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EDITORIAL COMMENT

Exercise Intolerance in Heart Failure With Preserved Ejection Fraction

Shifting Focus From the Heart to Peripheral Skeletal Muscle*

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A cardinal feature of the syndrome of heart failure, irrespective of ejection fraction, is exercise intolerance, which is strongly associated with quality of life and clinical outcomes (1). Methods to evaluate exercise tolerance include self-reports of activities of daily living, clinician assessment of New York Heart Association functional class, and provocative stress testing. Cardiopulmonary exercise testing has emerged as an objective and reproducible means of quantifying oxygen consumption (1), which is determined by multiple factors including lung function, cardiac output, hemoglobin, and peripheral factors that include the ability to vasodilate, ensuring adequate delivery of oxygenated blood to exercising muscles and the ability of these muscles to utilize oxygen during exercise (2).

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In this issue of the *Journal*, Haykowsky et al. (3) have further advanced our understanding of exercise intolerance in subjects with heart failure and a preserved ejection faction (HFPEF) by analyzing data from a small randomized clinical trial of cardiac rehabilitation. Such work is essential in that this form of heart failure now accounts for a majority of the incident cases, is poorly understood physiologically, and hence has no specific therapies that have been demonstrated to prolong life in this cohort (4). The investigators performed simultaneous measurement of oxygen consumption and measures of cardiac output using 2-dimensional Doppler echocardiography in a cohort of well-characterized, compensated subjects with HFPEF who were randomly assigned to undergoing exercise training. Such data have been employed to further our understanding of this complex clinical syndrome (5), which has led us to fundamentally question our understanding of the pathophysiology of this disorder (6). In this secondary analysis of a previously conducted small randomized clinical trial of cardiac rehabilitation that was shown to have clinical benefit for subjects with HFPEF, the investigators demonstrate that the mechanisms underlying the improvement in peak oxygen consumption (VO_2) in this population have a "peripheral" and not a "central hemodynamic" basis.

Mechanisms underlying exercise intolerance in heart failure have been primarily studied in patients with systolic heart failure and reduced ejection fraction (7–10). Early work showed a lack of correlation between impaired left ventricular function and exercise performance (11) and resulted in the analysis of peripheral factors contributing to impaired exercise performance on heart failure. Subsequent studies demonstrated a central role of skeletal muscle dysfunction and abnormal metabolism defining impaired exercise function in patients with heart failure. Ultrastructural analyses revealed a distinct quantitative shift in muscle fiber types from oxidative slow-twitch type I fibers to more glycolytic fast-twitch type II muscle fibers (8). This is accompanied by abnormal mitochondrial function and structure (8), sarcolemmal abnormalities with impaired skeletal muscle calcium homeostasis with decreased SERCA 1a levels (12), reduced phosphocreatine and glycogen content (9), increased oxidative stress (13), and endothelial dysfunction accompanied by reduced capillary density (14). Impaired skeletal muscle anabolic metabolism is characterized by decreased muscle bulk and fiber cross-sectional area (2,15), reduced local insulin-like growth factor-1 expression (15), and systemic growth hormone resistance (16). Local inflammation in skeletal muscle with increased levels of interleukin-1β and tumor necrosis factor-α as well as inducible nitric oxide synthase (17) might further contribute to the progressive deterioration of skeletal muscle structure, function, and metabolism.

Geriatricians have for decades recognized a progressive decline in muscle mass, strength, and function that occurs with normal human aging, termed sarcopenia, which is worsened by concomitant disorders such as heart failure (18). Sarcopenia is associated with poor endurance, physical inactivity, slow gait speed, and decreased mobility, all features of the frailty syndrome (19) and heart failure with a preserved ejection fraction (20). Similar to the aforementioned changes in muscle structure and function observed in the phenotype of systolic heart failure, sarcopenia has been associated with oxidative protein damage, cytokines, and insulin-like growth factor-1 (21). The geriatric cardiology community is beginning to embrace these findings with an emerging focus on functional capacity in older adults un-

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dergoing cardiovascular procedures (22,23), demonstrating independent prognostic value beyond traditional cardiovascular assessment. However, interventions to correct peripheral abnormalities in patients with heart failure or sarcopenia in general are very limited. Controversy exists as to whether pharmacologic interventions such as inhibition of the renin-angiotensin-aldosterone system or beta-adrenergic blockade have an impact on skeletal muscle derangements in heart failure (24). Exercise interventions, primarily aerobic exercise training, in patients with heart failure have resulted in beneficial molecular and functional changes in skeletal muscle, including improved oxidative function and higher mitochondrial number and density (25), increased insulin-like growth factor-1 expression (26), and reduced local oxidative stress and inflammation (13). These molecular changes correlate with increased exercise performance underlined by longer exercise duration and higher peak VO_2 as well as improved endothelial function (10,25–27). No clear data exist on the potential therapeutic role of anabolic interventions such as growth hormone, testosterone, oxandrolone, megestrol acetate, the orexigenic peptide ghrelin, high-dose fish oil, or amino acid supplements (28).

As most of these studies have been performed in patients with reduced left ventricular systolic function, the specific changes of skeletal muscle in patients with HFPEF are unclear. Previous data have demonstrated that subclinical electromyographic alterations indicative of myogenic myopathy as well as histologic alterations characterized by type 1 atrophy were common in patients with both dilated and hypertrophic cardiomyopathy and were unrelated to the degree of impairment of left ventricular function (29). The current study extends these observations, suggesting that skeletal muscle abnormalities contribute in large part to the observed impairment in exercise performance and that aerobic exercise training is beneficial. As most of these investigations are based on the molecular analysis of skeletal muscle biopsies, similar approaches are needed for the analysis of skeletal muscle ultrastructure and metabolism in the setting of HFPEF. Furthermore, noninvasive methods such as nuclear magnetic resonance spectroscopy might reveal abnormalities in metabolic intermediates, substrate utilization, and phosphocreatine and glycogen storage pools.

The encouraging results of the Haykowsky et al. (3) exercise intervention trial for HFPEF suggest that such nonpharmacologic interventions may be a potential first-line therapy for HFPEF. Ultimately, clinical trials aimed at treating sarcopenia and pathologic muscle abnormalities emerging from the heart failure syndrome hold great promise for ameliorating functional impairments and disability associated with the epidemic of HFPEF.

In conclusion, the current study provides evidence for a role of peripheral factors in patients with HFPEF and implicates skeletal muscle metabolism and function in the observed exercise intolerance in this subset of patients with heart failure. As there is growing recognition of this patient population and a lack of specific or symptomatic therapies, further studies on peripheral factors are highly warranted. While the field might feel disadvantaged and left behind in light of the overwhelming body of evidence accumulated on patients with heart failure and reduced ventricular function, that existing body of literature might stimulate focused and detailed studies on peripheral skeletal muscle function in HFPEF. The analysis of skeletal muscle oxidative metabolism, fiber typing, mitochondrial function, and overall capillarization on skeletal muscle biopsies and the nuclear magnetic resonance spectroscopic analysis of muscle metabolism might be initial steps for the characterization of skeletal muscle derangements in patients with HFPEF.

The syndrome of HFPEF is complex, and the underlying cardiac dysfunction appears secondary given the complexity of peripheral abnormalities that develop alongside the cardiac phenotype. First steps have been taken but more needs to be done, and certainly every step involves skeletal muscle function and metabolism.

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