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

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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.

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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

expression and reduced collagen volume fraction in the exercised animals.[28]

VASCULAR EFFECTS OF EXERCISE

Besides the myocardium, the vascular system is significantly impaired in patients with HF,[29] and several studies using ET as a therapeutic intervention during the past decades have proved beneficial effects on this system.[15,30] On a functional level, ET results in better endothelial function and a better compliance of the vessel (reduced stiffness). The following sections focus on molecular changes elicited by ET, especially in the vascular system.

Nitric Oxide System (Nitric Oxide–Reactive Oxygen Species Balance)

One of the most important factors regulating vascular function is NO generated in the endothelial cells (ECs) (reviewed by Feletou and colleagues[31]). In mammals, NO can be generated by 3 different isoforms of NO synthase (NOS), namely endothelial NOS (eNOS), neuronal NOS, and inducible NOS.[32,33] At least in ECs, the most important one for regulating vascular tone is eNOS. NO is responsible for vasodilation, which results in the lowering of peripheral resistance and increase of perfusion. eNOS expression was significantly reduced in animal models of HF, induced by either ventricular pacing or monocrotaline, compared with controls.[34,35] Its activity is upregulated by an increase in flow-mediated shear stress associated with physical exercise due to a complex pattern of intracellular regulation, such as acetylation,[36] phosphorylation,[37] and translocation to the caveolae.[38] Numerous investigations have documented that exercise or increased shear stress up-regulates eNOS activity in cell culture,[39–41] animal,[42,43] or human studies.[44] With respect to the signal transduction of increased shear stress and eNOS activation, the glycocalyx on the luminar side of the ECs seems to play an important role.[45,46] The deformation of the glycocalyx results in the activation of calcium ion channels, phospholipase activity leading to calcium signaling, prostaglandin I2 release, and cyclic AMP–mediated smooth muscle cell relaxation.[45] In addition, vascular endothelial growth factor receptor 2 is located at the luminal surface and can associate with vascular endothelial cadherin, ß-catenin, and phosphatidylinositol 3 kinase to phosphorylate Akt and induce Akt-mediated eNOS phosphorylation, leading to higher NO production.[47] High-density lipoprotein (HDL) is another factor known to modulate eNOS activity via phosphorylation.[48] This HDL-induced activation is impaired in patients with diabetes,[49] CAD,[50] and HF[51] and an ET program of 12 weeks is able to restore this HDL-mediated eNOS activation.[51]

The bioavailability of NO not only depends on its generation by eNOS but also is influenced by reactive oxygen species (ROS)-mediated breakdown. The low NO bioavailability is partly caused by the reaction of ROS with NO to form peroxynitrite. The application of laminar flow to intact vascular segments has been shown to increase ROS production for a short time period,[52] with NADPH the major source.[53] Extended periods of ET result, however, in a reduced expression of hypoxanthin,[54] NADPH oxidase,[55] and a stimulation of radical scavenging systems that include copper and zinc–containing superoxide dismutase (SOD),[56] extracellular SOD,[57] glutathione peroxidase,[58] and glutathione levels.[59] Another enzyme-generating ROS in the vascular system is eNOS itself. Under several pathologic conditions, the enzymatic reduction of molecular oxygen by eNOS is no longer coupled to L-arginine oxidation, resulting in ROS production.[60–62] NOS uncoupling has been implicated in several pathologies, including atherosclerosis,[63] diabetes,[64] and HF.[65] A critical factor for NOS uncoupling is the bioavailability of tetrahydrobiopterin (BH4), a cofactor for the enzymatic reaction.[66] Cell culture experiments using ECs provide some evidence that elevated blood flow increased BH4 levels.[67–69]

Apoptosis and Endothelial Regeneration

EC senescence and apoptosis are features of numerous human pathologies, including atherosclerosis, diabetic retinopathy, and HF.[70,71] The maintenance of an intact EC layer (repair of damaged or lost ECs) is one important action to counteract endothelial dysfunction. Endothelial progenitor cells (EPCs) or mesenchymal stem cells are mobilized from the bone marrow by specific stimuli and possess the potential to promote angiogenesis and endothelial repair.[72–74] Numerous studies have provided evidence that ET mobilizes EPCs or mononuclear cells (MNCs) from the bone morrow and influences its functional capacity.[75–78] Levels of circulating EPCs correlate inversely with the extent of endothelial dysfunction in humans at various degrees of CV risk.[79] Due to increased shear stress, NO concentration increases in the bone marrow, leading to the activation of MMPs (MMP-2 and MMP-9), leading to the mobilization of stem cells into the circulation.[80,81] This model is supported by the observation that exercise-induced mobilization of EPCs from the bone marrow is impaired in $eNOS^{-/-}$ mice.[82] After

mobilization of the cells, the most relevant factor for tissue engraftment is the local concentration of stromal-derived factor 1α and its cell receptor CXCR-4.[83] The expression of CXCR-4 can be up-regulated by either ET[84] or adiponectin,[85] both known to have an impact on EPC migration.[86]

MicroRNA

The coordinated regulation of angiogenesis and maintenance of the EC layer is essential for proper vascular function and prevention of endothelial dysfunction. In recent years miRNAs were identified as critical regulator of gene expression, due to their ability to suppress protein synthesis by inhibiting the translation of protein from mRNA or by promoting mRNA degradation.[87,88] With respect to miRNA and the impact of ET in HF to maintain proper endothelial function, 3 different miRNAs received closer attention: miRNA-21, miRNA-95a, and miRNA-126. miRNA-92a could be identified as an endogenous repressor of the angiogenic program in ECs.[89] In addition, large-scale miRNA profiling of human umbilical vein ECs exposed to different shear stress conditions identified miRNA-92a as an miRNA that is up-regulated by low shear stress.[90] A study of $LDLR^{-/-}$ mice fed a high-fat diet documented that the up-regulation of miRNA-92a by oxidized low-density lipoprotein (LDL) in atheroprone areas (areas of low shear stress) promoted endothelial activation and the development of atherosclerotic lesions.[91] A mechanistic explanation may be that an elevation of miRNA-92a by low or oscillatory shear stress leads to a down-regulation of Krüppel-like factor 2, resulting in a reduced expression of eNOS.[92] Another miRNA up-regulated by elevated shear stress is miRNA-21.[93] Transfection and inhibitions studies documented that an elevation of miRNA-21 led to enhanced NO production via Akt and eNOS phosphorylation.[93] MiRNA-126 is highly enriched in the vascular endothelium and was shown to play distinct roles in angiogenesis, vasculogenesis, and endothelial inflammation. Swim training in rats resulted in an increased expression of miRNA-126 in the myocardium and is related to exercise-induced cardiac angiogenesis, by indirect regulation of the vascular endothelial growth factor receptor pathway.[94] This essential role of miRNA-126 is further supported by the observation that antagomir-mediated silencing of miRNA-126 impairs ischemia-induced angiogenesis in a mouse model.[95]

MUSCULAR EFFECTS OF EXERCISE

Early fatigue and exercise intolerance are hallmarks for the diagnosis of chronic HF in patients. Investigations from the early 1990s documented that exercise intolerance cannot be predicted by LVEF. Based on these observations, the muscle hypothesis of HF was born: that alterations in the peripheral skeletal muscle are a main predictor for exercise intolerance and that these alterations are influenced by ET.[96,97]

Inflammation

During the development of HF, a derangement in inflammatory factors is evident.[98,99] The prototype of inflammatory cytokines elevated in HF is tumor necrosis factor α (TNF-α).[100,101] Besides TNF-α, other inflammatory cytokines, such as interleukin (IL)-6 and IL-1ß, have been described as elevated in patients with HF.[102,103] The elevation of inflammatory cytokines is not restricted to HFrEF but is also evident in HFpEF patients.[104] With respect to the origin of the circulating inflammatory cytokines, at least 3 different hypothesis are discussed: (1) production and secretion by circulating MNCs, like macrophages[105]; (2) secretion by injured cardiomyocytes or by cells from peripheral tissue, mainly skeletal muscle[106,107]; and (3) increased edema of the bowel wall and thereby an induction of TNF-α by lipopolysaccharides.[108–111]

Inflammatory cytokines, especially TNF-α, are able to induce muscle wasting, a phenomenon often observed in patients with end-stage HF, via the activation of the UPS by mitogen-activated protein kinases (MAPKs) and nuclear factor κB.[112] With respect to ET and the level of inflammatory cytokines, several investigators have demonstrated that depending on the severity of chronic heart failure (CHF), elevated baseline cytokine levels did not increase further [113] and in 2 studies even decreased in response to ET, both in the serum[114,115] and in the skeletal muscle.[116,117]

Catabolic/Anabolic Balance

Muscle weakness and muscle atrophy are hallmark characteristics in patients with end-stage HF. An imbalance between anabolic and catabolic factors is responsible for loss of muscle mass. Fortunately, this imbalance can be influenced by ET. With respect to anabolic factors, growth hormone, androgens (testosterone), insulin, and insulinlike growth factor 1 (IGF-1) play an important role, with IGF-1 in a central position due to its ability to regulate muscle cell proliferation and differentiation and muscle regeneration.[118–120] In support of this pivotal role of IGF-1, the transgenic overexpression of IGF-1 in the skeletal muscle is associated with muscle hypertrophy, increased muscle strength, and improved muscle regeneration.[119,120] Mechanistically, an overexpression of

IGF-1 seems to prevent muscle atrophy by inhibiting protein degradation pathways, like the UPS, in the skeletal muscle.[121] Analyzing skeletal muscles from animal models or patients with HF, a significant reduction of IGF-1 was evident,[122–124] which could be reversed by an ET program.[125]

On the catabolic site, the activation of the UPS in the skeletal muscle of HF[126] and the upregulation of myostatin[19] could be documented. A relation between the inflammation and the activation of the UPS could be identified. TNF-α seems to activate the UPS, and this activation is essential for the TNF-α–induced loss of muscle function.[127] Performing regular ET counteracts this dysregulation of the UPS[126,128] and myostatin.[19]

Energy Metabolism

HF is associated with an augmented energy demand and a diminished energy metabolism, resulting in an energetic imbalance.[129,130] The phosphocreatine (PCr) shuttle, in particular, transporting energy from the mitochondria to the cytosolic ATPases, and the recovery of the PCr after exercise are impaired.[131,132] Creatine kinase (CK) and mitochondrial CK expression is altered in the skeletal muscle of experimental HF[129] and in muscle biopsies obtained from HF patients.[132,133] When performing prolonged exercise, skeletal muscle metabolism adapts very fast by quantitative and qualitative changes in mitochondria and the capillary supply.[134,135] For all these adaptive responses, peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) plays an important and central role. It regulates mitochondrial biogenesis, as shown in animals overexpressing PGC-1α.[136] Besides PGC-1α, other signaling molecules, such as MAPKs, CaMKs, and AMP-activated protein kinase, are activated during exercise and are relevant for the exercise-induced changes observed in the skeletal muscle (for review Ventura-Clapier and colleagues[137] and Russell and colleagues[138]).

Structural Alterations

In skeletal muscle biopsies of patients with HF, a shift in fiber-type composition is evident compared with healthy controls. Patients with HF exhibit a relative increase in less aerobic type II and a relative decrease in aerobic type I fibers.[139,140] Recently, also in patients with HFpEF, the percentage of type I fibers, the type I–to–type II fiber ratio, and capillary-to-fiber ratio were reduced, whereas the percentage of type II fibers was greater.[141] Using ET as a therapeutic intervention in patients with HF resulted in a reversal of the changes observed in fiber-type composition and the reduced capillary-to-fiber ratio.[140,142] On the molecular level, PGC-1α seems to be an important regulator of fiber-type composition. This important role is supported by studies using transgenic animals[136] and by the positive correlation between PGC-1α expression and fiber type composition.[143]

EXERCISE TRAINING INTENSITY—INTERVAL VERSUS MODERATE CONTINUOUS TRAINING

Applying the knowledge obtained in sports medicine using HIIT, Wisloff and coworkers[144] demonstrated a superior CV effect of aerobic HIIT compared with moderate continuous training (MCT) in HF patients. From the molecular standpoint, it seems that HIIT improves endothelial function much better than MCT due to greater bioavailability of NO (increase of the antioxidant status in the plasma) and reduced oxidized LDL. In addition, the activation of PGC-1α in the skeletal muscle is more pronounced after HIIT. It is speculated that higher shear stress during the on phase of HIIT triggers larger responses at the cellular and molecular level compared with MCT. In myocytes, HIIT partly reversed contractile dysfunction and impaired Ca^{2+} handling in rats with postinfarction HF.[145] In recent years, several studies were performed to confirm the result of Wisloff and colleagues,[144] with mixed results. Performing a meta-analysis on 7 randomized trails comparing HIIT with MCT,[146–152] the investigators came to the conclusion that in clinically stable HF patients, HIIT is more effective than MCT in improving peak $\dot{V}O_2$, but no difference is obvious with respect to altering LV remodeling.[146] Nevertheless, all these results have to be taken with care, because this meta-analysis is only based on 180 patients in total, with all studies using a single-center design. Therefore, results of larger, multicenter trials comparing the different training intensities in HF or CAD, such as SmartEx[153] or SAINTEX-CAD,[154] currently underway, must be awaited.

EXERCISE AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

HFpEF is the only CVD with increasing prevalence and incidence and a mortality rate similar to HFrEF.[155] The poor clinical outcome in patients with HFpEF is not explained by age, gender, or the high prevalence of CV risk factors and comorbidities.[156] Thus, the underlying mechanisms and, therefore, treatment options are incompletely understood. The pharmacologic therapy of HFpEF to improve outcome and symptoms has been particularly disappointing. Several large clinical

trials using established pharmacologic strategies in HFpEF, such as angiotensin-converting enzyme inhibitors (PEP-CHF),[157] angiotensin II receptor blockers (PARAMOUNT,[158] CHARM-Preserved,[159] and I-Preserve[160]), or spironolactone (Aldo-DHF[161]), have failed to convincingly demonstrate substantially improved symptoms, morbidity, or mortality. Currently, no pharmacologic agent has shown to improve symptoms, exercise capacity, or prognosis in this severely debilitated patient population. From a pathophysiologic point of view, ET could be one possible therapeutic option to improve symptoms in this patient population. Small randomized trials in HFpEF patients showed improvements in peak $\dot{V}O_2$ of approximately 20%.[162–164] With respect to the molecular basis for these beneficial training effects, not much is known so far. A recent study analyzing the training effects in heart and diaphragmatic muscles in a mouse model of HFpEF revealed alterations in the titin isoform composition.[165] With respect to endothelial function and arterial stiffness, no impact of a 16-week ET program in older HFpEF patients could be documented.[163] More studies investigating the molecular basis for the beneficial effects of ET in HFpEF are warranted.

SUMMARY

The evidence discussed in this article from clinical and bench-type studies has demonstrated that ET does reverse the HF-associated pathology at the clinical and molecular levels. There are clinically relevant exercise-induced changes of LV function and reverse remodeling, of the vascular system, of the skeletal muscle, and even in HFpEF. Even though this debilitated patient population refers to patients with CHF has resulted in a class I recommendation for ET in chronic HF in all major national and international guidelines, further research is warranted to investigate molecular changes induced by ET in patients with preserved ejection fraction. Furthermore, mechanisms underlying the supposedly superior effects of HIIT need to be further elucidated.

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