

Training the Left Ventricle With Preserved Ejection Fraction or Cardiorespiratory Fitness?

Rocking the Boat

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Heart failure with preserved ejection fraction (HFpEF) is a significant and costly health problem that develops from abnormalities in left ventricular filling as a result of impaired relaxation, increased stiffness,¹ and a combination of these with reduced vascular compliance.² These hemodynamic abnormalities make patients symptomatic for dyspnea and fatigue and undermine quality of life and exercise performance.³

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Exercise intolerance can be measured objectively during cardiopulmonary exercise testing as decreased peak oxygen uptake ($\dot{V}O_2$), a strong determinant of adverse outcome. A clear understanding of the pathophysiology of exercise intolerance is helpful to guide clinical decision-making and monitor therapeutic interventions.⁴

A host of effective therapies improves outcome in heart failure with reduced ejection fraction, and when on appropriate treatment, this population benefits the highest survival rates. Conversely, HFpEF does not benefit from the same advantages, and heterogeneity of the HFpEF population poses a major challenge to the development of therapies for the entire HFpEF phenotypes with no currently established treatment of this syndrome.⁵

One of the most challenging nonpharmacological interventions to contrast HF progression is exercise training, which is an approach used, since early 1990s, in heart failure with reduced ejection fraction to mitigate the abnormal pathophysiology of heart failure and its influence on clinical outcomes.⁶ Its practice to HFpEF is more recent and under progressive scrutiny. Although trials are underway,⁷ some single-site⁸⁻¹⁰ and multicentre randomized trials¹¹ have already been completed.

In this issue of *Circulation: Heart Failure*, Pandey et al¹² take an important step forward to summarize and inform current practices concerning the potential targets of benefit of exercise training programs in HFpEF.

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Their results were obtained using a meta-analysis approach refined on 6 selected studies, including a total of 276 HFpEF patients with EF>45% and with systemic hypertension as the main comorbidity. Everyone was in a stable clinical condition, optimized therapy, and without recent hospitalization. An important strength is represented by the homogeneous characteristics of patients enrolled, in terms of age and comorbid disorders.

Overall, training interventions provided evidence of benefit in the quality of life and the cardiorespiratory fitness (CRF). Peak $\dot{V}O_2$ increased in a range between 8% and 23%, whereas no training effect on LV diastolic function and ejection fraction was reported.

The analysis is robust and challenges what it can be conceivably predicted as the major target of exercise intervention, pointing the attention on mechanisms out of the left ventricle as mediators of the observed training-induced CRF improvement.

Some caveats may be anticipated and are not related to the analysis per se, but to the design of studies. The cardiac effects were assessed at rest rather than during exercise whose hemodynamic burden may uncover improved LV performance. The assessment of LV diastolic function was limited to load-dependent echo-Doppler-derived indexes (mitral E/A ratio and deceleration time). All the examined studies were planned on moderate intensity programs of endurance training, and a lack of comparison among different training modalities (endurance versus resistance or their combination) and types (continuous moderate versus high intensity interval)¹³ should be acknowledged as a limitation.

So, how to reconcile the finding that in HFpEF symptoms and $\dot{V}O_2$ may improve without any measurable effect on LV diastolic function and systolic reserve and what the mechanisms sustaining a higher CRF may be?

The pathophysiology of exercise intolerance in HFpEF is complex and has been associated to several mechanisms and organ systems that involve the vascular endothelial function and tone regulation¹⁴; the alveolar gas exchange process and the ventilatory adaptive response to incremental CO_2 production and its reflex control¹⁵; and the biochemical¹⁶ and histological patterns of muscle fibers.¹⁷

In HFpEF, how much exercise programs may effectively affect these noncardiac determinants of CRF is unexplored. However, it seems a good starting point to examine directly the hemodynamic determinants of $\dot{V}O_2$ as defined by Fick equation, that is, the product of cardiac output times arteriovenous O_2 difference ($A-\dot{V}O_2$ diff). Although studies report a rather variable extent of stroke volume changes during exercise in

HFpEF,^{18,19} a wealth of evidence is suggestive of a role of chronotropic insufficiency and impaired heart rate sympathovagal control in the unfavorable hemodynamic response to exercise^{17,19} and its negative prognostic implications.²⁰

The other determinant of Fick principle is O₂ extraction, a biological phenomenon related to O₂ delivery and diffusion from capillaries to mitochondria. When O₂ is adequately dispatched by cardiac output, its extraction depends on the amount of blood flow redistribution to vascular beds of exercising muscles and several molecular facilitating mechanisms, including P_{O₂}, the Hb concentration and the pressure of O₂ corresponding to the 50% of Hb half saturation with O₂ (P₅₀). The relative contribution of these molecular mediators has been investigated in heart failure with reduced ejection fraction and was found to be as higher as lower as peak V_{O₂} and the functional capacity.²¹

Whether a low A–VO₂ diff is a limiting step in elderly deconditioned HFpEF patients^{18,19} and how training may affect the fine biology behind this process phenomenon is a matter of growing interest and stimulating discussion.⁹ In a small study, including 11 HFpEF patients with similar characteristics of those examined in the present analysis, Behlil et al¹⁸ found a high cardiac output/V_{O₂} ratio, an unexpected and unusual pattern associated to low oxidative phosphorylation and high glycolytic energy expenditure. More recently, Dhakal et al²² directly measured the A–VO₂ diff through maximal exercise and found a reduced peak exercise O₂ extraction as major determinant of exercise impairment in HFpEF in distinction to heart failure with reduced ejection fraction. Whether this may be related to a predominant anemic condition typical of HFpEF populations or to a specific signature of the impaired molecular components of the O₂ extraction chain that are peculiar of HFpEF disease remains unknown. Nonetheless, it is interesting to foresee that exercise intolerance in HFpEF may be driven by peripheral abnormalities reproducing in some extent a mitochondrial myopathy condition and a dis-ease of the microcirculation or a combination of both.

These hypotheses, if confirmed, may considerably widen the spectrum of targets treatable by exercise training.

Thus, the Pandey et al¹² analysis has rocked the boat; the message of their meta-analysis is clear, that is, look at CRF and quality of life rather than at left ventricular diastolic function and systolic performance as the main end points of training-induced effects. In practice, it invites clinicians and researchers to further focus on the physiological key mediators of CRF without limiting their results to a simple quantitative analysis. Once these mediators and their pathophysiological significance are better clarified, the challenging perspective is to substantiate exercise training programs tailoring the most appropriate type, modality, and intensity protocol with the aim to hasten symptoms deterioration, reverse the deconditioned phenotype, and hopefully contribute to shift the paradigm in the treatment of HFpEF.

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