exchange vessels and muscle units. Decreased AVO2D diff may suggest a potential role of impaired skeletal muscle vasodilatory capacity in small resistance vessels. Moreover In healthy individuals, there is a net increase in level of O2 extraction relative to O2 delivery during exercise. This is indicated by an exercise-related fall in O2 levels in venous blood, consistent with increased utilization of O2 by respiring mitochondria relative to the rate of increase in O2 delivery. It is known that in conditions in which there is a defect in oxygen utilization, such as mitochondrial myopathies, the peak VO2 is depressed despite normal cardiac function.

Esposito and colleagues have demonstrated that HFrEF severely reduces muscle oxygen diffusion conductance and this may also account for poor muscle function and exercise intolerance. It is well known that in HFrEF every facet of the O2 transport pathway is compromised, which can explain the premature fatigue in this condition. In addition, morphologic and histochemical changes in skeletal muscle have been described in HFrEF, including marked abnormalities in skeletal muscle mass, density, fiber type, oxidative metabolism, mitochondrial mass, and mitochondrial function. The multinational SICA-HF study found that muscle wasting is a frequent co-morbidity among patients with chronic HFrEF and associated with worse exercise capacity.

As most of these studies have been performed in patients
with HFrEF, the specific changes of skeletal muscle in patients with HFpEF were limited.

6 Skeletal muscle mass, oxygen utilization and exercise intolerance in HFpEF

Using dual energy X-ray absorptiometry, Haykowsky and colleagues found percent body fat and percent leg fat were significantly increased, whereas percent body lean and leg lean mass were significantly reduced, in older HFpEF patients versus healthy controls. Moreover, the slope of the relation of peak VO2 with percent leg lean mass was markedly reduced in the HFpEF versus healthy control group. These investigators extended these results by directly characterizing thigh muscle composition using phase-contrast MRI, which showed abnormal fat infiltration into the thigh skeletal muscle and that this was associated with reduced peak exercise VO2 in HFpEF (Figure 2).

![Figure 2. Magnetic resonance imaging axial image of the mid-thigh in a patient with HFpEF and HC.](image)

HC subject

Skeletal muscle = 810 cm²
Intermuscular fat = 14.2 cm²
Subcutaneous fat = 106.6 cm²
Total thigh area = 207.1 cm²

HFpEF subject

Skeletal muscle = 70.9 cm²
Intermuscular fat = 27.6 cm²
Subcutaneous fat = 96.1 cm²
Total thigh area = 260.7 cm²

In adipose tissue, either adipocytes directly or infiltrating macrophages produce pro-inflammatory cytokines, and these cytokines have direct catabolic effects on skeletal muscle. Thus, a pro-inflammatory state may be one of the key factors in creating a vicious cycle of decreased muscle strength among older adults. Moreover, it has been hypothesized that muscle fat infiltration causes insulin resistance in obese individuals. Insulin resistance promotes muscle catabolism, mitochondrial dysfunction, and impairs protein synthesis in skeletal muscle. Heinonen, et al., using positron emission tomography, found that adipose tissue blood flow adjacent to the active muscles increased sevenfold during continuous isometric knee-extension exercise in non-obese younger healthy sedentary women. Thus, increased thigh intermuscular fat in older patients with HFpEF may “steal” blood that would normally be delivered to the active muscles during exercise thereby reducing perfusive oxygen delivery to the thigh muscle. Thus, fatty infiltration of skeletal muscle is associated with reduced strength and functional status, muscle dysfunction, decreased contractility, and reduced mitochondrial mass, biogenesis, oxidative metabolism. Indeed, using phosphate-31 magnetic resonance spectroscopy during and after performing static leg lifts, they revealed impaired skeletal muscle oxidative metabolism in patients with HFpEF.

Together, these findings support the concept that altered skeletal muscle composition (remodeling) and poor “quality” of skeletal muscle may contribute to the reduced peak VO2 found in older HFpEF patients.

Kitzman, et al., further showed compared with HC subjects, older HFpEF patients had a shift in skeletal muscle fiber type distribution with a reduced percentage of slow twitch type I fibers and reduced type I-to-type-II fiber ratio and reduced capillary-to-fiber ratio. Furthermore, both the capillary-to-fiber ratio and percentage of type I fibers were significant, independent predictors of peak VO2 (Figure 3). A reduction in the percentage of type I fibers could be associated with reduced oxidative capacity and mitochondrial density and thereby contribute to the reduced peak VO2 in HFpEF. The reduction in blood flow to exercising muscle may lead to greater reliance on anaerobic glycolysis, predisposing to earlier exhaustion. The pattern of altered skele-
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7 Impact of aging, frailty and comorbidities

Aging is associated with a progressive decline in exercise capacity and decreased physiological reserve in cardiovascular function as well as in most other organ systems. Aging is associated with a decline in a variety of neural, hormonal and environmental trophic signals to muscle that can result in loss of muscle mass and mass-specific strength. This can also contribute to aging associated characteristic changes in body composition, including decreases in lean body mass and muscle strength, and increases in adiposity. In addition, aging is associated with a systemic pro-inflammatory state, and associated with increased levels of cytokines, that may lead to a functional decline in multiple organs even in absence of a specific disease.

The majority of older HFpEF patients have multiple comorbidities and high proportions are frail. The adverse impacts of aging, frailty and comorbidities on functional capacity and clinical outcomes are cumulative and synergistic. This synergy may be mediated in large part by the reduction in physical activity that accompanies each condition. Muscle atrophy leads to reduction in metabolic rate both at rest and during physical activity, thus further aggravating the sedentary state, all of which can cause obesity. Approximately 85% of elderly HFpEF patients are overweight or obese, and the HFpEF epidemic has largely paralleled the obesity epidemic. Obesity has a similar pathophysiological burden on skeletal muscle with aging, including inflammation, oxidative stress, and insulin resistance.

Furthermore, aging and obesity, which are well established, risk factors for both HFpEF and several common respiratory diseases [like chronic obstructive lung disease (COPD)]. In addition, COPD occurs in approximately one-third of HF patients, with a slightly higher prevalence in HFpEF patients compared with HFrEF patients. Moreover, patients with preserved EF do not have the alternative diagnosis of low EF; they may be more likely to receive a COPD diagnosis as an explanation for dyspnea. Interestingly, in a recent pilot study, lung function abnormalities are seen among 94% in patients with HFpEF, in that cohort, 93% of patients with a restrictive ventilatory abnormality were overweight (BMI > 25 kg/m²). Thus, these lung functional abnormalities can be due to either HFpEF itself and/or to the presence of concomitant comorbid respiratory diseases.

It is noteworthy that patients with multiple comorbidities have often been actively excluded from clinical HF studies, thereby producing results that may not be applicable to typical older HFpEF patients. Mounting evidence indicates that in the elderly HFpEF population, non-HF hospitalizations dominate and non-cardiac reasons account for a large proportion of overall deaths. Given such a multi-factorial,
Therapeutic options and clinical outcomes

Pharmacological trials in HFpEF to improve outcomes and symptoms have been particularly disappointing. Of the three large randomized trials of angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin II type I receptor blocker (ARB) performed to date in HFpEF, only the CHARM-preserved study found nominal benefit for candesartan in reducing HF hospitalizations over three years of follow-up. I-PRESERVE was a very large, multi-center trial of HFpEF and enrolled 4,128 patients and randomly assigned them to the ARB, irbesartan or placebo. Mortality or rates of hospitalizations for cardiovascular causes were not improved by treatment with an ARB. The Aldo-DHF trial of 12 months treatment of spironolactone aldosterone inhibitor improved some measures of diastolic function, though maximal exercise capacity, clinical symptoms, and quality of life were not changed. The large TOPCAT trial of spironolactone failed to show statistically significant benefit for the clinical composite primary end-point. Similarly, the role of β-blockers remains uncertain and data to date have not been encouraging. Both carvedilol (the J-DHF study) and nebivolol (ELANDD study) had neutral effects on their primary outcomes in HFpEF patients. In the Digitalis Interaction Group trial (DIG), there was a trend noted towards decreased hospitalization and improved exercise tolerance in a subgroup of 988 patients with EF > 45% who were randomized to placebo or to digoxin.

Novel pharmacological agents

In a recent RELAX trial, sildenafil did not improve 6-min walk distance or quality of life, and was associated with modest worsening of renal function. The DILATE-I study showed that riociguat, a soluble guanylate cyclase stimulator, did not have any impact on the primary end-point of peak change in mean pulmonary artery pressure in patients with HFpEF and pulmonary hypertension. Even though observational data in HFpEF patients suggest a mortality benefit with use of HMG-Co-A reductase inhibitors, definitive trials have not been performed yet. In a seven-day study, ivabradine, a selective sinus node If sodium channel inhibitor increased peak VO₂ in 61 patients with HFpEF. Compared to valsartan alone, the LCZ696 (Neprilysin, the zinc-dependent metalloprotease that degrades biologically active natriuretic peptides) group had significantly lower NT-pro BNP levels and at 36 weeks, decreased LA size and showed a trend toward improved functional class in PARAMOUNT study. The findings of this phase-2 study are promising and a large, multi-center trial, PARAGON, is underway comparing LCZ696 to valsartan in patients with HFpEF. Serelaxin, a recombinant form of human relaxin-2, administered to acute HF patients, caused in improvement of symptoms with a reduction in 180-day mortality, compared with placebo. In HFpEF patients, treatment with a sitaxsentan sodium selective endothelin type A receptor antagonist appeared to increase exercise time on the treadmill. This agent (as were other endothelin type A antagonists) was not beneficial in multiple outcomes trials of HFpEF; it had hepatotoxicity, and has been removed from development. Thus, novel agents tested for HFpEF to date have fared only a little better than the standard agents adapted from treatment of HFrEF.

The most evidenced-based promising way strategy at present to improve exercise intolerance in HFpEF patients appears to be exercise training, but the optimal approach is still unknown. Four months of endurance exercise training increased peak VO₂, ventilatory anaerobic threshold, 6-min walk distance, and physical quality-of-life scores in patients with HFpEF. These results were confirmed in a subsequent multicenter study of 64 HFpEF patients randomized to three months of combined exercise training and strength training. In four months of upper and lower extremity endurance exercise training, Kitzman, et al. found a significant increase in peak VO₂ without altering carotid arterial stiffness or brachial artery flow mediated dilation in HFpEF patients. Taken together, the few studies performed to date indicate that endurance exercise training is an effective nonpharmacologic therapy that improves clinically stable patients with HFpEF exercise tolerance. In a recent meta-analysis, exercise training improves physical function and quality of life in patients with HFpEF. This improvement appears to occur primarily through non-cardiac mechanisms, such as improved arterial and skeletal muscle function.

Traditional exercise training programs for patients with HFpEF have primarily focused on moderate intensity endurance exercise training. Despite favorable anti-remodeling and quality of life benefits, moderate-intensity training is associated with relatively moderate improvements in peak VO₂. A meta-analysis of seven small trials showed that high-intensity aerobic interval training in HFrEF patients was more effective than traditional continuous moderate-intensity exercise in increasing peak VO₂ whereas...
changes in LVEF were not significant.\textsuperscript{111} Recently, Angadi, \textit{et al.}\textsuperscript{44} showed that in HFpEF patients four weeks of high intensity interval training significantly improved peak VO$_2$ compared to moderate-intensity aerobic continuous training. Even though this study had a small sample size, it suggests that high intensity interval training might provide a more robust stimulus than moderate-intensity aerobic continuous training for early exercise training adaptations in HFpEF. A randomized multi-center study comparing three months supervised moderate intensity continuous training versus high intensity interval training versus a control group followed by nine months of telemedically monitored home-based training is under way.\textsuperscript{112}

Furthermore, the effects of aging, multiple comorbidities, and frailty on the use of exercise training in older HF patients are profound. The marked impairment of aerobic capacity, ambulatory function, strength, and balance often seen in this population presents major challenges to effectively and safely implement exercise training. Progress will likely require innovative multidisciplinary team approaches that recognize the importance of non-cardiac factors.

10 New avenues for HFpEF

In addition, emerging evidence suggests that enhancing nitric oxide bioavailability by beetroot juice or inorganic nitrate supplementation can effectively lower the mitochondrial O$_2$ cost of ATP production, thereby lowering the exercising VO$_2$ requirement.\textsuperscript{113} Recently, Zamani, \textit{et al.}\textsuperscript{114} found that a single dose of inorganic nitrate administered before exercise significantly improves peak VO$_2$ in subjects with HFpEF by improving the peripheral response to exercise and by providing greater O$_2$ delivery to exercising muscles. Several current clinical trials are testing novel agents to regenerate skeletal muscle in elderly with multiple comorbidities and sarcopenia; if successful, these could inform new approaches to HFpEF. If HFpEF is triggered by systemic inflammation, then a promising signal is the novel agent LCZ696, an angiotensin receptor neprilysin inhibitor, which is currently being tested in a large clinical trial. This agent appears to reduce tumor necrosis factor-\textalpha levels and cardiac muscle. A paradigm shift in our understanding of the mechanisms that may be targeted in HFpEF, and the patients most likely to benefit from these targeted approaches, is needed.

11 Conclusions

In summary, recent work indicates that peripheral abnormalities contribute significantly to symptoms of exercise intolerance in elderly HFpEF patients. Future therapeutic strategies are needed to improve exercise tolerance by targeting the integrated functions of these systems. This is particularly relevant since skeletal muscle and microvascular function often have greater capacity for regeneration than cardiac muscle. A paradigm shift in our understanding of the mechanisms that may be targeted in HFpEF, and the patients most likely to benefit from these targeted approaches, is needed.

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