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The Case for Skeletal Muscle Myopathy and Its Contribution to Exercise Intolerance in HFpEF

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Thirty-five years ago, Robert Luchi provided the first description of heart failure (HF) with preserved ejection fraction (HFpEF). HFpEF is now the most common form of HF in older adults, particularly women, and its prevalence is increasing and its prognosis is worsening. The primary symptom in chronic HFpEF, even when patients are well compensated and non-edematous, is severe exercise intolerance, characterized by exertional fatigue and dyspnea, associated with reduced quality-of-life.[1] Thus, understanding the pathophysiology of exercise intolerance in HFpEF is critical for improving patient-centered outcomes.

Exercise intolerance can be objectively and reproducibly measured as reduced peak exercise oxygen consumption (VO_2) by expired gas analysis. Using this technique, we and others have shown that the reduction in peak VO_2 in HFpEF is at least as severe as in age-matched persons with HF with severely reduced EF (HFrEF; mean EF 30%).[1] By the Fick equation, reduced peak VO_2 must be due to either reduced cardiac output (CO), reduced arterio-venous oxygen content difference (A-VO_2Diff), or a combination of these factors.[2] It has conventionally been assumed that reduced exercise CO is the sole driver of exercise intolerance in HFpEF. However, we showed that reduced exercise A-VO_2Diff accounts for at least 50% of the reduction in peak VO_2, and is a stronger independent predictor of peak VO_2 than exercise CO,[3] results confirmed by several others.[4]

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Reduced A-VO_2Diff during exercise can be caused by either reduced convective and diffusive oxygen delivery to and/or impaired oxygen utilization by the exercising skeletal muscle.[2] Indeed, it is now known that, as has been previously established in HFrEF, there are multiple skeletal muscle abnormalities in HFpEF that impair oxygen utilization and appear to contribute to reduced peak VO_2 [Table 1].[2, 5–11] Among these, growing evidence indicates that impaired mitochondrial function may be among the most consequential. As the sole mechanism for utilizing oxygen and fuel substrate to produce energy, mitochondrial health is obviously a critical determinant of peak VO_2. Multiple reports support that muscle mitochondrial function is impaired in HFpEF and is a significant contributor to reduced peak A-VO_2Diff and consequently peak VO_2. Our group showed that HFpEF patients have a downward-shifted relationship of peak VO_2 to % lean leg muscle mass, indicative of impaired oxygen utilization during exercise.[5] Using skeletal muscle biopsy, we showed that HFpEF patients have 3 separate findings relatively specific for mitochondrial dysfunction and that were significant independent predictors of their reduced peak VO_2: reduced type 1 (oxidative) muscle fibers;[6] reduced mitochondrial density;[7] and reduced citrate synthase, a key enzyme regulating oxidative metabolism.[7] We also found evidence of impaired mitochondrial fusion that was associated with reduced peak VO_2.[7] In an animal model of HFpEF, Bowen and colleagues found multiple abnormalities, including reduced *in situ* mitochondrial respiratory reserve capacity, a key measure of skeletal muscle oxidative phosphorylation that correlates well with peak VO_2 in humans.[9]

However, the strongest proof that a specific abnormality contributes to exercise intolerance is provided when the factor is measured *during* exercise. This is enabled by phosphorous magnetic resonance spectroscopy (MRS), a technique that allows continuous assessments of ATP and creatine phosphate (PCr) concentrations and turnover rates during and following exercise. 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, and PCr kinetics serve as an excellent indirect measure of mitochondrial oxidative capacity. Bhella and colleagues were the first to use MRS to report abnormal PCr kinetics during and after exercise in HFpEF, however only 2 patients were studied.[8]

In this issue of the journal, Weiss and colleagues report an elegantly designed study with sophisticated MRS measurements that markedly extends prior literature.[11] Weiss performed serial MRS measurements of PCr during calf extensor exercise to exhaustion and during recovery in HFpEF patients compared to HFrEF patients and healthy controls. Calf extensor exercise was an important feature, since the small mass of exercising muscle excludes reduced CO as a cause of exercise limitation, since even a severely weakened heart would have ample capacity for the work involved. Weiss found that compared to normal subjects, HFpEF patients had severe exercise intolerance, and this was associated with rapid depletion of high-energy phosphate, which was observed very early during exercise, further excluding reduced CO and muscle blood flow reserve as a cause. Furthermore, HFpEF patients had markedly delayed repletion of high-energy phosphate during recovery. These abnormalities were significantly worse in HFpEF than in HFrEF.[11] These data provide the strongest proof to date that HFpEF patients have significantly impaired skeletal muscle bioenergetics that contribute to their severe exercise intolerance.

Weiss also found markedly increased intermuscular adipose tissue in HFpEF, a finding we originally reported and showed to be correlated with reduced peak VO_2.[10] Excess intermuscular adipose tissue is inversely related to mitochondrial density and appears to suppress mitochondrial biogenesis.[10] Surprisingly, Weiss found no significant correlation between intermuscular adipose and PCr kinetics.

These findings of abnormal skeletal muscle mitochondrial function in HFpEF and their contribution to exercise intolerance should not be a surprise, because HFrEF patients have the same abnormalities that significantly contribute to their severe exercise intolerance, highlighting that in HF patients in general, skeletal muscle dysfunction is a major contributor to exercise intolerance.[2, 12]

Together with other abnormalities previously reported in skeletal muscle in HFpEF patients,[2, 5–11] these data make a strong case for a 'skeletal muscle myopathy' in HFpEF, similar to that described in HFrEF.[2, 12] Importantly, these abnormalities are *not merely secondary to deconditioning*, since: 1) they develop even when physical activity is forcibly maintained during the development of HFrEF;[12] 2) the pattern of abnormalities differs from deconditioning, particularly the fibertype shift which is the exact opposite from deconditioning. Further, multiple lines of evidence strongly support that these abnormalities are also *not due merely to reduced CO*, since: 1) they persist even when CO is relatively preserved, and when CO is normalized with inotropes or cardiac transplant;[12] 2) their improvement does not correlate with changes in CO.[12]

Thus, the skeletal muscle abnormalities are likely *intrinsic* to the HFpEF syndrome and not a secondary consequence or an epiphenomenon. The intrinsic nature of skeletal muscle dysfunction is consistent with the current paradigm of HFpEF as a *systemic* syndrome, likely triggered by circulating factors, such as inflammation or other as yet undiscovered factors, that then cause dysfunction in multiple organ systems.[13] If it were not so, then why would the circulating triggering factors only damage myocardial muscle, while sparing skeletal muscle, which shares many fundamental characteristics with cardiac muscle? Indeed, infusion of blood from an old animal into a young animal not only creates HFpEF-like changes in the heart, but also in skeletal muscle. This also is not necessarily unique to HFpEF, since in many ways HFrEF is a systemic syndrome as well.

These data have potentially important therapeutic implications. Exercise training is the only intervention definitively proven to improve peak VO_2 in HFpEF.[14] We previously showed that >90% of the improvement in peak VO_2 with exercise training is due to improved A-VO_2Diff, and a meta-analysis of 6 trials indicates that training improves peak VO_2 in HFpEF without significantly altering resting systolic or diastolic function.[14] Bowen showed that the impaired mitochondrial dysfunction in their HFpEF animal model was prevented by exercise training.[9] Thus, it's quite possible that improvement in skeletal muscle mitochondrial function is a significant contributor to training-related improvements in peak VO_2 in human HFpEF, which is known to be the case for HFrEF.[12] Furthermore, caloric restriction, which can improve mitochondrial function, improves peak VO_2 in obese HFpEF.[15]

How could exercise training (and caloric restriction) improve peak VO_2 when nearly all of the pharmacological agents tested in clinical trials to date, spanning several drug classes, have failed? Pharmacologic trials have targeted cardiac and / or vascular mechanisms. However, myocardium is terminally differentiated, with limited capacity for improvement. Arterial stiffness, the most consistently observed vascular abnormality in HFpEF, develops over decades, is associated with medial calcification, and has not been modifiable in HFpEF, even with prolonged therapy and novel agents. In contrast, skeletal muscle, including mitochondrial biogenesis, has robust capacity for rapid rejuvenation and repair, with detectable improvements within 3 days after initiating exercise training. This makes a strong case for targeting skeletal muscle, including mitochondrial dysfunction, in order to improve exercise intolerance in HFpEF.

Further supporting the value of targeting skeletal muscle abnormalities in HFpEF is that, compared to myocardium, obtaining objective measurements of skeletal muscle mass and function, including mitochondrial function, is relatively easy and safe. Moreover, there are now multiple agents in phase 2 clinical trials, primarily of older patients with physical disability associated with sarcopenia, targeting a variety of skeletal muscle abnormalities, including mitochondrial dysfunction. There are also several agents shown in animal models to improve muscle mitochondrial dysfunction. Of particular note, a recently launched study (PANACHE, NCT#03098979) may be the first trial to test whether a pharmacological agent (neladenoson bialanate, BAY1067197) targeted specifically to skeletal muscle and myocardial mitochondrial dysfunction, can improve exercise intolerance in HFpEF.

Thus, while continuing the quest for agents that address the cardiac and arterial abnormalities contributing to exercise intolerance in HFpEF, there is a compelling case to target the skeletal muscle abnormalities that contribute at least as strongly to exercise intolerance and that are more plastic and may be more easily remediable. While treating HFpEF with agents aimed at skeletal muscle may seem counter-intuitive, HFpEF patients will be grateful for their improved exercise tolerance and quality-of-life regardless of from which muscle the improvement derives.

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Table 1

Skeletal Muscle Abnormalities in HFpEF

Reduced % lean muscle mass
Fiber atrophy
Increased intermuscular adipose
Increased ratio of thigh intermusclar adipose / muscle areas
Reduced capillary density (capillary/fiber ratio)
Downward shifted relationship between %leg lean mass / peak VO_2 (impaired oxygen utilization)
Reduced % type 1 (oxidative) muscle fibers
Shift in type 1/ type 2 fiber ratio
Reduced citrate synthase activity
Reduced mitochondrial density
Impaired mitochondrial fusion
Reduced mitochondrial respiratory reserve capacity (maximal respiratory control ratio)
Accelerated high-energy phosphate depletion during exercise
Delayed high-energy phosphate repletion after exercise
Increased fatigability
Increased oxidative stress

Most of these abnormalities have been correlated with reduced exercise capacity