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Editorial Comment

Exercise Training in Heart Failure with Preserved Ejection Fraction: A Potential Mechanism and Benefit from Exercise Training

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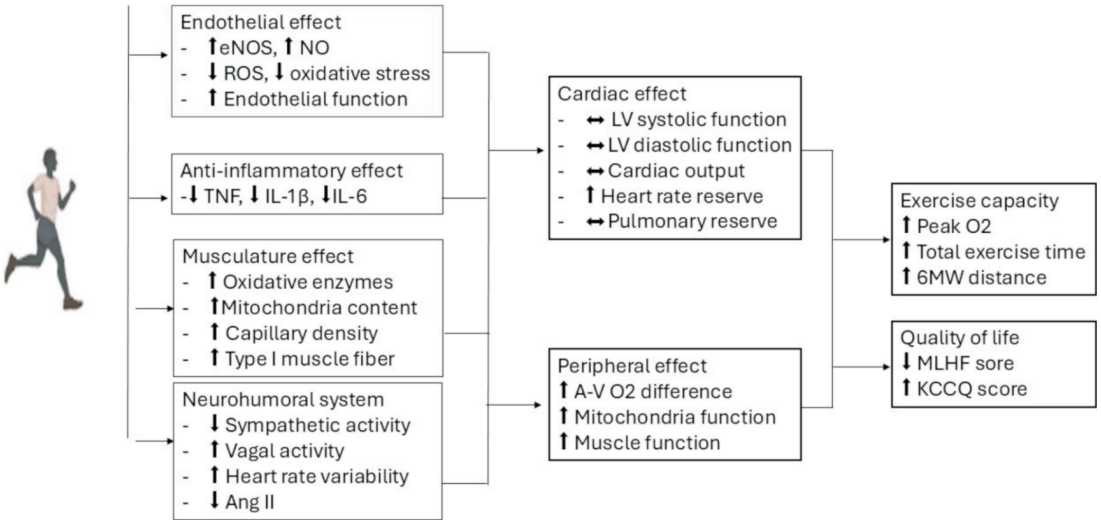

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Central Illustration. Pleiotropic effects and clinical benefit of exercise training in HFpEF patients. ENoS, endothelial nitric oxide synthase; NO, nitric oxide; ROS, reactive oxygen species; TNF, tumor necrosis factor; IL-6, interleukin-6; AngII, angiotensin; 6MW, six minute walk; MLHF, Minnesota Living With Heart Failure Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire.

Heart failure with preserved ejection fraction (HFpEF), a significant public health problem that is rising in prevalence, is associated with high morbidity and mortality. Expert opinions support that HFpEF is a multiorgan, systemic syndrome of multiple pathophysiological abnormalities above and beyond cardiac abnormalities.[1] Exercise intolerance or low exercise capacity measured objectively as peak oxygen uptake (peak VO_2) during maximal exercise is a hallmark symptom in patients with HFpEF. It is a strong determinant of prognosis and of reduced quality of life (QOL).[2] In contrast to heart failure with reduced ejection fraction (HFrEF), there is no established pharmacotherapy to improve survival in HFpEF. Thus, improvement of exercise capacity and QOL presents another crucial clinical outcome in HFpEF patients.[1]

Several pathophysiological mechanisms are responsible for the reduced exercise capacity in patients with HFpEF.[3] These can be broadly categorized as central and peripheral mechanisms. Reduced cardiac and pulmonary reserve contribute to exercise intolerance in patients with HFpEF. Reduced cardiac reserve is related to systolic dysfunction, ventricular diastolic dysfunction, functional mitral regurgitation, left and right atrial dysfunction, chronotropic incompetence, and ventriculo-arterial uncoupling. Reduced pulmonary reserve is related to impaired pulmonary vasodilation and vascular recruitment (exercise-induced pulmonary hypertension), ventilation-perfusion mismatch, decreased alveolar oxygen diffusion due to capillary stress failure and pulmonary congestion, abnormal ventilatory reserve due to increased respiratory muscle work and reduced lung compliance (altered ventilatory mechanics), and abnormal ventilatory regulation.

Peripheral factors contributing to exercise intolerance include muscle atrophy and apoptosis, decreased capillary and mitochondrial densities, a shift from fatigue-resistant Type I muscle fibers to fatigue-prone Type II muscle fibers, and decreased levels of oxidative enzymes. These changes lead to increased muscle fatigability, decreased oxidative metabolism, increased oxidative stress, and ineffective high-energy phosphate use, resulting in early accumulation of lactate during exercise, muscle fatigue, and reduced exercise capacity.[4]

Compared with most HFpEF trials of pharmacological therapy, which have failed to show benefits, exercise training has consistently improved exercise capacity and QOL in patients with HFpEF. A systematic review and meta-analysis[5] of 7 randomized controlled trials assessed the efficacy of the exercise training for patients with HFpEF. They significantly improved peak oxygen consumption and increased

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walking distance on the Six Minute Walk Test (6MWT). Although the exact mechanisms underlying increased exercise capacity with exercise training remain elusive, several potential mechanisms have been proposed.

Exercise training has a broad range of benefits associated with numerous pulmonary, cardiovascular, and skeletal muscle metabolic adaptations that benefit patients with HFpEF (Central Illustration). These pleiotropic systemic effects are well-suited for treating exercise intolerance in HFpEF patients.[6–8] First, exercise training increases shear stress on the vascular endothelial cell, promoting endothelial nitric oxide synthase expression and reducing nitric oxide scavenging, enhancing nitric oxide production and causing vasodilation. Evidence suggests that improved endothelial function and neoangiogenesis could be related mechanisms by which exercise training can benefit heart failure patients. Second, enhanced inflammatory response has been proposed as an essential factor in the pathophysiology of heart failure. The abnormal level of inflammatory cytokines would result in some aspects of the heart failure syndrome, such as endothelial dysfunction, impaired myocardial contractility, and a deleterious effect on skeletal and myocardial muscle contractility and metabolism.[9] Exercise training can reduce plasma levels of interleukin-6, tumor necrosis factor, and other inflammatory cytokines. Exercise training is a valuable and anti-inflammatory therapeutic strategy for subjects with heart failure. Third, exercise training also improves several skeletal muscle structural and functional alterations needed to support oxidative metabolism, including increased intramuscular capillary density, muscle fiber type distribution, increased mitochondrial content, and oxidative enzyme activity. These changes improve peak VO_2 and lactate threshold, delay the onset of anaerobic metabolism, and reduce muscle fatigue after exercise training. Finally, heart failure is often associated with neurohumoral changes, such as sympathetic hyperactivity with elevation of circulating catecholamines and reduced parasympathetic activity with decreased heart rate variability. Persistent neurohumoral excitation might result in deterioration of myocardial function with inflammatory response, end-organ damage, and skeletal muscle derangement, which lead to worsened exercise capacity. Exercise shifts the autonomic balance to favor parasympathetic activity, increasing heart rate variability and responses during exercise. By reversing the long-term detrimental effects of neurohumoral abnormalities in heart failure patients, there is enhanced cardiac function and reduced peripheral vessel resistance, which improves exercise tolerance and functional capacity.

Multiple studies have examined exercise's central and peripheral effects in patients with HFpEF to understand the mechanisms underlying the pleiotropic effects. Numerous studies have assessed changes in resting cardiac function following exercise training in patients with HFpEF. However, these studies have reported conflicting data about the ability of exercise training to induce favorable changes in the left ventricle (LV) volumes and ejection fraction. A systematic review and meta-analysis[5] of 7 randomized controlled trials assessed the efficacy of exercise training on exercise capacity and cardiac function has recently been reported. The meta-analysis showed that exercise training improved exercise capacity and heart rate reserve without changes in left ventricular structure and function. Studies evaluating peripheral adaptations have reported that exercise training significantly increased peak VO_2, primarily driven by increased increases in peak arteriovenous O2 difference and vastus lateralis muscle oxygenation, with little to no changes in peak exercise cardiac output or stroke volume.[1] These findings suggest that improvements in peak VO_2 after exercise training are attributable predominantly to peripheral adaptations (e.g., increased mitochondrial density and function, myoglobin content, and capillary density).[1] However, the neutral effect of exercise training on cardiac function should be interpreted with caution. First, the exercise intervention period in these studies was relatively short. Cardiac responsiveness to training requires prolonged and more intense exercise training programs. Second, Doppler measurements of left ventricular diastolic function at rest may be insufficient to detect subtle changes in diastolic function with exercise training. Third, many HFpEF patients experience dyspnea only during exertion. In these patients, LV filling pressure becomes markedly elevated during exercise. However, no included trials examined the effect of exercise training on LV function or LV filling pressure during exercise. Finally, because HFpEF patients are so heterogeneous, it may be the case that the magnitude of responsiveness of each factor to training depends on the patient's profile of defects.[10]

Understanding the mechanisms responsible for exercise-mediated improvements in exercise capacity is critical for tailoring therapeutic interventions designed to improve exercise capacity in HFpEF patients.[11] A future large study, stratifying patients by the profile of defect (central vs. peripheral impairment), using prolonged training period and optimal training intensity is warranted.

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