Reversing Heart Failure–Associated Pathophysiology with Exercise
What Actually Improves and by How Much?

Volker Adams, PhD[a], Josef Niebauer, MD, PhD, MBA[b,*]

KEYWORDS

• Endothelium • Exercise training • Nitric oxide • Oxidative stress • Skeletal muscle

KEY POINTS

- Improvement in peak oxygen consumption ($\dot{V}O_2$) is due to reverse cardiac remodeling as well as peripheral adaptations in the skeletal muscular and vascular system.
- Central mechanisms include improved myocardial anabolic/catabolic balance, calcium handling, and neurohormonal adaptations; the periphery benefits from less inflammation; and improvement in the catabolic/anabolic balance, energy metabolism, and structural alterations.
- Vascular effects comprise improved endothelial function and regeneration, including positive effects on the nitric oxide (NO) system, microRNA (miRNA), and apoptosis.
- Clinical trials suggest that high-intensity interval training (HIIT) might be superior to other forms of exercise training (ET); underlying molecular mechanisms need to be further elucidated.
- Patients with heart failure with preserved ejection fraction (HFpEF) benefit from ET; molecular mechanisms, however, are only poorly understood.

INTRODUCTION

The first scientific evidence regarding the beneficial effects of work-associated ET was published by Morris and colleagues, in 1953,[1] who examined the incidence of coronary artery disease (CAD) in London bus driver teams. He documented that the incidence of CAD was less in the middle-aged conductors than in the sedentary drivers of the same age. Subsequently, studies in more than 100,000 individuals showed that the higher the level of physical fitness, the less likely an individual would suffer premature cardiovascular (CV) death (reviewed by Lee and colleagues[2]). In a recent meta-analysis, including 883,372 subjects, it became evident that physical activity is associated with a marked risk reduction in CV (risk reduction of 35%) and all-cause mortality (risk reduction of 33%).[3] In addition, exercise capacity or cardiorespiratory fitness is inversely correlated with CV or even all-cause mortality, even after adjustment for confounding factors.[4–6] Based on these studies, all major CV societies made physical activity part of their guidelines for prevention of CV disease (CVD) (class I recommendation), recommending at least 30 minutes of moderate-intensity aerobic activity on 3 to 7 days per week

Disclose: Nothing to disclose.

[a] Department of Internal Medicine/Cardiology, University of Leipzig – Heart Center, Strümpelstraβe 39, Leipzig 04289, Germany; [b] University Institute of Sports Medicine, Prevention and Rehabilitation, Research Institut of Molecular Sports Medicine and Rehabilitation, Institute of Sports Medicine of the State of Salzburg, Sports Medicine of the Olympic Center Salzburg-Rif, Paracelsus Medical University Salzburg, Lindhofstrasse 20, Salzburg 5020, Austria

* Corresponding author.

E-mail address: j.niebauer@salk.at

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(ie, greater than 150 min/wk).[7–9] In recent years, molecular biology helped understand the impairment of exercise capacity in patients with chronic heart failure (HF) and the beneficial effects elicited by ET. It also became clear that different organ systems, such as the heart, skeletal muscle, and vascular function, are involved in disease progression and modulation by ET.

This review summarizes current knowledge with respect to molecular changes elicited by ET in HF in different organ systems: the heart, the endothelium, and the skeletal muscle. The last part of the review discusses and summarizes current knowledge on training intensity and if ET is also a potential therapeutic option in patients with HFpEF.

CARDIAC EFFECTS OF EXERCISE TRAINING

Training Effects on Left Ventricular Function and Reverse Remodeling

One of the first small prospective studies, performed by Sullivan and coworkers[10] in HF patients with HF with reduced ejection fraction (HFrEF) (n = 12), demonstrated that 4 to 6 months of training did not worsen left-ventricular ejection fraction (LVEF) and tended to improve maximal cardiac output. The extent of the cardiac changes did not, however, explain the large 23% improvement in peak $\dot{V}O_2$ so that peripheral changes in limb perfusion and oxidative metabolism most likely account for the larger part of the beneficial symptomatic training effects. The first larger prospective randomized study to provide evidence for a training-induced reverse remodeling came from Hambrecht and colleagues,[11] who demonstrated that endurance training led to reverse left ventricular (LV) remodeling, with modest improvements in EF from 30% to 35% as well as reductions of LV end-diastolic diameter. The results of these studies were confirmed in 2 meta-analyses performed in 2007[12] and 2012.[13] In summary, these meta-analyses showed that aerobic training, especially greater than 6 months' duration, significantly reversed LV remodeling, whereas strength training alone or combined with aerobic training had no effect on reverse remodeling.

Mechanisms Explaining Reverse Remodeling in Heart Failure

In the absence of myocardial biopsies for molecular analysis of myocardial changes induced by training, most investigators interpreted this favorable training effect as secondary to afterload reduction with reduced resting blood pressure due to improved endothelial function.[11,14,15] Animal models reveal, however, that there are direct myocardial effects of training that are related to signaling pathways of myocardial hypertrophy and fibrosis.[16,17]

Anabolic/catabolic balance in the myocardium

Animal studies in which a left anterior descending artery ligation model was used demonstrated a significant up-regulation of components of the ubiquitin-proteasome system (UPS) as well as of myostatin.[18,19] Both were significantly reduced by ET over a period of 4 weeks.[18,19]

Calcium handling

Alterations in calcium handling are also associated with pathologic hypertrophy and transition from hypertrophy to failure: sarcoplasmic reticulum CA^{2+} ATPase (SERCA2a) protein levels were reduced in mouse and dog models of HF and were normalized by ET.[20,21] In addition, ET activates Ca^{2+}/calmodulin-dependent protein kinase (CaMK) II, leading to a hyperphosphorylation of phospholamban,[22] which in its phosphorylated form no longer inhibits SERCA2a. In conjunction with an increased expression of Na^{+}-$Ca2^{+}$ exchanger,[23] higher myocardial SERCA-2 and phospholamban lead to improved calcium cycling and thus to better cardiomyocyte function. For more detailed information on exercise-induced improvements on the contractile apparatus and calcium cycling, see the detailed review by Kemi and Wisloff.[24]

Neurohormonal adaptations

An aerobic ET program in patients with HF leads to a reduction in sympathoadrenergic drive. This has also been confirmed for serum catecholamine levels: Coats and colleagues[25] showed a 16% reduction of radiolabeled norepinephrine secretion after 8 weeks of ET. In addition to the reduction in circulating catecholamines, Braith and coworkers[26,27] described a 25% to 30% reduction of angiotensin II, aldosterone, arginine vasopeptide, and atrial natriuretic peptide after 4 months of walking training in patients with HF. In a rat model of ischemic HF, the beneficial training effects on local neurohumoral balance were analyzed in the noninfarcted LV myocardium. Xu and colleagues[28] found a significant reduction of myocardial angiotensin-converting enzyme mRNA expression and angiotensin II, type 1, receptor expression after 8 weeks of treadmill ET. This finding is of special importance given that approximately 90% of angiotensin II is produced locally in the myocardium and implies that local angiotensin II levels are significantly reduced by ET. This reduction also translates into reduced fibrogenesis, as indicated by reduced tissue inhibitor of metalloproteinase-1 expression with unchanged matrix metalloproteinase (MMP)-1