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Exercise in Patients with Heart Failure

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Abstract

For the patient with heart failure, dyspnea and fatigue resulting in diminished exercise tolerance are among the main factors contributing to decreased social and physical functioning and quality of life. There has long been evidence that measures of cardiac function such as ejection fraction and cardiac output only poorly correlate with a patient's capacity to exercise, suggesting the involvement of factors other than those impacting the central circulation. The lack of a close correlation between central hemodynamics and exercise tolerance has led to investigations into alterations in the periphery, such as abnormalities in vascular endothelial function, hyperactivation of the sympathetic nervous system, and changes in structure and oxidative capacity of skeletal muscle, which are commonly seen in patients with heart failure. Over the past two decades, numerous clinical studies have demonstrated the beneficial impact of exercise training on skeletal muscle energy metabolism, vascular function, and ventilatory capacity, which correlate with measures of exercise tolerance, improvements in hospitalization rates and quality of life of patients with heart failure. In accordance with recent guidelines set forth by the leading cardiology societies in the United States and Europe, physicians are urged to emphasize exercise training for all clinically stable patients with heart failure using individualized protocols that feature early mobilization after acute exacerbations of disease and gradual increases in intensity.

Keywords

Heart failure; skeletal muscle; vascular function; exercise capacity; exercise training

INTRODUCTION

Heart failure is a prevalent disease affecting approximately five million Americans and 10% or more of those aged 70 years and older.^{1,2} Despite significant advances in therapy, heart failure remains a significant cause of hospital admissions and patients who are symptomatic have a one-year mortality rate approaching 45%.² For the patient, dyspnea and fatigue resulting in diminished exercise tolerance are among the main factors contributing to decreased social and physical functioning and quality of life.³ There has long been evidence that measures of cardiac function such as ejection fraction and cardiac output only poorly correlate with a patient's capacity to exercise, suggesting the involvement of factors other than those impacting the central circulation. Furthermore, many studies of the effects of exercise in patients with heart failure have failed to demonstrate improvements in cardiac output, stroke volume, or ejection fraction, despite showing gains in exercise capacity and peak oxygen uptake (VO_2),⁴ which has been validated as an excellent isolated predictor of outcome in this population⁵. The lack of a close correlation between central hemodynamics

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and exercise tolerance has led to investigations into alterations in the periphery, such as abnormalities in vascular endothelial function, hyperactivation of the sympathetic nervous system, and changes in structure and oxidative capacity of skeletal muscle, which are often seen in patients with heart failure.

PERIPHERAL FACTORS THAT DETERMINE EXERCISE CAPACITY IN HEART FAILURE

MUSCLE

The myopathy associated with heart failure affects both cardiac and skeletal muscle, and encompasses alterations in structure and function. Mitochondrial oxidative capacity is impaired due to decreased oxidative enzyme activity, mitochondrial volume density and biogenesis, as well as increased reliance upon glucose rather than fatty acid oxidation. There is a shift from fatigue-resistant type I fibers that primarily rely on mitochondrial oxidative phosphorylation to generate ATP to type II fibers that have a higher glycogen content and derive most of their energy from glycolysis. Additionally, skeletal muscle in heart failure patients has decreased capillary density⁶, which correlates with maximal VO_2 and total exercise time⁷. Fiber atrophy and decreased muscle mass also occur, and have been demonstrated to account for much of the variability in peak VO_2 .⁸

In an effort to determine the link between changes in muscle mass, strength, fiber type, and parameters of exercise capacity, Vescovo et al. showed that heart failure patients with low peak VO_2 and high fatigability have increased myocyte apoptosis. Fiber cross-sectional area and prevalence of apoptosis were found to correlate with reduction in peak VO_2 and endurance during repetitive exercise.⁹ Further, skeletal muscle wasting has been attributed in part to the elevated levels of angiotensin II known to occur in heart failure, which reduce appetite and enhance catabolism. Tabony et al. infused mice with angiotensin II and found they had a significant additional decrease in skeletal muscle mass when controlling for decreased caloric intake.¹⁰

VASCULATURE

The endothelium plays an important role in regulating vascular tone, and abnormalities in vascular endothelial function shown to occur in heart failure patients are associated with a generalized reduced vasodilatory capacity and increased mortality risk.^{11–13} Endothelium-derived nitric oxide-mediated vasodilation is decreased in the peripheral, coronary, and pulmonary circulations of patients with HF.^{14–16} The inability of the peripheral vasculature to respond physiologically to variations in cardiac output, peripheral blood flow and positional changes results in increased peripheral vascular resistance and imbalance in blood pressure regulation in patients with advanced heart failure. The underlying mechanisms are still unclear. Endothelial cell apoptosis¹⁷ and increased oxidative stress¹⁸, as well as the impact of reduced cardiac output and lower blood pressure waveforms, have been suggested to contribute to this phenomenon.

VENTILATORY SYSTEM

Patients with heart failure are known to have exaggerated increases in minute ventilation during exercise disproportionate to the increase in carbon dioxide production¹⁹, and this has been associated with poor prognosis for patients with moderate to severe heart failure²⁰. Even in those patients with preserved exercise tolerance, abnormal enhancement of the ventilatory response to exercise indicates dysregulation of the cardiorespiratory reflex and independently predicts increased mortality.²⁰ Elevated pulmonary pressures, ventilation/perfusion mismatch, earlier onset of metabolic acidosis, dysregulation of reflex control, deconditioning, and an abnormal pattern of rapid, shallow respirations have been proposed

mechanisms for the exaggerated ventilatory response to exercise in patients with heart failure.²¹

Several studies have also established the presence of inspiratory muscle weakness, which is likely a manifestation of global skeletal muscle myopathy. A prospective study of nearly 250 patients showed that degree of respiratory muscle weakness is related to the severity of heart failure, as evidenced by a correlation between maximum inspiratory pressure ($P_{i_{max}}$) and New York Heart Association (NYHA) class. Furthermore, there was a striking difference in survival between the lowest quartile of $P_{i_{max}}$ (approximately 50%) and the highest quartile (15%) over the 3-year follow-up period.²²

EFFECTS OF EXERCISE ON PERIPHERAL DERANGEMENTS IN HEART FAILURE

MUSCLE

There is significant evidence of a link between the enhancement of peak oxygen uptake and exercise capacity seen after training and correction of skeletal muscle derangements in patients with heart failure. Several small studies conducted in the 1990s demonstrated correlations between improved parameters of exercise tolerance and amelioration of some of the changes thought responsible for reduced oxidative capacity of skeletal muscle.^{23–25} Exercise training was shown to induce increased mitochondrial volume density as well as a shift from type II back to type I fibers.²⁶ More recently, Williams et al. conducted a small randomized controlled trial to study the impact of resistance training on skeletal muscle mitochondrial ATP production rate, metabolic enzyme activity and capillary density and found significant improvements with training compared to usual care alone. Furthermore, these changes in the oxidative capacity of skeletal muscle correlated with improvements in peak VO_2 .²⁷

Insulin resistance, which is commonly seen even in nondiabetic patients with heart failure, has also been associated with reduced exercise capacity.²⁸ One proposed explanation for the prevalence of insulin resistance has been functional resistance to adiponectin, an insulin-sensitizing adipocytokine. Van Berendoncks et al. studied heart failure patients who underwent 4 months of combined endurance and resistance exercise training and found, at baseline, a negative correlation between levels of adiponectin mRNA in skeletal muscle and VO_2 peak and muscle strength, as well as a positive correlation between measures of exercise capacity and mRNA expression of the skeletal muscle receptor for adiponectin, AdipoR1, and the downstream signaling molecules AMPK- α 1 subunit and PPAR- α , all suggesting a link between functional adiponectin resistance and decreased exercise capacity. After exercise training, adiponectin mRNA in skeletal muscle decreased by 67% and mRNA expression of AdipoR1, PPAR- α , and AMPK all increased significantly, approaching normal levels.²⁹ By improving skeletal muscle responsiveness to adiponectin, exercise training may increase insulin sensitivity in patients with heart failure.

VASCULATURE

A significant amount of research on the mechanisms responsible for the decreased cardiovascular risk associated with exercise training has focused on its direct effects on the microstructure of the peripheral vasculature. A prospective cohort study of 16 patients participating in a 3-month exercise training program (aerobic exercise with or without strength training) found that oxygen reperfusion rate and vascular reactivity following the release of vascular occlusion, both indirect indices of endothelial function, increased significantly after exercise training. The study authors postulated that improved peripheral circulation seen after exercise training could be due to improved peripheral vascular

resistance, anti-inflammatory effects of exercise, and attenuation of neuroendocrine activation.³⁰

Maiorana et al. found that identical exercise regimens corrected endothelial dysfunction and induced improvement in nitric oxide-mediated acetylcholine-induced vasodilator function in subjects with heart failure and type II diabetes mellitus³¹, but not in asymptomatic age-matched controls³², which suggests that it may be difficult to enhance function above a “normal” level in healthy persons. Nevertheless, the changes in shear stress associated with acute exercise are a potent stimulus of vasodilator adaptation in patients with heart failure.

Animal studies have shown that exercise training leads to changes in the elastin, collagen, and smooth muscle content in the aortic wall. The thoracic aorta, which has a higher elastin/collagen ratio than distal arteries, has an important role in dampening pressure oscillations and thus minimizing pulsatility. In both human and animal models, hypertension has been associated with microstructural remodeling and mechanical changes in the aorta, contributing to increased wall stiffness and transmission of pressure oscillations which have been associated with end organ damage. Animal studies have demonstrated that aerobic exercise training reversed altered vascular structure and normalized the wall/lumen ratio of the arteriole.³³

VENTILATORY SYSTEM

In a small randomized controlled trial, Myers et al. demonstrated that 2 months of aerobic endurance training led to improved ventilatory response, increased efficiency of ventilation, reduced lactate levels in the blood throughout exercise, and delayed lactate threshold, factors all known to impact exercise capacity.²¹ Additionally, Guazzi et al. found that patients with heart failure have impaired gas-diffusion across the alveolar capillary membrane that improved after exercise training. Increased diffusion capacity and conductance of the alveolar capillaries correlated with improvement in peak VO_2 after 8 weeks of aerobic endurance exercise.³⁴

Targeted training of the diaphragm and other muscles of respiration, either alone or as an adjunct to global exercise training, also leads to improvements in ventilatory function, as evidenced by increased $\text{P}_{\text{i,max}}$ and peak circulatory power, as well as in exercise capacity, demonstrated by enhanced peak VO_2 and oxygen uptake efficiency slope. Furthermore, inspiratory muscle training has been shown to improve patients' quality of life and functional status.³⁵ Most studies that have demonstrated the benefits of inspiratory muscle training have been conducted in patients with inspiratory muscle weakness ($\text{P}_{\text{i,max}} < 70\%$ of predicted) at baseline.

EXERCISE AS A NON-PHARMACOLOGIC INTERVENTION IN HEART FAILURE

DIFFERENT MODALITIES OF EXERCISE

There are three main types of exercise training programs: 1) aerobic endurance (continuous or interval), 2) strength/resistance, and 3) respiratory. In particular, several groups have studied the impact of incorporating strength/resistance training into the more traditionally prescribed endurance training regimens. A randomized study of nearly 60 heart failure patients assigned to either endurance training alone or combined training demonstrated that maximal exercise capacity and work-economy increased significantly more in the combined group.³⁶ Similarly, Anagnostakou et al. randomized heart failure patients to interval cycle training alone or a combined program including strength training of targeted large muscle groups and found that although peak oxygen uptake increased in both groups, a significant

improvement in flow-mediated arterial dilation occurred only in the combined group.¹² These and similar studies suggest that resistance training may confer additional, perhaps unique, improvements in muscle strength and endurance, as well as vascular reactivity and favorable remodeling of conduit arteries.³⁷

HF-ACTION TRIAL

To date, there has only been one large, multi-center, randomized controlled trial to investigate the effect of adding exercise training to optimized medical treatment on mortality, hospitalizations, and patients' self-reported health status and quality of life. Data from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) showed that exercise training led to reductions in all-cause mortality and hospitalizations that reached a modest level of significance after adjustment for highly prognostic baseline characteristics such as duration of the cardiopulmonary exercise test and history of atrial fibrillation or flutter.^{38,39}

Despite previous smaller studies which suggested positive effects of exercise training on physical function, quality of life, biomarkers and even survival and hospitalizations, there was lingering concern about safety. Though the American College of Cardiology and the American Heart Association recommend that physical activity be considered for medically stable patients with systolic dysfunction, the lack of strong evidence from adequately powered studies likely prevented widespread adoption of this practice.³⁸ HF-ACTION was important in establishing the safety of exercise training in patients with NYHA II–IV heart failure showing comparable event rates in both groups but reduced hospitalizations and better quality-of-life in the exercise arm of the trial.³⁹

Investigation of the impact of exercise training on patients with heart failure is ongoing following the results of HF-ACTION. Recently, Nishi et al. examined the efficacy and safety of exercise training in patients with advanced heart failure on β -blocker therapy who all had a left ventricular ejection fraction less than 25%, compared to those enrolled in HF-ACTION in which half of the patients had an ejection fraction greater than 25%, and found a significant increase in peak VO_2 , peak work rate, and decreased plasma BNP levels solely in the group that underwent exercise training.⁴⁰ One patient (3%) in the exercise training group experienced worsening of heart failure during the study, and there were no serious cardiac events such as death or cardiopulmonary arrest.

CURRENT RECOMMENDATIONS FOR EXERCISE IN HEART FAILURE

In 2009, the American College of Cardiology and the American Heart Association established updated guidelines for the diagnosis and management of heart failure and recommended that exercise training be prescribed in conjunction with drug therapy for all stable outpatients.⁴¹ Likewise, in 2008, the European Society of Cardiology firmly recommended regular physical activity and structured exercise training for patients with heart failure.⁴²

A consensus document of the European Association for Cardiovascular Prevention and Rehabilitation and the Heart Failure Association provides practical guidelines for implementation. Stable patients with NYHA class I–III heart failure should undergo exercise training using individualized protocols that begin with gradual mobilization, initially done without weights or equipment. Early mobilization after hospitalizations for acute exacerbations is recommended.⁴³

Both endurance and strength/resistance training have been shown to improve exercise time and peak VO_2 , as well as submaximal exercise capacity as assessed by the 6-min walking

test. Patients, particularly those with inspiratory muscle weakness, may derive additional benefit from respiratory muscle training. Physicians are encouraged to take into account the patient's preferences, abilities, and access to equipment and facilities when prescribing an exercise training program. However, patients over the age of 65 years accustomed to a sedentary lifestyle should utilize modalities other than resistance/strength training until they are better conditioned (VO_2 peak $>18\text{ml/kg/min}$ or $>450\text{m}$ on 6-min walking test).⁴³

In conclusion, exercise training is a safe non-pharmacological intervention in clinically stable patients with heart failure on standard medical therapy with positive effects on both morbidity and quality of life.

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Figure 1. Central and peripheral derangements in patients with heart failure contributing to impaired exercise tolerance. HR – heart rate; HTN – hypertension; LV – left ventricle; SV – stroke volume.

Table 1

Impact of exercise training on peripheral derangements associated with heart failure.

FUNCTIONAL EFFECTS OF EXERCISE TRAINING IN HEART FAILURE	
<u>Skeletal Muscle</u>	
•	Increased mitochondrial volume density and ATP production rate
•	Shift from type II back to type I fibers
•	Increased capillary density
•	Increased strength and endurance
•	Improved sensitivity to adiponectin
<u>Vasculature</u>	
•	Improved endothelium-mediated vasodilation
•	Favorable remodeling of conduit arteries
•	Increased diameter of arterioles
•	Decreased total peripheral resistance
<u>Ventilatory System</u>	
•	Increased $P_{i_{max}}$
•	Enhanced efficiency of ventilation
•	Reduced lactate levels during exercise
•	Improved gas diffusion across alveolar capillaries

Table 2

Summary of selected studies of aerobic endurance training in patients with heart failure.

Study	Year	Study design	# of patients	Duration	Improvement in peak VO ₂	Other findings
Maiorana et al. ³⁷	2011	Randomized controlled trial	12	12 wks	14.5 → 17.2 (18.6% ↑)	Increased brachial artery diameter
Bouchla et al. ⁴⁴	2011	Randomized trial	10	12 wks	15.9 → 17.2 (8.2% ↑)	Improved peak workload
Teffaha et al. ⁴⁵	2011	Randomized trial	24	3 wks	19.1 → 21 (9.9% ↑)	Increased LVEF and decreased HR at rest
O'Connor et al. ³⁹	2009	Randomized controlled trial	1159	Median: 30 mos	Median: 4% ↑	Decreased mortality and hospitalization
Beckers et al. ³⁶	2008	Randomized trial	30	24 wks	21.2 → 22.2 (4.7% ↑)	Improved work-economy, circulatory power, muscle strength and health-related quality of life
Hambrecht et al. ⁴⁶	2000	Randomized controlled trial	31	26 wks	18.2 → 23.0 (26.4% ↑)	Increased resting LVEF, decreased TPR and plasma epinephrine, improved NYHA class
Belardinelli et al. ⁴⁷	1999	Randomized controlled trial	50	8wks + 1 yr	15.7 → 19.9 (26.8% ↑)	Decreased mortality and hospitalization for heart failure
Coats et al. ²³	1992	Randomized cross-over study	17	8 wks	13.2 → 15.6 (18.2 ↑)	Improved ventilation and autonomic function

Legend: HR – heart rate; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; SV – stroke volume; TPR – total peripheral resistance

Table 3

Summary of selected studies of strength/resistance training in patients with heart failure.

Study	Year	Study design	# of patients	Duration	Improvement in peak VO ₂	Other findings
Savage et al ⁴⁸	2011	Prospective cohort	13	18 wks	14.6 → 15.6 (6.8% ↑)	Increased muscle strength and physical function
Maiorana et al ³⁷	2011	Randomized controlled trial	12	12 wks	13.7 → 16.4 (19.7% ↑)	Favorable remodeling of the brachial artery
Dean et al. ⁴⁹	2011	Prospective cohort	9	4 wks	Not assessed	Improved FMD
Williams et al ²⁷	2007	Randomized controlled trial	13	11 wks	13.8 → 15.5 (12.3% ↑)	Increased mitochondrial ATP production and capillary density in skeletal muscle
Selig et al ⁵⁰	2004	Randomized trial	39	12 wks	15.3 → 16.9 (10.5% ↑)	Improved muscle strength and endurance, FBF, and HRV

Legend: ATP – adenosine triphosphate; FBF – forearm blood flow; FMD – flow-mediated dilation; HRV – heart rate variability