Current Heart Failure Reports (2018) 15:323–331
https://doi.org/10.1007/s11897-018-0408-6

PATHOPHYSIOLOGY: NEUROENDOCRINE, VASCULAR, AND METABOLIC FACTORS (S. KATZ, SECTION EDITOR)

Impaired Exercise Tolerance in Heart Failure: Role of Skeletal Muscle Morphology and Function

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Published online: 3 September 2018

Abstract

Purpose of Review To discuss the impact of deleterious changes in skeletal muscle morphology and function on exercise intolerance in patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), as well as the utility of exercise training and the potential of novel treatment strategies to preserve or improve skeletal muscle morphology and function.

Recent Findings Both HFrEF and HFpEF patients exhibit a reduction in percent of type I (oxidative) muscle fibers and oxidative enzymes coupled with abnormal mitochondrial respiration. These skeletal muscle abnormalities contribute to impaired oxidative metabolism with an earlier shift towards glycolytic metabolism during exercise that is strongly associated with exercise intolerance. In both HFrEF and HFpEF patients, peripheral "non-cardiac" factors are important determinants of the improvement in exercise tolerance following aerobic exercise training. Adjunctive strategies that include nutritional supplementation with amino acids and/or anabolic drugs to stimulate anabolic molecular pathways in skeletal muscle show great promise for improving exercise tolerance and treating heart failure-associated sarcopenia, but these efforts remain early in their evolution, with no immediate clinical applications.

Summary There is consistent evidence that heart failure is associated with multiple skeletal muscle abnormalities which impair oxygen uptake and utilization and contribute greatly to exercise intolerance. Exercise training induces favorable adaptations in skeletal muscle morphology and function that contribute to improvements in exercise tolerance in patients with HFrEF. The contribution of skeletal muscle adaptations to improved exercise tolerance following exercise training in HFpEF remains unknown and warrants further investigation.

Keywords Cardiorespiratory fitness · Exercise training · Oxidative metabolism · Mitochondrial function · Magnetic resonance spectroscopy · Amino acids

Abbreviations

a-vO_2diff	Arterial-venous oxygen content difference
CO	Cardiac output
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
NYHA	New York Heart Association
PCr	Phosphocreatine
VO_{2peak}	Cardiorespiratory fitness

This article is part of the Tropical Collection on *Pathophysiology: Neuroendocrine, Vascular, and Metabolic Factors*

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Introduction

Heart failure (HF) is a major healthcare problem associated with high morbidity and mortality [1]. Approximately 50% of HF patients have reduced ejection fraction (HFrEF) while the remainder of patients have preserved ejection fraction (HFpEF) [2•]. While both HFrEF and HFpEF increase with age, incidence of HFpEF is particularly prominent, doubling

in incidence with each decade after age 65 [3]. The cardinal symptom in clinically stable HFrEF and HFpEF patients is reduced exercise tolerance [4, 5, 6••, 7, 8]. Heart failure patients' peak cardiorespiratory fitness (VO_{2peak}) is ~65% of age-matched healthy controls [2•, 6••, 7, 9••, 10]. Moreover, declines in cardiorespiratory fitness in older HF patients are compounded by comorbidity, sarcopenia, malnutrition, and other aging sequela that exacerbate declines in cardiorespiratory fitness as well as strength and balance, and progressively jeopardize quality of life and functional independence [2•, 11].

The reduced VO_{2peak} is secondary to impaired cardiac and pulmonary performance, as well as peripheral vascular, and skeletal muscle abnormalities that result in reduced convective and diffusive O_2 transport coupled with decreased O_2 utilization by exercising muscle [2•, 6••, 12, 13]. A number of invasive hemodynamic studies have shown that both HFrEF and HFpEF have reduced maximal cardiac output (CO) secondary to a lower heart rate and stroke volume response [7, 9••, 10, 14]. However, non-cardiopulmonary peripheral factors also contribute to the lower VO_{2peak} [6••, 7, 9••, 10, 15, 16••].

The aim of this brief review is to discuss the impact that abnormal skeletal muscle morphology and function play in limiting exercise tolerance in HF patients, and the role of both exercise training and novel treatment strategies to improve skeletal muscle morphology and function.

Role of Skeletal Muscle Abnormalities in HFrEF

It has been long known that HFrEF patients have multiple histological and metabolic skeletal muscle abnormalities including skeletal muscle atrophy [17–21], decreased oxidative (type I) fibers and enzymes [22–26], mitochondrial volume density [22], and capillary-fiber ratio [23, 26] (Table 1). Prior studies demonstrate that skeletal muscle atrophy and reduced lower extremity muscle mass contribute to decreased VO_{2peak} and muscle strength in HFrEF [18, 20, 21, 27, 28]. Moreover, a reduction in the percent of type I fibers and oxidative enzymes coupled with abnormal mitochondrial respiration contributes to impaired oxidative metabolism with an earlier shift towards glycolytic metabolism resulting in decreased aerobic endurance (Table 1).

Weiss et al. [16••], using ^{31}P skeletal muscle spectroscopy, examined skeletal muscle energetics (PCr depletion and inorganic phosphate accumulation rates) at rest and during graded (plantar flexion) exercise test in healthy subjects as well as those with HFrEF and HFpEF. A novel finding was that both NYHA class II and III HF patients had significantly faster rates of exercise-induced PCr depletion compared with healthy individuals and NYHA class I HFrEF patients. Finally, the rate of PCr decline during plantar flexion exercise was correlated ($r^2 = 0.83$) with overall exercise time indicating that a rapid exercise-induced depletion of PCr in symptomatic HFrEF and HFpEF patients is closely related to exercise intolerance.

Role of Skeletal Muscle Abnormalities in HFpEF

Emerging evidence demonstrates that peripheral "non-cardiopulmonary" factors are important determinants of reduced VO_{2peak} in HFpEF [6••, 9••], mirroring many of the concepts previously only associated with HFrEF. Haykowsky et al. [6••] reported that the strongest independent predictor of VO_{2peak} was the change in a-vO_2diff from rest to peak exercise in elderly HFpEF patients. The mechanisms responsible for this impaired ability to augment a-vO_2diff during peak exercise were not studied; however, it was hypothesized that it may relate to intrinsic skeletal muscle abnormalities that underlie reduced skeletal muscle oxygen delivery and/or impaired oxygen utilization.

Given that the majority of oxygen consumed during exercise occurs in the exercising muscle [2•, 10, 42], a decline in metabolically active tissue may limit exercise tolerance. Using dual-energy X-ray absorptiometry and maximal exercise testing, Haykowsky et al. [30] measured lean body mass and VO_{2peak} in older HFpEF patients and age-matched healthy controls. Older HFpEF patients had significantly reduced percent total and leg lean mass, and decreased peak VO_2 indexed to lean body mass versus healthy controls [30] (Table 1). Also, the change in VO_{2peak} with increasing percent leg lean mass was blunted in HFpEF compared to healthy controls [30].

These investigators also reported significantly increased intermuscular adipose tissue and ratio of intermuscular adipose to skeletal muscle area in HFpEF patients [43, 44] (Table 1). Both intermuscular adipose area and intermuscular adipose to skeletal muscle area were independent predictors of VO_{2peak} in HFpEF [43], suggesting it is not only the loss of lean body mass, but the quality of muscle that determines VO_{2peak}. Notably, skeletal muscle atrophy and increased intermuscular adipose tissue detected in HFpEF is similar to skeletal muscle changes that occur as part of aging physiology [45]. This raises important considerations regarding the overlap of HFpEF and aging physiology.

Additional histological and metabolic skeletal muscle abnormalities [31••, 33••, 35] (Table 1) have also been demonstrated in HFpEF patients. Kitzman et al. [31••] showed a shift in skeletal muscle fiber type distribution towards a higher percentage of glycolytic (type II) fibers, with a subsequent reduction in percent type I (oxidative) fibers, type I/type II fiber ratio, and capillary-to-fiber ratio compared to age-matched healthy controls. Molina et al. [33••] extended those findings by demonstrating that skeletal muscle oxidative capacity, mitochondrial content, and mitochondrial fusion were abnormal in older patients with HFpEF, and that they were associated with reduced VO_{2peak} and 6-min walk distance. Cumulatively, these findings suggest that a fiber type shift

Table 1 Summary of skeletal muscle abnormalities that contribute to exercise intolerance in patients with heart failure with reduced or preserved ejection fraction

Variable	HFrEF vs control	HFpEF vs control
Morphology		
Percent lean body mass	↓ [17–20, 27, 28] ↔ [29]	↓ [30]
% type I fibers	↓ [22–24, 26]	↓ [31••]
% type II fibers	↑ [22–24, 26]	↑ [31••]
Capillary density	↓ [22, 23, 25, 26, 32] ↔ [24]	↓ [31••]
Mitochondrial volume density	↓ [22–26]	↓ [33••]
Mitochondrial enzyme density	↓ [22]	↓ [33••]
Function		
Peak exercise a-vO_2diff	↔ [7, 8, 9••, 10] ↑ [34]	↓ [6••, 9••, 35] ↔ [14, 36]
Sub-maximal exercise oxidative metabolism	↓ [15, 16••, 21, 37–41]	↓ [16••, 35]

↑ increase,↓ decrease, ↔ stays the same, a-vO_2diff arterial-venous oxygen content difference, HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction

from oxidative to glycolytic fibers coupled with abnormal mitochondrial function also contributes to impaired oxidative metabolism during exercise in HFpEF. Consistently, prior studies assessing skeletal muscle metabolism during small muscle mass exercise with ^{31}P magnetic resonance spectroscopy showed a marked reduction in leg muscle oxidative metabolism in HFpEF patients compared to healthy individuals [16••, 35] (Table 1). Overall, impaired mitochondrial oxidative metabolism appears to be an important contributor to reduced exercise tolerance in HFpEF.

Exercise Interventions Improve Exercise Tolerance and Skeletal Muscle Function in HFrEF

Aerobic exercise training has been shown to increase VO_{2peak} by 2.6–5.4 ml/kg/min [46, 47] compared to usual care in patients with HFrEF. Whereas many cardiovascular experts assumed this was determined by cardiac performance, in fact much of this performance improvement is mediated by favorable adaptations in skeletal muscle morphology and function [42, 48–52] (Table 2). Hambrecht et al. [48–50] found that 6 months of aerobic exercise training (walking and cycling) significantly increased skeletal muscle mitochondrial and cytochrome c oxidase volume density, percentage of type I (oxidative) fibers, and number of capillaries that supply each of these fibers in HFrEF. Cytochrome c oxidase volume density also increased, and was associated with improved VO_{2peak} [50].

Improvements in skeletal muscle oxidative capacity, capillary density, and mitochondrial volume density have also been demonstrated after small muscle mass exercise training in patients with HFrEF [42, 51, 59] (Table 2). Esposito et al. [42] showed that 8 weeks of unilateral knee extension exercise significantly increased vastus lateralis muscle fiber cross-sectional area, percent type I fibers, muscle capillarity, and mitochondrial volume density. The improvement in skeletal muscle morphology with training correlated with the increase in VO_{2peak} assessed during maximal cycle exercise [42]. Overall, these studies highlight the ability of aerobic exercise training to induce rapid adaptations in skeletal muscle morphology and function in patients with HFrEF, and to improve exercise tolerance and VO_{2peak}.

Improvements in exercise tolerance and VO_{2peak} have also been observed following resistance training performed alone [53, 67–69] or combined with aerobic exercise training [68, 70] in HFrEF. Despite the paucity of studies investigating the peripheral adaptations associated with resistance exercise [53], it appears that increases in oxidative muscle fiber cross-sectional area and oxidative enzyme capacity are likely contributors. Pu et al. [53] demonstrated that 10 weeks of high-intensity progressive resistance exercise training in older women with HFrEF increased skeletal muscle type I fiber area and citrate synthase activity, and were predictive of improvements in functional capacity (assessed by 6-min walk distance).

Exercise Interventions Improve Exercise Tolerance and Skeletal Muscle Function in HFpEF

Similar to HFrEF, aerobic exercise training has been shown to increase VO_{2peak} by 2.1–3.0 ml/kg/min [71–74, 75•] compared to usual care in patients with HFpEF [58••, 62, 76–79]. However, in contrast to HFrEF, this form of training is not associated with increased peak exercise cardiac output [62, 63••]. Specifically, Haykowsky et al. [63••] demonstrated that 84% of the improvement in VO_{2peak} following 16 weeks of aerobic exercise training was attributed to increases in peak exercise a-vO_2diff (Table 2). Similarly, Fu et al. [62] recently reported that 12 weeks of high-intensity interval exercise training significantly increased VO_{2peak}, with the

improvements in VO_{2peak} driven by increases in estimated peak exercise a-vO_2diff and leg muscle oxygenation, with little or no change in peak exercise cardiac output. The mechanisms responsible for these exercise-mediated peripheral adaptations that underlie improvements in peak exercise a-vO_2diff seem likely to relate to improved peripheral muscle perfusion and/or enhanced mitochondrial function.

Novel Therapies to Target Skeletal Muscle Abnormalities in HF

As the key role of skeletal muscle in exercise tolerance has been recognized, multiple initiatives have been underway to improve skeletal muscle performance. Supplementing nutrition has demonstrated benefit as it responds to the hypercatabolic and malnourished state of typical HF patients [80]. Paradoxically, it has also been demonstrated that caloric restriction is also beneficial [81]. In the latter, benefits are mediated by healthful molecular signaling that stimulates clinical benefits [82]. In addition to dietary manipulations, a multitude of pharmacological-based research efforts are underway in which novel therapies are being studied to promote skeletal muscle growth in adults with sarcopenia, and which can presumably be applied to those with HF.

Nutrition

Several HFrEF studies have substantiated the premise of amino acid supplementation to improve exercise tolerance [83•, 84•, 85]. In a randomized controlled trial by Aquilani et al. [83•], the benefits of an oral nutritional mixture of amino acids (4 g twice daily) versus a placebo were compared in 95 stable elderly HFrEF patients (NYHA Class II–III). VO_{2peak} improved in the nutrition supplemented group. More recently, Lombardi et al. [84•] demonstrated that supplementing HFrEF patients (NYHA Class II–III) with one specific amino acid (L-carnosine) every day (500 mg dosage) for 6 months significantly improved exercise tolerance and functional capacity. These findings suggest that amino acid supplementation may improve exercise tolerance in patients with HFrEF as a result of correcting an amino acid deficiency either within cardiac or skeletal muscle. While it seems probable that similar nutritional supplementation would benefit patients with HFpEF as much as those with HFrEF, studies in this population have not yet been completed.

In contrast to nutritional supplements, nutritionally balanced caloric restriction has been demonstrated to trigger vital subcellular benefits in older adults through a very different mechanism of action [86]. Key molecular signaling pathways (e.g., mTor and AMPkinase) are suppressed or stimulated, with downstream clinical benefits [86]. In older, obese individuals without HF, caloric restriction has been shown to improve LV mass and diastolic function, exercise capacity, body composition, and skeletal muscle function [87–90].

Kitzman et al. [58••] studied similar principles in older, obese HFpEF patients, comparing the effects of 20 weeks of caloric restriction or aerobic exercise training alone, or in combination, on VO_{2peak} and quality of life. Aerobic exercise training (+ 1.2 ml/kg/min) and caloric restriction (+1.3 ml/kg/min) both yielded similar improvements in VO_{2peak} and functional capacity, while a combination of both (aerobic exercise + caloric restriction) caused an additive effect on VO_{2peak} (+ 2.5 ml/kg/min). Both aerobic exercise training and caloric restriction reduced body weight and fat mass, while caloric restriction improved muscle leg muscle quality, and reduced abdominal and thigh subcutaneous fat. In addition, the change in VO_{2peak} was positively correlated with both the change in percent lean mass and the change in thigh muscle to intermuscular fat ratio. These findings demonstrate that caloric restriction alone or combined with aerobic exercise yield favorable improvements in body composition (including improved muscle quality).

Nonetheless, the long-term efficacy of caloric restriction for improving clinical outcomes in HF patients entails many aspects of clinical complexity that are inherently problematic. Older adults who are prone to developing HF are also susceptible to sarcopenia and frailty. Benefits of caloric restriction must be counterbalanced by the risks it may impose as it undercuts vital nutrition in patients who are relatively more enfeebled. Furthermore, observational studies report an obesity paradox in this patient population [91, 92], with overweight and obese HFpEF patients having better survival outcomes than those who are normal or underweight according to body mass index.

Novel Pharmacological Approaches

Pharmacological approaches to skeletal muscle growth remain an active area of research. Initiatives primarily target age-related sarcopenia, but with a common presumption that older HF patients may benefit disproportionately due to the additive effects of aging and disease on skeletal muscle atrophy and weakening. Pharmacotherapies targeting myostatin inhibition remain a particularly compelling consideration [93]. Myostatin is a highly conserved member of the transforming growth factor-beta superfamily that signals through the activin receptor type IIB (ActRIIB). Myostatin stimulates catabolic processes, and inhibits transcription of genes that underlie proliferation of skeletal muscle precursor cells. Thus, myostatin inhibition may moderate or reverse skeletal muscle loss and functional decline. Nonetheless, trials of myostatin inhibitors have revealed many side effects that heretofore have diminished enthusiasm for clinical application (e.g., aseptic meningitis, diarrhea, confusion, fatigue, involuntary muscle contractions) [93]. Nonetheless, ongoing studies with the anti-ActRII

Table 2 Summary of exercise training-mediated skeletal muscle adaptations that contribute to improved exercise tolerance in patients with heart failure with reduced or preserved ejection fraction

Variable	HFrEF	HFpEF
Morphology		
Lean body mass	↔ [53–57]	↔ [58••]
% type I fibers	↑ [42, 49, 53] ↔ [51, 59]	Not studied.
% type II fibers	↓ [42, 49] ↔ [51, 59]	Not studied.
Capillary density	↑ [42, 48, 51]	Not studied.
Mitochondrial volume density	↑ [42, 49, 50]	Not studied.
Mitochondrial enzyme density	↑ [42, 49–53, 59]	Not studied.
Function		
Peak exercise a-vO_2diff	↑ [42, 50, 60, 61] ↔ [62]	↑ [62, 63••]
Sub-maximal exercise oxidative metabolism	↑ [56, 64–66]	Not studied.

↑ increase,↓ decrease, ↔ stays the same, a-vO_2diff arterial-venous oxygen content difference, HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction

antibody "Bimagrumab" (BYM338) remain an eagerly anticipated focus of investigation [94].

Related research is focused on integrated regulatory mechanisms that determine muscle metabolism and growth. In part, this also relates to myostatin pathways, as myostatin also inhibits anabolic pathways in skeletal muscle in response to pro-growth signals (e.g., insulin and insulin-like growth factor-1). Moreover, in addition to myostatin inhibition, supplementation of anabolic agents (e.g., testosterone) has been an active area of investigation. While persistent concerns regarding secondary risks of testosterone (e.g., fluid retention, gynecomastia, prostate tumors, and adverse lipid profiles) have diminished enthusiasm for clinical applications, there is still strong interest in its therapeutic potential. In contrast to early studies that utilized high-dose testosterone, those using more physiological testosterone doses achieve greater safety and benefit [95]. Furthermore, as compared to oral formulations, transdermal or intramuscular administration is safer and better tolerated [96]. Furthermore, interest in selective androgen-receptor modulators (SARMs) like enobosarm has advanced as an alternative means of treating muscle and bone disorders, with relatively fewer side effects than testosterone [97].

Conclusions

Heart failure is associated with multiple skeletal muscle abnormalities (reduced lean mass, oxidative fiber percentage, capillarity, oxidative enzyme capacity, and mitochondrial volume), which impair oxygen uptake and utilization and contribute greatly to exercise intolerance. Large and small muscle mass exercise training induces favorable adaptations in skeletal muscle morphology and function (increased oxidative fiber percentage, capillarity, oxidative enzyme capacity, and mitochondrial volume) in patients with HFrEF. Further, these adaptations are associated with increased exercise tolerance. In patients with HFpEF, improvements in exercise tolerance following aerobic exercise training are primarily mediated through peripheral "non-cardiac" factors with little to no change in cardiac output. The contribution of skeletal muscle adaptations to improved exercise tolerance in HFpEF remains unknown and warrants further investigation. Furthermore, adjunctive strategies, both to supplement nutrition with amino acids, and to stimulate anabolic molecular pathways in skeletal muscle with caloric restriction are beneficial, with synergy observed when combined with exercise training. Parallel investigations are exploring the utility of pharmacological strategies to similarly stimulate healthful molecular signaling and anabolic cell metabolism for older patients who have both sarcopenia and HF, but these efforts remain early in their evolution, and no immediate clinical applications.

Funding Information Dr. Tucker is financially supported by the American Heart Association (AHA) Postdoctoral Fellowship Grant (AHA Award Number: 18POST33990210). Dr. Haykowsky is financially supported by the Moritz Chair in Geriatrics at the University of Texas at Arlington, and the National Institutes of Health (NIH) R15NR016826-01 grant. Dr. Forman is financially supported by the National Institute of Health grants R01AG060499-01 (NIA), R01AG051376 (NIA), U01 AR071130 (Commonwealth Fund), and P30 AG024827 (NIA). He is also funded by the Veterans Affairs (VA) Rehabilitation Research and Development Service (RR&D) F0834-R grant.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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