Prognosis
Does Exercise Training Reduce Adverse Events in Heart Failure?

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KEYWORDS

• Prognosis • Oxygen uptake • Aerobic capacity • Cardiac rehabilitation • Cardiac output

KEY POINTS

- Exercise training in patients with heart failure (HF) is associated with numerous physiologic benefits.
- The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial along with systematic reviews and meta-analyses using the Cochrane database have greatly enhanced our understanding of the outcome benefits associated with endurance exercise training in patients with HF.
- Recent studies demonstrate that the benefits of training are similar between men and women with HF.

INTRODUCTION

Exercise intolerance, frequently exhibited by fatigue or shortness of breath with a minimal degree of exertion, is a hallmark of chronic heart failure (HF). Quantifying exercise intolerance has profound implications for the determination of disability, quality of life (QOL), prognosis, and the capacity to perform daily activities in patients with HF. One of the principal goals of treatment in HF is therefore to improve exercise capacity; therapies designed to improve exercise capacity in patients with HF are thus critical to improving outcomes. The pathophysiologic features of HF that underlie reduced exercise tolerance have been the focus of numerous investigations for several decades.[1,2] These features involve both central (cardiac) and peripheral (skeletal muscle and vascular) abnormalities, including impaired cardiac output responses to exercise, abnormal redistribution of blood flow, reduced mitochondrial volume and density, abnormal oxidative enzyme activity, impaired vasodilatory capacity, heightened systemic vascular resistance, and autonomic nervous system changes.[1–4] Until the late 1980s, patients with HF were commonly excluded from exercise programs because of concerns over safety, whether training caused further harm to an already damaged myocardium, and questions as to whether these patients could benefit from exercise. These concerns have been allayed by numerous studies performed over the last 25 years documenting that exercise training in stable patients with HF is safe; that training causes no further damage to the myocardium; and that training is associated with numerous physiologic, musculoskeletal, and psychosocial benefits.[1,4,5] Many studies preformed over the last 2 decades

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have also demonstrated improved clinical outcomes following exercise training in HF, including reductions in morbidity, mortality, and hospitalization, along with enhanced QOL.[1,4,6,7] This article provides an overview of the benefits of exercise training in HF and the implications of these benefits for improving outcomes. The application of recent meta-analyses, novel observations on exercise training and outcomes among women, and recent findings from the landmark HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial are discussed.

MECHANISMS OF BENEFIT WITH EXERCISE TRAINING AND IMPLICATIONS FOR IMPROVING OUTCOMES

Potential mechanisms by which exercise training may improve exercise capacity and reduce cardiac events in HF are outlined in **Table 1**; importantly, the extent to which one or a combination of these mechanisms may affect an individual patient's exercise tolerance varies considerably. Peak oxygen consumption (V_{O_2}) is strongly related to prognosis in patients with HF, and exercise training generally improves peak V_{O_2} in the range of 10% to 25%[1,4]; however, even small changes in peak V_{O_2} are associated with significantly improved outcomes.[8] Numerous central and peripheral factors influence peak V_{O_2}, but increases in peak V_{O_2} and related benefits from training are fundamentally related to the combination of an improvement in peak cardiac output, improved vascular reactivity, better utilization of oxygen through metabolic changes in the skeletal muscle, and more efficient ventilation. These mechanisms are outlined in the following section.

Central Adaptations

A general consensus exists that the benefits of exercise training in patients with HF are caused largely by adaptations in the peripheral vasculature and skeletal muscle rather than the heart itself.[4,9] Although the focus of these studies has been on patients with HF and reduced ejection fraction (HFrEF), this also seems to be the case among patients with HF and preserved EF (HFpEF).[10] This consensus evolved in part because of the recognition that EF is poorly correlated with exercise capacity.[1,3,4] However, although the preponderance of studies have reported that EF and other measures of contractility show minimal change following training, several studies have reported significant improvements in these indices.[11–14] Most of these studies have focused on resting EF, and less is known regarding indices of contractility during exercise. Because of the difficulty measuring cardiac output directly, it has not been widely reported; but studies using thermodilution techniques have reported increases in maximal cardiac output following training in the range of 5% to 20%.[15] A meta-analysis of 104 patients reported a mean increase in maximal cardiac output of 2.5 L/min, corresponding to a 21% increase.[9] Whether this increase in cardiac output is a result of increases in maximal heart rate or stroke volume is unclear;

Table 1
Potential mechanisms by which exercise training improves outcomes

System	Response to Training	Effect on Outcomes
Cardiac function	• Increased cardiac output • Increase or no change in contractility • Increased peak V_{O_2} • Improved ventilatory efficiency	• Increased exercise capacity • Improved QOL • Reduced mortality • Reduced hospitalizations
Regional blood flow	• Increased vasodilatory capacity • Improved endothelial function • Improved redistribution of flow	• Increased exercise capacity
Skeletal muscle	• Increased aerobic enzymes • Increased mitochondrial volume and density • Increased capillary density • Decreased muscle receptor sensitivity	• Increased exercise capacity • Improved physical function • Reduced ventilatory response • Reduced mortality
Autonomic nervous system	• Decrease in plasma norepinephrine • Increased heart rate variability • Reduced chemoreceptor and ergoreceptor sensitivity • Reduced ventilatory response	• Reduced cardiac rhythm disturbances • Reduced or no change in mortality

Abbreviation: V_{O_2}, peak oxygen consumption.