Exploring the Mechanisms of Exercise Intolerance in Patients With HFpEF

Are We too “Cardiocentric?”*

Eugene E. Wolfel, MD

Despite having a normal left ventricular ejection fraction, patients with heart failure with preserved ejection fraction (HFpEF) have limited exercise capacity, represented by a peak oxygen consumption (VO₂) that is less than what would be predicted for age, and comorbidities including obesity, metabolic syndrome, diabetes, or hypertension. Exercise intolerance is their main symptom, even when fluid balance, systemic blood pressure, and heart rate are optimized. In addition to a reduction in quality of life, reduced peak VO₂ in these patients has also been shown to determine prognosis. Knowledge of the physiological factors that limit exercise capacity in these patients may result in approaches to improve functional capacity and perhaps alter the natural history of the syndrome.

There is no doubt that reductions in cardiac output and inappropriate increases in cardiac filling pressures contribute to reduced exercise capacity in patients with HFpEF. Reports by various investigators have demonstrated chronotropic incompetence (1), alterations in diastolic function with exaggerated filling pressures during exercise (2), reductions in cardiac output during exercise (3), and abnormalities in ventricular-arterial coupling (4) in these patients. Despite these central cardiac abnormalities, several studies have shown that only 60% of the reduction in peak VO₂ can be explained by a reduction in cardiac output. Patients with HFpEF also have impaired oxygen extraction during exercise, with a reduced arteriovenous oxygen content difference despite a reduction in cardiac output (5), and this is a major determinant of diminished exercise capacity (6). This finding differs from the results in patients with heart failure with reduced ejection fraction, where peripheral oxygen extraction is increased in an attempt to compensate for a reduction in cardiac output. Thus, there appears to be a peripheral maladaptation that limits exercise performance in HFpEF. Exercise training in patients with HFpEF results in an increase in peak VO₂ that was associated with increased oxygen extraction but no increase in cardiac output (7). These findings suggest that peripheral, noncardiac factors play an important role in the limitations in exercise capacity in patients with HFpEF.

Impaired O₂ extraction during exercise can be the result of abnormal diffusive O₂ transport (local blood flow), diminished O₂ utilization, or both. Decreased diffusive O₂ transport can result from abnormalities in either the macrovascular or microvascular beds. Reductions in central arterial distensibility and reductions in both exercise and post-exercise leg blood flow and leg venous conductance have been reported in these patients (8,9). Endothelial dysfunction seems to be less common in patients with HFpEF and may not play a prominent role in decreased diffusive O₂ transport during exercise. Studies utilizing exercise training have demonstrated an improvement in peak VO₂ without improvement in macrovascular function, thereby questioning a predominant role of these vascular changes in determining exercise capacity (10). Microvascular function does appear to be abnormal in these patients and could be associated with impaired diffusive O₂ transport (11).

Perhaps a greater factor in the impaired O₂ extraction during exercise is abnormal O₂ utilization.
by exercising skeletal muscle. Although there are minimal data from patients with HFpEF, skeletal muscle abnormalities have been reported in patients with HFpEF, including impaired skeletal muscle oxidative metabolism, decrease in percent of type 1 oxidative fibers, decrease in type 1 to 2 fiber ratio, and decrease in capillary density. The relationship between peak VO₂ and lean leg mass is decreased in patients with HFpEF compared with normal control subjects, and this finding suggests that a decrease in muscle mass cannot explain the peripheral abnormalities in local O₂ transport and utilization.

In this issue of JACC: Heart Failure, Molina et al. (12) from the laboratory of Dr. Kitzman have further tested the hypothesis that an abnormality in skeletal muscle oxygen utilization is a major component of exercise intolerance in patients with HFpEF (12). They examined skeletal muscle mitochondrial content, oxidative capacity by determining the activity of citrate synthase, and the expression of key mitochondrial outer membrane proteins (Mitofusin 1 and 2) involved in the fusion of mitochondria and their function in stable patients with HFpEF and age-matched control subjects. They compared the skeletal muscle findings to 2 measurements of exercise capacity, peak VO₂, and 6-min walk distance. Due to confounding variables that could influence exercise capacity and potentially skeletal muscle biology, they adjusted their data for sex, body mass index, and race, but they still found significant differences between the patients with HFpEF and control subjects. Their results clearly demonstrated abnormalities in mitochondrial content and function that were associated with diminished peak VO₂ and 6-min walk distance in patients with HFpEF compared with control subjects. There was a 46% decrease in mitochondrial content, a 29% decrease in citrate synthase enzymatic activity, and a 54% decrease in the expression of Mitofusin 2. This is the first study to describe alterations in skeletal muscle mitochondrial content and function in patients with HFpEF. These data are congruent with prior information describing decreased oxidative capacity and a decrease in oxidative type 1 muscle fibers in the skeletal muscle of patients with HFpEF. Taken together, these data clearly support the potential role of diminished O₂ utilization as a factor in the reduced peak VO₂ in these patients.

There are some limitations to this study that may influence the overall interpretation of the results. The control subjects were described as sedentary, but it is likely that they were more active than the subjects with HFpEF. The effect of “deconditioning” on mitochondrial content and function remains to be determined, although the change in fiber type composition observed in patients with HFpEF is different than in deconditioned patients, where a reduction in both type 1 and 2 fibers has been reported. The effect of hypertension on elderly patients without HFpEF also needs to be evaluated, as 95% of the patients with heart failure in this study were hypertensive. More detailed analyses of oxidative capacity and mitochondrial content and function need to be performed, along with interventions that would improve mitochondrial function, to determine if exercise capacity would improve with such an intervention. It is interesting that the relationship between mitochondrial function and exercise capacity was less significant when only the data from patients with HFpEF was analyzed. It is difficult to determine if this finding was related to subject number and selection or whether other modulating factors not evaluated in this study are important in this relationship.

What are the potential mechanisms that result in decrease mitochondrial content and function in the skeletal muscle of these patients? Reasonable candidates would include neuroendocrine activation, excessive sympathetic nerve activity, oxidative stress, inflammation, abnormal calcium handling, and potentially, a component of deconditioning. Several of these mechanisms should be modified by pharmacological therapy for heart failure and thereby improve exercise capacity. However, all clinical trials with agents that alter neuroendocrine or sympathetic activity have not improved symptoms or outcomes in patients with HFpEF. Exercise training improves peak VO₂ in these patients without improvements in cardiac systolic or diastolic function in the majority of studies (13). This finding suggests that the improvement in exercise capacity occurs primarily through improved peripheral O₂ extraction. Exercise training improves functional status (peak VO₂) and quality of life, but what are the potential effects on clinical outcomes and the natural history of this syndrome? In patients with heart failure with reduced ejection fraction, exercise training has been shown to improve clinical outcomes (14). By improving the peripheral maladaptations in HFpEF, there may be an improvement in the natural history of at least a subset of these patients in the earlier stages of this syndrome. Cardiac pathophysiology remains an important aspect of the functional impairment in patients with HFpEF, but therapies targeted at the peripheral abnormalities in these patients may yield greater overall clinical benefits. It remains to be determined if the skeletal
muscle abnormalities reported in these patients can be significantly improved by exercise training or other therapies and if these will result in improved functional and clinical outcomes. The findings reported by Molina et al. (12) are an important initial step in further characterizing a potential mechanism of impaired O₂ utilization in patients with HFrEF.

REFERENCES

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