Exercise Physiology in Heart Failure and Preserved Ejection Fraction

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KEYWORDS

• Heart failure and preserved ejection fraction • Exercise physiology • Physical conditioning

KEY POINTS

- Heart failure with preserved ejection fraction (HFPEF) is the most common and fastest growing form of heart failure.
- HFPEF is associated with markedly increased morbidity, mortality, and health care expenditures.
- The prognosis of HFPEF is worsening, its pathophysiology is poorly understood, and no medications have been proved to be effective.
- The primary chronic symptom in patients with HFPEF, even when well compensated, is severe exercise intolerance, measured objectively as decreased peak oxygen uptake (peak V_{O_2}).
- Recent advances in the pathophysiology of exercise intolerance in HFPEF suggest that noncardiac peripheral factors contribute to the reduced peak V_{O_2}, and are the major contributor to its improvement after supervised endurance exercise training.

INTRODUCTION

Heart Failure with Preserved Ejection Fraction: A Major Health Care Problem with No Proven Therapy

Heart failure (HF) with preserved ejection fraction (HFPEF) is a recently recognized disorder and the fastest growing form of HF.[1,2] HFPEF is nearly exclusively found in older persons, particularly women, in whom 90% of new HF cases are HFPEF.[3] HFPEF is associated with markedly increased morbidity, mortality, and health care expenditures.[4–7] Despite its importance, the prognosis of HFPEF is worsening, its pathophysiology is poorly understood, and no medication trials have had positive effect on their primary end points.[2] Consequently, there are no evidence-based guideline recommendations for improving clinical outcomes in the growing population of elderly patients with HFPEF.

Exercise Intolerance is the Primary Symptom in Patients with HFPEF

The primary chronic symptom in patients with HFPEF, even when well compensated, is severe exercise intolerance, which can be measured objectively during whole body exercise as decreased peak V_{O_2} (peak exercise oxygen uptake).[8–19] Specifically, peak V_{O_2} in patients with

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HFPEF is 40% lower than age-matched and sex-matched controls (Fig. 1). Reduced exercise tolerance is a strong determinant of prognosis and reduced quality of life.[10,20] A clear understanding of the pathophysiology of exercise intolerance is necessary to guide future therapies aimed at improving patients with HFPEF symptoms.

Pathophysiology of Exercise Intolerance in Patients with HFPEF

In accordance with the Fick principle, the amount of oxygen consumed per minute is equal to the product of cardiac output and arterial-venous oxygen content difference; therefore, the reduced peak V_{O_2} in patients with HFPEF may be caused by decreased oxygen delivery to or impaired oxygen extraction by the exercising skeletal muscles (Fig. 2).[10] Cross-sectional studies by Borlaug and colleagues[16,17,19] have suggested that the lower peak V_{O_2} in patients with HFPEF compared with age-matched healthy or comorbidity-matched controls without HF was associated with reduced peak cardiac output, which was caused primarily by blunted heart rate response, myocardial contractility, and peripheral vascular vasodilator reserve.[18] A series of studies by Kitzman and colleagues[8] extended these results by showing that the lower peak V_{O_2} in older patients with HFPEF versus age-matched healthy controls was caused not only by reduced peak exercise cardiac output but also by an equal contribution of reduced systemic arterial-venous oxygen content difference.[12] Moreover, the change in arterial-venous oxygen content difference from rest to peak exercise was the strongest independent predictor of peak V_{O_2} for both patients with HFPEF and controls.[12] Bhella and colleagues[15] confirmed that noncardiac peripheral factors play an important role in limiting exercise tolerance, because the reduced peak V_{O_2} in older patients with HFPEF compared with age-matched healthy controls occurred despite no significant difference in peak exercise cardiac output between groups. Potential peripheral mechanisms that may limit exercise capacity include decreased skeletal muscle mass, reduced type I (oxidative fatigue-resistant) muscle fibers, and impaired blood flow to or extraction by the active skeletal muscles.[10]

Skeletal Muscle Mass and Oxygen Utilization and Exercise Intolerance in Patients with HFPEF

Most of the oxygen consumed during the transition from rest to peak cycle exercise occurs in the active muscles, therefore a loss in metabolically active tissue may contribute to exercise intolerance in patients with HFPEF.[14,21] Our group tested this hypothesis and compared lean body mass and peak V_{O_2} in 60 older patients with HFPEF and 40 age-matched healthy controls.[14] Three novel findings were reported. First, the percent total lean body mass and percent leg lean mass were significantly lower in patients with HFPEF compared with healthy controls.[14] Second, peak V_{O_2} indexed to total lean body mass or leg lean mass was significantly lower in elderly patients with HFPEF versus healthy controls.[14] Third, the change in peak V_{O_2} with increasing percent leg lean mass was markedly reduced in patients with HFPEF compared with

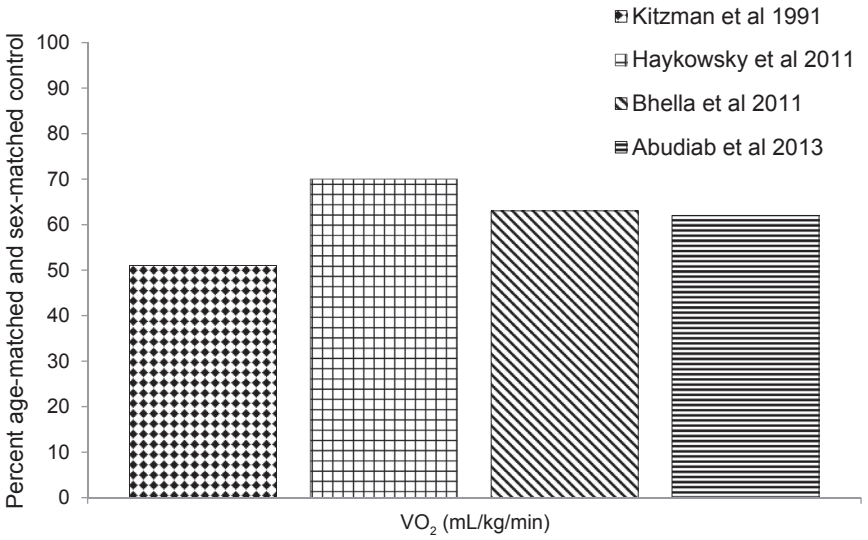

Fig. 1. Peak oxygen uptake in patients with HFPEF. (*Data from* Refs.[8,12,15,18])