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Skeletal muscle abnormalities in heart failure with preserved ejection fraction

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Abstract

Almost half of all heart failure (HF) disease burden is due to HF with preserved ejection fraction (HFpEF). The primary symptom in patients with HFpEF, even when well compensated, is severe exercise intolerance and is associated with their reduced quality of life. Recently, studies showed that HFpEF patients have multiple skeletal muscle (SM) abnormalities, and these are associated with decreased exercise intolerance. The SM abnormalities are likely intrinsic to the HFpEF syndrome, not a secondary consequence of an epiphenomenon. These abnormalities are decreased muscle mass, reduced type I (oxidative) muscle fibers, and reduced type I-to-type II fiber ratio as well as a reduced capillary-to-fiber ratio, abnormal fat infiltration into the thigh SM, increased levels of atrophy genes and proteins, reduction in mitochondrial content, and rapid depletion of high-energy phosphate during exercise with markedly delayed repletion of high-energy phosphate during recovery in mitochondria. In addition, patients with HFpEF have impaired nitric oxide bioavailability, particularly in the microvasculature. These SM abnormalities may be responsible for impaired diffusive oxygen transport and/or impaired SM oxygen extraction. To date, exercise training (ET) and caloric restriction are some of the interventions shown to improve outcomes in HFpEF patients. Improvements in exercise tolerance following aerobic ET are largely mediated through peripheral SM adaptations with minimal change in central hemodynamics and highlight the importance of targeting SM to improve exercise intolerance in HFpEF. Focusing on the abnormalities mentioned above may improve the clinical condition of patients with HFpEF.

Keywords HFpEF · Exercise intolerance · Skeletal muscle abnormalities · Skeletal myopathy · Oxygen extraction

Introduction

Heart failure (HF) is a known cause of significant mortality and morbidity worldwide in middle-aged and older adults. In the USA, the lifetime risk of HF is estimated to be 1 in 5 at age 40 [1], and is projected to increase by 46% by 2030 [2]. Almost half of all HF disease burden is due to HF with preserved ejection fraction (HFpEF) [2]. In the highest age decile (≥ 90 years old), nearly all patients with HF have preserved EF. HFpEF is a clinical syndrome associated with poor health-related quality of life (HRQOL), substantial healthcare resource utilization, and mortality, in large part related to high rates of hospitalizations in patients with HF [3]. After HF hospitalization, the 5-year survival of HFpEF is a dismal 35%, worse than many cancers [4], although HFpEF was initially considered a hemodynamic disorder characterized by hypertension, cardiac hypertrophy, and diastolic dysfunction, which is now recognized as a systemic syndrome involving the heart, lungs, kidneys, skeletal muscle (SM), adipose tissue, and vascular system [5].

The primary symptom in patients with HFpEF is reduced exercise tolerance (peak exercise oxygen uptake, VO_2peak) and is associated with their reduced HRQOL [6, 7]. In addition, declines in VO_2peak in older HF patients are compounded by comorbidities, aging, sarcopenia, and myosteatosis (increased muscle fat infiltration), malnutrition, and physical inactivity [6–8]. VO_2peak is defined as the highest achievable rate at which oxygen can be transported

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from air to tissues and utilized by the mitochondria during maximal exercise. In accordance with the Fick principle [VO_2 = Cardiac output (CO) × Arterial-venous oxygen difference (a-vO_2Diff)], the decreased VO_2peak in HFpEF may be due to abnormalities in convective and diffusive O_2 transport and/or impaired SM extraction and utilization [9].

It has traditionally been assumed that reduced exercise CO was the primary factor limiting exercise intolerance in HFpEF. Later, other investigators found that the blunted CO was secondary to chronotropic incompetence (CI) [7, 10, 11]. Indeed, approximately 30 to 50% of patients with HFpEF are thought to have CI manifested by a lower than predicted maximal HR during symptom-limited exercise [7, 10, 11]. Although VO_2peak has been observed to correlate with both changes in CO and a-vO_2Diff, recent studies showed that reduced O_2 extraction accounts for at least 50% of the reduction in VO_2peak and is a stronger independent predictor of VO_2peak than exercise CO (Fig. 1) [6, 12, 13]. Moreover, Haykowsky et al. has shown that the improvement in peak a-vO_2Diff accounted for the nearly all of the increase VO_2peak following exercise training (ET) [14]. The mechanisms responsible for this impaired ability to augment a-vO_2Diff during peak exercise might relate to impaired diffusive oxygen transport due to peripheral/microvascular dysfunction and/or SM abnormalities that result in impaired oxygen extraction and utilization (Fig. 2) [6, 9, 12–21].

This review combines current clinical knowledge and fundamental biological mechanisms to address the essential and emerging issue of SM abnormalities in HFpEF. We will briefly discuss the role of ET and novel treatment strategies to improve SM morphology and function.

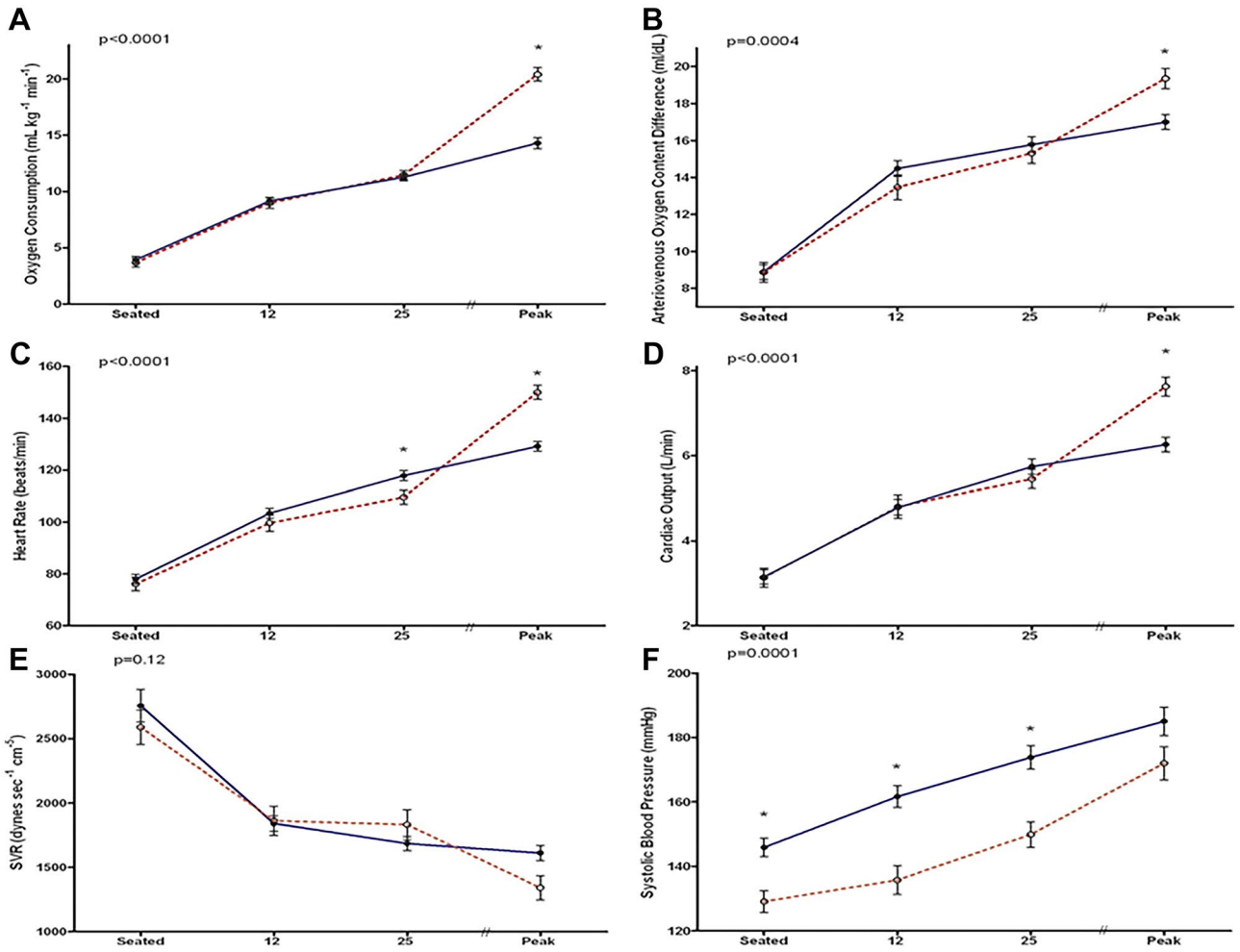

Fig. 1 Comparison at seated rest, 12 W, 25 W, and peak exercise between HFpEF patients and HCs. **A** Oxygen consumption, **B** arteriovenous oxygen content difference, **C** heart rate, **D** cardiac output, **E** systemic vascular resistance (SVR), and **F** systolic blood pressure. All variables adjusted for sex (*$p < 0.05$). The p-value at the upper left of each panel represents the group-by-intensity interaction. Dashed lines represent healthy controls (HC), and solid lines represent patients with heart failure with preserved ejection fraction (HFpEF) (reproduced from JACC with permission. J Am Coll Cardiol. 2011; 58:265–74)

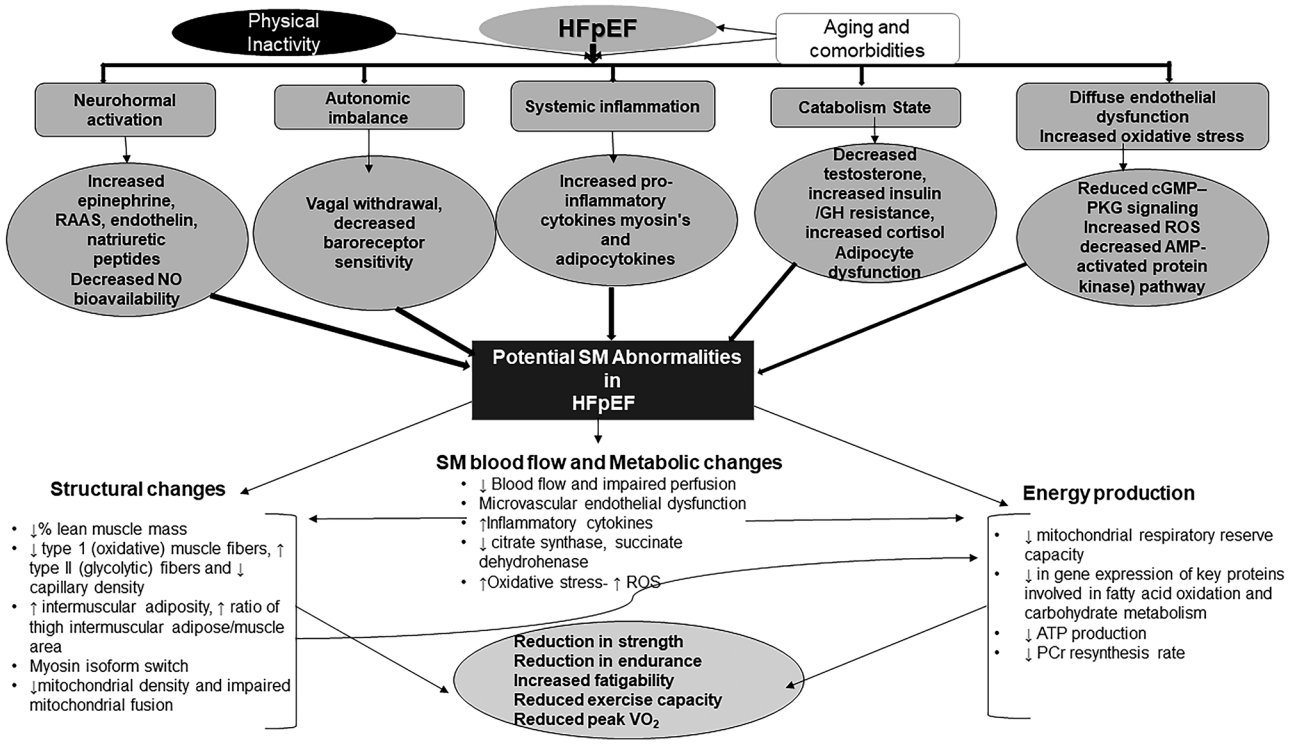

Fig. 2 Potential causes for the skeletal muscle abnormalities in HFpEF. HFpEF, heart failure with preserved ejection fraction; RAAS, renin angiotensin aldosterone system; NO, nitric oxide; GH, growth hormone; ROS, reactive oxygen species; cGMP, cyclic guanosine monophosphate; PKG, protein kinase; SM, skeletal muscle; VO_2, oxygen consumption; ATP, adenosine triphosphate; Pcr, phosphocreatine

Impaired SM blood flow in HFpEF

SM is one of the largest organs in the human body, accounting for approximately 40% of total body mass, and acts as a major site for protein storage and glucose disposal. Muscle-specific blood flow can increase almost 100-fold from rest to maximal exercise [22, 23]. The overall regulation of SM blood flow is achieved through sympathetic-mediated redistribution of blood from non-exercising regions to the working muscles coupled with metabolic-mediated vasodilation "autoregulation" in the exercising muscles [24, 25]. Within SM, blood flow regulation and oxygen delivery result from integrating several stimuli, including the mechanical effects of contraction, local metabolic and endothelium-derived substances, vasoactive factors associated with erythrocytes, and the sympathetic nervous system.

Prior animal studies showed that obese-HFpEF rats demonstrated an abnormal leg blood flow response to contractions with fiber type-specific structural capillary loss [26, 27]. Supporting this finding, clinical studies found that non-invasive (ultrasound) measurements of leg blood flow and vascular conductance are markedly decreased in patients with HFpEF during exercise [28–31]. This suggests that impaired autoregulation in the exercising SM vasculature may play a key role in exercise intolerance. However, abnormal blood flow response to exercise is inconsistent in HFpEF studies [15, 21, 32, 33]. This may be due to differences in the muscles studied or different measurement techniques or heterogeneity.

Additionally, Houstis et al. found that the deficit in a-vO_2Diff was related to a 36% reduction in the patient's SM diffusion capacity, and improved diffusion capacity resulted in increased VO_2peak [15]. Regional vasodilation in SM is mediated in part by nitric oxide (NO) and prostaglandin-induced vasodilation. Patients with HFpEF have impaired NO availability, particularly in the microvasculature, which might contribute to SM diffusion capacity (Fig. 3) [7, 34, 35]. Borlaug et al. found that systemic vascular conductance and microvascular reserve were positively related to VO_2peak in HFpEF [7]. Similarly, microvascular endothelial dysfunction was an independent predictor of poorer prognosis, mainly readmission, in patients with HFpEF [36]. A consequence of the blunted microvascular reserve is that it may be associated with decreased diffusive oxygen transport to the exercising muscle, which would reduce exercise tolerance. Indeed, peripheral endothelial dysfunction might impair matching of perfusion to regional demand in SM microcirculation [37].

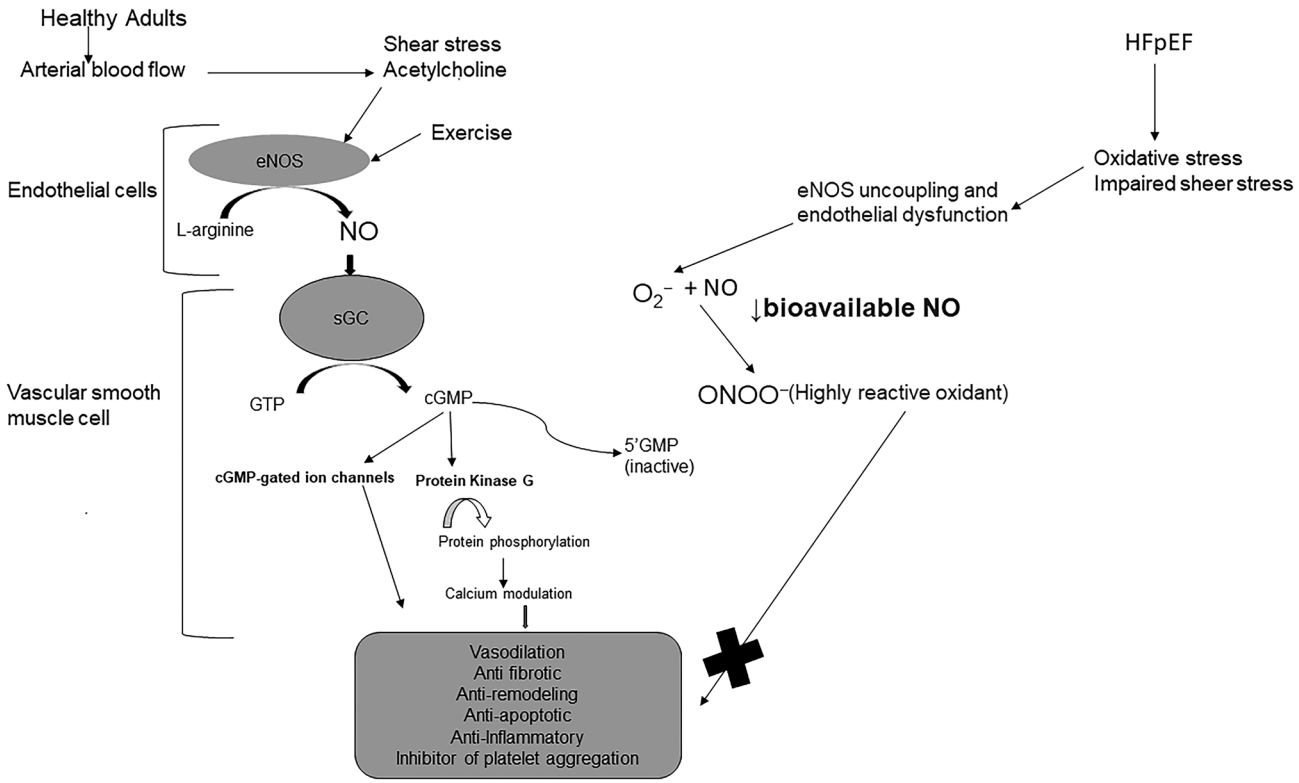

Fig. 3 Role of nitric oxide in skeletal muscle autoregulation. eNOS, nitric oxide synthase; NO, nitric oxide; sGC, soluble guanylate cyclase; GTP, guanosine-5′-triphosphate; cGMP, cyclic guanosine monophosphate; HFpEF, heart failure with preserved ejection fraction; O2-, superoxide; ONOO-, peroxynitrite

In addition, Kitzman's group reported that compared with healthy controls (HCs), older HFpEF patients had a reduced capillary-to-fiber ratio ($1.35 \pm .32$ versus 2.53 ± 1.37, $p = .006$) (Fig. 4) [18] and were a significant independent predictor of VO_2peak (partial $r = .34$, $p = .02$). Capillary rarefaction disrupts the microvascular oxygenation dynamics in SM, and one of the mechanisms that could contribute to such rarefaction is impaired NO-mediated vasodilation [38, 39]. Of note, the reduced microvascular density in SM in older HFpEF patients matches a similar finding in cardiac

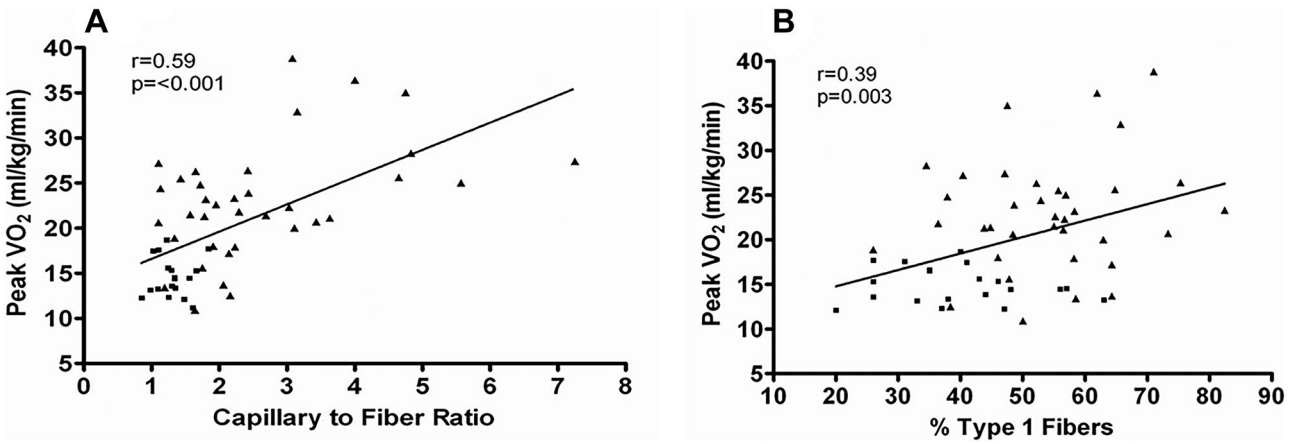

Fig. 4 Relationship of capillary-to-fiber ratio (**A**) and percentage of type I muscle fibers (**B**) with peak O_2 uptake (VO_2) in older patients with heart failure with preserved ejection fraction (■) and age-matched healthy control subjects (▲) (reproduced from Heart Failure Clinic with permission. Heart Fail Clin. 2017; 13: 485–502)

muscle as reported by Mohammed et al. [40]. If a systemic process is responsible, then adverse effects on striated muscle in both cardiac and SM compartments would be expected [41]. In addition, HFpEF patients are commonly obese. The obligate perfusion to excess adipose tissues might diminish proper flow matching to metabolism, contributing to a lower peak a-vO_2Diff [42, 43].

Abnormalities in SM mass and composition

Most of the oxygen consumed during exercise occurs in the active muscles; therefore, a loss in metabolically active tissue (sarcopenia) may contribute to exercise intolerance in HFpEF patients. Animal models of HFpEF (hypertensive or cardiometabolic) have shown decreased muscle mass [26, 27]. A recent cardiometabolic obese-HFpEF rat model induced multiple SM alterations in the rat hindlimb, including impaired muscle mechanics related to shortening velocity, fiber atrophy, and the capillary loss that implies a perfusive oxygen delivery limitation [26]. Haykowsky et al. measured lean body mass and VO_2peak in older HFpEF patients and age-matched HCs using dual-energy X-ray absorptiometry and maximal exercise testing [17]. Older HFpEF patients had significantly reduced total and lean leg mass and decreased VO_2peak indexed to lean body mass versus HCs. Also, the change in VO_2peak with increasing percent leg lean mass was blunted in HFpEF compared to HCs (the slope of the relationship of peak VO_2 with percent leg lean mass, HFpEF (11 ± 5 ml/min) versus HCs (36 ± 5 ml/min; $p < .001$)), suggesting that SM hypoperfusion or impaired O_2 utilization by the active muscles may play an important role in limiting exercise performance in older HFpEF patients. Haykowsky et al., using phase-contrast magnetic resonance imaging, extended these results by directly characterizing thigh muscle composition and found that older patients with HFpEF had increased thigh intramuscular fat (IMF), whether expressed as absolute area or as a proportion of the thigh compartment (TC) despite the similar amount of subcutaneous fat. Furthermore, the ratio of IMF/SM was increased, and both IMF area (partial $r = -.51$, $p = .002$) and IMF/SM ratio (partial $r = -.45$, $p = .006$) were significant independent predictors of peak exercise VO_2 (HFpEF versus HC group, IMF area (35.6 ± 11.5 versus 22.3 ± 7.6 cm^2, p = .01), percent IMF/TC (26 ± 5 versus $20 \pm 5\%$, $p = .005$), and the ratio of IMF/SM ($.38 \pm .10$ versus $0.28 \pm .09$, $p = .007$)) (Fig. 5) [20].

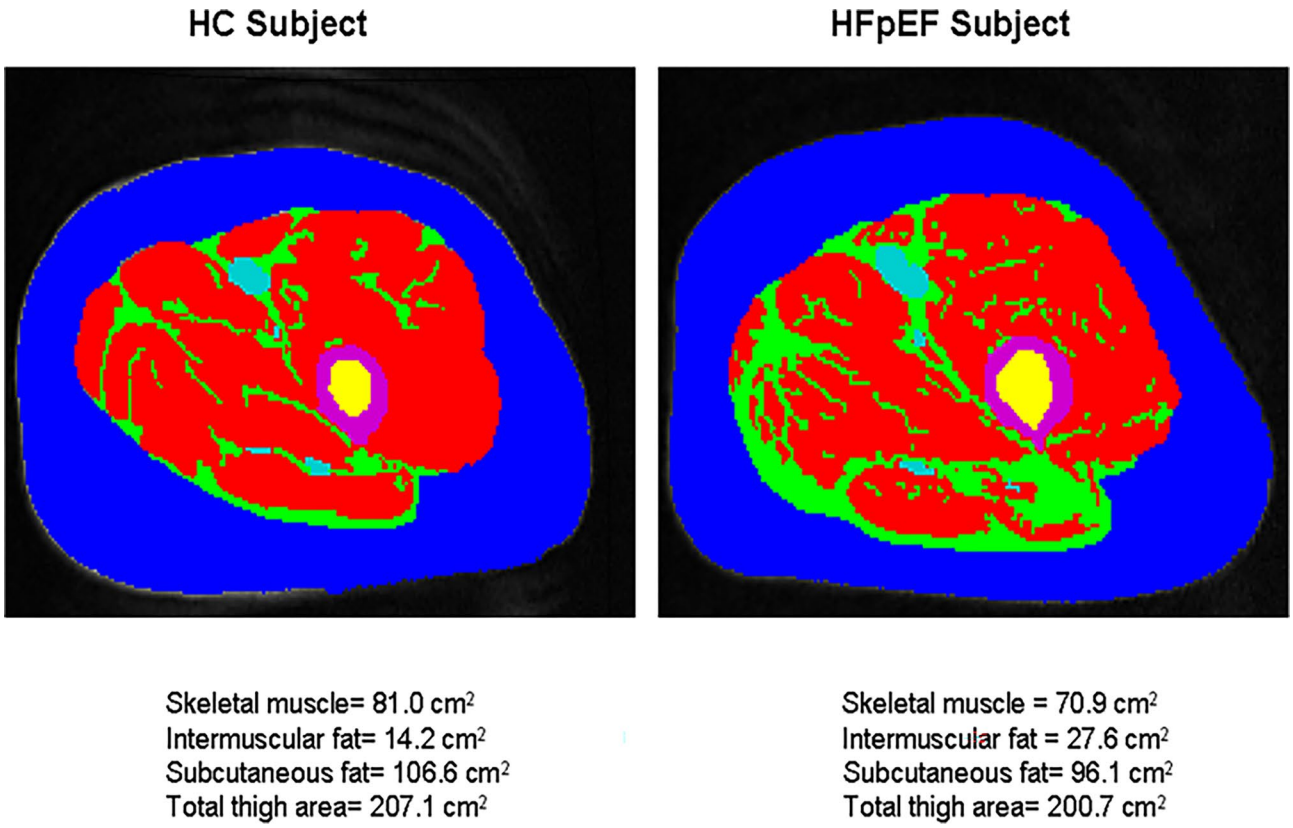

Fig. 5 Magnetic resonance imaging axial image of the mid-thigh in a patient with heart failure with preserved ejection fraction (HFpEF) and healthy controls (HC) (reproduced from Heart Failure Clinic with permission. Heart Fail Clin. 2017; 13: 485–502)

Increased myosteatosis is inversely related to the mitochondrial density and suppresses mitochondrial biogenesis [44]. Weiss et al. also found markedly increased intermuscular adipose tissue in HFpEF compared to HF with reduced ejection fraction (HFrEF) patients (SM fat fraction was increased almost threefold in HFpEF patients as compared to HCs, in contrast, nonsignificantly increased in HFrEF patients) [45].

Myosteatosis may reduce VO_2peak in patients with HFpEF through several mechanisms described previously. 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 nonobese younger healthy sedentary women [46]. Interestingly, Zamani et al. recently found that body composition (measured by whole-body DEXA), particularly the degree of adiposity, was correlated with a-vO_2Diff, with increasing fat associated with decreased a-vO_2Diff (correlation coefficient − .61. $p < .001$) [21]. Thus, increased thigh IMF in older patients with HFpEF may "steal" the blood usually delivered to the active muscles during exercise, thereby reducing oxygen delivery to active muscles. Adipose within the SM is also metabolically active and can impair oxidative metabolism and mitochondrial function. Inflammatory cytokines produced by adipocytes also have direct catabolic effects on SM [41, 44].

SM is divided into two broad types based on fiber types—type I (slow-twitch "oxidative") and type II (fast-twitch "glycolytic") muscle fibers. At the microscopic level, SM biopsies (vastus lateralis muscle) from HFpEF patients showed a reduced percentage of type I fibers and reduced type I-to-type II fiber ratio as well as a reduced capillary-to-fiber ratio (in HFPEF versus HC patients, the percentage of type I fibers ($39.0 \pm 11.4\%$ versus $53.7 \pm 12.4\%$, $p < .001$), type I-to-type II fiber ratio ($.72 \pm .39$ versus $1.36 \pm .85$, $p = .001$)) (Fig. 4) [18]. The lower type 1 fibers correlate to decreased VO_2peak (partial $r = .40$, $p = .004$). Similarly, recently, Zamani et al. identified a marked difference in myofibre type present in HFpEF subjects, with a much lower percentage of type I fibers than either HCs or hypertensive subjects of similar age (70% in HCs versus 50% in HFpEF ($p < 0.01$) [47]. Compared with type II fibers, type I fibers have the greater oxidative capacity and mitochondrial density and contribute disproportionately to the ability to perform sustained aerobic exercise. While speculative, a reduction in the percentage of type I fibers could be associated with reduced oxidative capacity and mitochondrial density and contribute to prolonged oxygen uptake kinetics and reduced VO_2peak in HFpEF [48].

Recently, a study demonstrated increased levels of SM atrophy genes and proteins (transforming growth factor-β1, cathepsin L, myostatin-2, F-box only protein-32) in stable outpatients with HFpEF compared with HF HFrEF and HCs [49]. They also showed reduced gene expression of Akt-2, which is a rate limiting and a crucial step in protein synthesis. Cathepsin L plays a significant role in autophagy, a further important mechanism of muscle atrophy. Myostatin is a highly conserved member of the transforming growth factor-beta superfamily that signals through the activin receptor type IIB. The activation of the myostatin pathway was shown to negatively regulate muscle size primarily by inhibiting the Akt pathway leading to reduced protein synthesis and increased protein degradation [50].

Abnormalities in SM oxidative function in HFpEF

There are multiple SM abnormalities in HFpEF that impair oxygen utilization and appear to contribute to reduced VO_2peak (Fig. 2). Among these, growing evidence indicates that impaired mitochondrial function may be among the most consequential. When a muscle repeatedly contracts for long periods, the ATP supply needs to be constantly replenished through mitochondrial oxidative phosphorylation. If the intricate metabolic pathways within the mitochondria were to become altered and less efficient, endurance within the SM would decrease. As the sole mechanism for utilizing oxygen and fuel substrate to produce energy, mitochondrial health is obviously a critical determinant of VO_2peak. The rate of breakdown and resynthesis of high-energy phosphates during and following exercise are fundamental determinants of whole-body VO_2 during exercise and recovery.

In an animal model of HFpEF, Bowen et al. found multiple abnormalities, including reduced in situ mitochondrial respiratory reserve capacity, a key measure of SM oxidative phosphorylation that correlates well with VO_2peak in humans [27]. Among the patients with mitochondrial myopathies, VO_2peak is decreased despite normal cardiac function. These patients suffer from impaired oxidative metabolism in SM. SM relies more on substrate-level phosphorylation for energy production during exercise, leading to exaggerated circulatory and ventilatory responses (decreased VO_2 and increased CO response to exercise) [51]. Using [30] Phosphate magnetic resonance spectroscopy, Bhella and colleagues found the abnormal hemodynamic response to exercise, similar to that observed in patients with mitochondrial myopathies; however, only two patients were studied [13]. They suggested that HFpEF patients might display a hyperdynamic cardiac response to exercise with CO higher than expected for a given VO_2. This impairment may limit functional capacity by two mechanisms: (1) early SM fatigue and (2) metabolic signals to increase the CO response to exercise, which a left ventricle may poorly tolerate with elevated filling pressure [13]. Due to the relatively smaller sample size, these results cannot be generalized to broader patient populations with HFpEF. These preliminary results were

confirmed by Weiss et al., who performed serial magnetic resonance spectroscopy measurements of creatinine phosphate during calf extensor exercise to exhaustion and recovery in HFpEF patients compared with HFrEF patients and HCs. HFpEF patients had severe exercise intolerance associated with rapid high-energy phosphate depletion, which was observed early during exercise [45]. Furthermore, HFpEF patients had markedly delayed repletion of high-energy phosphate during recovery [45]. There was a strong correlation between the average rate of phosphocreatine decline during exercise and the maximum exercise time ($R^2 = .83$, $p < .001$).

Analyzing muscle biopsies from 20 HFpEF patients and 17 age-matched HCs, Molina et al. measured the expression of mitofusins 1 and 2 (Mfn1 and Mfn2), proteins localized to the mitochondrial outer membrane that plays an essential role in the fusion of these organelles (Mfn2 plays an important role in mitochondrial quality control by mediating complementation of organelles and the elimination of dysfunctional mitochondria by autophagy and citrate synthase is the key enzyme regulating oxidative metabolism). Protein expression of porin, Mfn2 (normalized to porin), and citrate synthase was significantly lower ($p = .01$, $p = < .001$, and $p = .01$ respectively) in SM tissue of patients with HFpEF compared to HCs (Fig. 6) [19]. In a recent study, Zamani et al. showed (mass spectrometry in muscle biopsy samples from 13 HFpEF participants) broad reductions in the proteins and complexes involved in energy fuel metabolism, including tricarboxylic acid cycle enzymes and the mitochondrial complexes that make up the electron transport chain in patients with HFpEF SM that correlated with exercise capacity, independent of peak oxygen delivery [47]. Bekfani et al. identified smaller mitochondria and reduced mitochondrial volume density in HFpEF SM compared with similarly aged controls [49]. They also described reductions in gene expression of key proteins involved in fatty acid oxidation and carbohydrate metabolism, alongside increased gene expression of proteins associated with muscle atrophy [49].

These observations suggest that HFpEF patients relied less on oxidative pathways during exercise, as evidenced by decreased oxidative phosphorylation ATP production rates, and more on anaerobic metabolism, as evidenced by increased anaerobic glycolysis ATP production rates [13, 15, 17–19, 45, 47, 49]. In addition, a previous study showed that AMP-activated protein kinase/glucose transporter-4 signaling is suppressed in SM in obese/hypertensive HFpEF rats and patients with metabolic syndrome (but not HFpEF), but might suggest that SM glucose metabolism is diminished in HFpEF [52]. It has also been described that increased circulating lipid

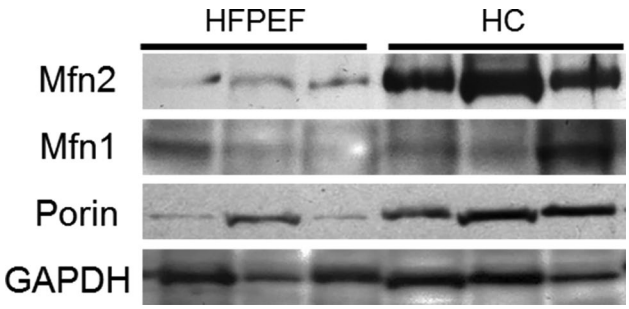

Fig. 6 Representative western blot bands from 3 patients with HFpEF and 3 healthy controls (HCs). For each protein, images were obtained from the same blot and exposure. A potential difference in skeletal muscle mitochondrial content was determined by analysis of porin expression. The samples were electrophoretically transferred to nylon polyvinyl difluoride (PVDF) membrane and the blots were incubated with commercially available primary antibodies to Mfn1 (1:1000), Mfn2 (1:1000), porin (1:1000), and GAPDH (1:2000) (Abcam, Cambridge, MA). Densitometry values for Mfn1 and Mfn2 were normalized to porin in order to account for differences in mitochondrial content. Measurement of porin was normalized to GAPDH. Normalization of mitofusins to porin, rather than GAPDH, was appropriate because these proteins reside on the mitochondrial outer membrane (reproduced from JACC with permission. JACC Heart Fail. 2016; 4:636–645)

metabolites, particularly the long-chain acylcarnitine metabolites derived from β-oxidation of free fatty acids (FFA) in HFpEF patients, may indicate that FFA metabolism is predominant in HFpEF [53]. Interestingly, and in contrast to HFrEF or HCs, patients with HFpEF cannot lower venous PO_2 during exercise and therefore demonstrate a blunted peripheral O_2 extraction response [13, 15, 171819, 45, 47, 49]. The extent of this impaired muscle O_2 extraction in HFpEF is likely explained, at least in part, by the significant mitochondrial abnormalities reported in patients with HFpEF [13, 15, 171819, 45, 47, 49]. Clearly, more studies are warranted to clarify the role of limitations to muscle O_2 diffusion in HFpEF. Potential causes for the SM abnormalities in HFpEF are shown in Fig. 2.

In addition to locomotory muscle, studies also linked respiratory muscle dysfunction to exercise intolerance in HFpEF, as shown by direct diaphragm contractility measures in experimental models. Multiple alterations to the diaphragm have been reported in the HFpEF rat model, including in vitro muscle weakness and fatigue alongside a type II-to-I fiber-type shift, fiber atrophy, and impaired in situ mitochondrial respiration [27]. These diaphragm alterations and dysfunction are not reversed following 8 weeks of aerobic ET [54]. Inspiratory (i.e., diaphragm) muscle weakness is evident and closely associated with symptoms of dyspnea and poor prognosis in patients with HFpEF [55–58].

Interventions to improve exercise intolerance and SM function in HFpEF

Exercise interventions

To date, ET, in addition to caloric restriction (CR), is one of the interventions shown to improve outcomes in HFpEF patients [59–61]. Several randomized controlled trials have examined the efficacy of ET to improve VO_2peak, 6-min walk distance, and HRQOL in patients with HFpEF [14, 61–71]. It appears that structured and supervised moderate continuous training, high-intensity interval training, and resistance training can benefit the patients with HFpEF [59]. Currently, no studies have examined the role of ET on SM morphology or function in HFpEF. However, studies suggested that peripheral mechanisms, such as improved SM perfusion and metabolism, likely play a major role in adapting ET in HFpEF [59, 60]. Specifically, Kitzman group demonstrated that 84% of the improvement in VO_2peak following 16 weeks of aerobic ET was attributed to increases in peak exercise a-vO_2Diff [14]. This is further supported by Fu et al. who reported that 12 weeks of high-intensity interval ET significantly increased VO_2 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 CO [67]. In fact, Bhella et al. reported that ET could favorably shift to more efficient muscle O_2 utilization in older HFpEF patients [13]. In addition, studies showed that ET in patients with HFpEF is associated with an improvement in VO_2 and HRQOL without significant changes in LV systolic or diastolic function [72, 73]. Even small muscle mass exercises, single-leg knee extensor exercises where the limiting role of the heart is minimized have been shown to induce various peripheral structural and functional adaptations improving VO_2 without changing CO in HF patients [74]. The possible mechanisms responsible for these exercise-mediated peripheral adaptations that underlie improvements in peak exercise a-vO_2Diff may be related to improved peripheral muscle perfusion and enhanced mitochondrial function. SM oxidative capacity and efficiency conceivably improved by ET in HFpEF patients since ET increased capillary and mitochondrial density, changed muscle fiber subtypes distribution, leg oxygen delivery, and diffusive conductance, and increased red blood cell capillary transit time through the SM vasculature in an animal model of HFpEF [26, 27, 54]. Bowen et al. showed that in Dahl salt-sensitive HFpEF rats, ET could prevent SM contractile dysfunction in the diaphragm and soleus, associated with preserved mitochondrial function [27]. Theoretically, improvement in SM mitochondrial function may significantly contribute to training-related improvements in VO_2peak in human HFpEF, which is known to be the case for HFrEF [60]. This can make a strong case for targeting SM, particularly mitochondrial function, to improve exercise intolerance in HFpEF.

Nutritional interventions

In contrast to nutritional supplements, CR has been demonstrated to trigger vital subcellular benefits in older adults through molecular signaling pathways (e.g., mTor and AMP kinase) that are suppressed or stimulated, with downstream clinical benefits [75]. In older, obese individuals without HF, CR has improved SM function. Kitzman et al. showed that CR improved muscle leg muscle quality and reduced abdominal and thigh subcutaneous fat in older HFpEF patients. In addition, the change in VO_2peak was positively correlated with both the change in percent lean mass ($r = 0.32$; $p = 0.003$) and the change in thigh SM to IMF ratio ($r = .27$; $p = .02$) [61].

Novel pharmacological interventions

Pharmacological approaches to SM growth remain an active area of research. The randomized clinical trial INDIE-HFpEF (Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure With Preserved Ejection Fraction) showed that inhaled inorganic nitrite (NO donor) did not improve VO_2peak and exercise capacity in HFpEF patients. However, inadequate drug delivery from the nebulizer was raised as an issue [76]. Recently, the same group showed the beneficial effects of inhaled and intravenous sodium nitrite on SM O_2 conductance, VO_2 kinetics, O_2 utilization during submaximal exercise, and alveolar-capillary membrane O_2 conductance HFpEF patients [77]. Several promising biologic and small molecule interventions are currently developing to rejuvenate SM, including myostatin inhibitors, selective androgen receptor modulators, and an activator of the fast SM troponin complex [78]. Nonetheless, trials of myostatin inhibitors have revealed many side effects that heretofore have diminished enthusiasm for clinical application.

There are now multiple agents in phase 2 clinical trials, primarily of older patients with physical disability associated with sarcopenia, targeting a variety of SM abnormalities, including mitochondrial dysfunction. Neladenoson bialanate is a partial adenosine A_1 receptor agonist that has been shown in preclinical models to improve SM mitochondrial function, enhance sarco/endoplasmic reticulum 2a activity, and optimize energy substrate utilization [77]. Among the HFpEF patients, the Partial AdeNosine A_1 Receptor Agonist in Patients With Chronic Heart Failure and Preserved Ejection Fraction (PANACHE) study showed no significant dose–response relationship detected for neladenoson with regard to the change in exercise capacity from baseline to 20 weeks [79].

Key knowledge gaps

1. How much do aging and non-cardiac comorbidities contribute to the SM abnormalities in HFpEF?
2. Are SM alterations a consequence of the disease process?
3. In future studies, do we need to study the SM morphology and function of much older, sedentary, and older active non-HF controls?
4. Are there overarching, systemic processes in HFpEF that trigger SM impairments?
5. Do pre-existing SM characteristics determine responses to HF?
6. Does exercise training ameliorate SM alterations in HFpEF, and what are the improvement mechanisms?

Conclusions

HFpEF is associated with multiple SM abnormalities, including (1) decreased muscle mass, reduced type I fibers, and type I-to-type II fiber ratio; (2) reduced capillary-to-fiber ratio; (3) myosteatosis; (4) reduction in mitochondrial content; (5) rapid depletion of high-energy phosphate during exercise with markedly delayed repletion of high-energy phosphate during recovery in mitochondria; (6) reductions in gene expression of key proteins involved in fatty acid oxidation and carbohydrate metabolism; and (7) increased gene expression of proteins associated with muscle atrophy. These abnormalities may be responsible for impaired diffusive oxygen transport and utilization by the active muscles and contribute significantly to exercise intolerance. To date, ET, in addition to CR, is one of the interventions shown to improve outcomes in HFpEF patients. In patients with HFpEF, improvements in VO_2peak following aerobic ET are largely mediated through peripheral "non-cardiac" factors with minimal change in CO. Specifically, SM oxidative capacity and efficiency can be improved by ET, which increases capillary and mitochondrial density, changes muscle fiber subtypes distribution, and increases red blood cell capillary transit time through the SM vasculature. Accordingly, SM may be an important target of therapy to improve HFpEF patients' aerobic endurance and VO_2peak.

Declarations

Conflict of interest Dr. Upadhya reported receiving honoraria from Novartis. Dr. Brubaker reported receiving honoraria from Merck and Boehringer Ingelheim.

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