Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 58, No. 6, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.04.020

STATE-OF-THE-ART PAPER

The Role of Exercise Training in Heart Failure

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Exercise training in patients with systolic heart failure (HF) is an accepted adjunct to an evidence-based management program. This review describes the pathophysiologic features that are thought to be responsible for the exercise intolerance experienced in the HF patient. Significant research has expanded our appreciation of the interplay of hemodynamic, ventilatory, and skeletal myopathic processes in this common, chronic condition. Randomized, controlled exercise trials designed to measure endothelial function, inflammatory markers, sympathetic neural activation, and skeletal muscle metabolism and structure have further defined the pathophysiology, documented the impact of exercise training on these processes, and confirmed the benefit of this therapy. Consistent with prior clinical research and patient experience are the recently published results of the HF-ACTION (Heart Failure–A Controlled Trial Investigating Outcomes of exercise TraiNing), which demonstrated a modest improvement in exercise capacity, reduction of symptoms, and improved self-reported measures of quality of life without adverse events. Consideration is given in this review to the benefits of variable intensity programs and the addition of resistance exercise to a standard aerobic prescription. Despite increasing validation of the role exercise training plays in the modification of exercise intolerance, challenges remain in its routine therapeutic application, including acceptance and use as an adjunctive intervention in the management of the patient with HF, limited insurance coverage for HF patients in cardiac rehabilitation, tailoring of exercise programs to best address the needs of subgroups of patients, and improved short- and long-term adherence to exercise training and a physically active lifestyle. (J Am Coll Cardiol 2011;58:561–9) © 2011 by the American College of Cardiology Foundation

Prevalence rates for heart failure (HF) have continued to rise throughout the first decade of the 21st century in the United States and globally (1). Interwoven in this phenomenon is the increasing financial burden at national levels and the individual disability resulting from this chronic disease, which is manifest as exercise intolerance due to dyspnea and fatigue. Advancements in the understanding of oxidative metabolism and intracellular energy transfer in both skeletal and cardiac muscle, mechanisms of endothelial dysfunction, and the role of sympathetic neural activation and inflammatory cytokines provide possible mechanistic explanations of the pathophysiologic factors involved in the development of exercise intolerance (Table 1). Elegant, controlled studies designed to evaluate exercise training as a therapeutic intervention in the HF population suggest that many of these factors improve with training and are associated with beneficial changes in exercise tolerance. A growing body of clinical experience and published research data consistently demonstrates improvement in functional capacity, symptoms, and quality of life with exercise training in HF patients. Furthermore, recent data suggest a modest but positive impact on repeat hospital stay rates and mortality reduction (2). The majority of training trials include only patients with left ventricular (LV) systolic dysfunction. Because data on exercise in the patient with diastolic HF are limited to small observational studies with heterogeneous study populations and variable methods of evaluation, our discussion is limited in this area.

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Manuscript received February 8, 2011; revised manuscript received April 12, 2011, accepted April 19, 2011.

Impairment of Exercise Capacity in HF

Central circulation. The classic presentation of HF is that of exercise intolerance due to dyspnea and fatigue. In attempting to answer the question of exercise intolerance, consideration has been given to the systems involved in the exercise response, namely the central circulation, the ventilatory system, and peripheral vessels and skeletal musculature. Although abnormalities in the central hemodynamic response have been described, there remains the paradox that measures of resting ventricular function—such as ejection fraction—demonstrate a poor correlation with exercise capacity (3,4). However, a growing body of studies demonstrates an improvement in exercise capacity after cardiac resynchronization therapy, which might be in part due to the improvement in systolic function rendered by such treatment (5). The response of the central circulation to exercise in the patient with systolic HF is characterized by inadequate LV shortening with increases in end-systolic and

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Abbreviations and Acronyms

AHA = American Heart Association
AIT = aerobic interval training
Ang = angiotensin
BMI = body mass index
CO_2 = carbon dioxide
HF = heart failure
HR = heart rate
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
6MWD = 6-min walk distance
NADPH = nicotinamide adenine dinucleotide phosphate oxidase
NO = nitric oxide
RAAS = renin-angiotensin-aldosterone system
ROS = reactive oxygen species
VO_2 = oxygen uptake

end-diastolic volumes. An increase in ventricular filling pressures can give rise to secondary pulmonary hypertension, resulting in right ventricular dysfunction. Mitral regurgitation can result if annular dilation or papillary muscle dysfunction is present. A decreased cardiac output at submaximal and peak levels of effort is a result of a reduction in stroke volume coupled with a lower heart rate (HR) reserve (6). Diastolic dysfunction, if present, is defined by an increased resistance to ventricular filling. Left ventricular diastolic filling involves ventricular chamber pressure, compliance, and duration of diastole. The greater diastolic filling rate required during exercise is accomplished in the normal LV by an increase in chamber distensibility, which results in an increase in LV diastolic volume without a pressure increase. With diastolic dysfunction, ventricular distensibility during exercise is impaired, resulting in a rapid rise in LV diastolic pressure and pulmonary capillary wedge pressure and the subsequent experience of dyspnea. Several Doppler-echocardiographic studies (7–9) have found abnormalities of LV diastolic function (including the ratio of early diastolic peak transmitral velocity to myocardial tissue velocity and ratio of early to late transmitral diastolic velocity) to be independent predictors of diminished exercise capacity in those with preserved LV function.

Ventilatory system. Structural abnormalities of the ventilatory system, including pulmonary vascular damage and fibrosis from persistent pulmonary venous hypertension have been demonstrated in patients with HF. Also seen is a reduction in diaphragmatic strength (10). Despite the absence of pulmonary congestion, there is an exaggerated increase in minute ventilation with exercise, out of proportion to the increase in carbon dioxide production (11,12). It is apparent, however, that ventilatory abnormalities do not limit peak exercise performance in most patients. Breathing reserve remains high (13), arterial hypoxia does not generally occur (6), ventilatory threshold occurs early during progressive exercise testing (14), systemic and regional venous oxygen desaturation are maximal (6), and oxygen uptake (VO_2) frequently plateaus—all suggestive of a circulatory rather than a pulmonary limitation (Table 2) (15).

The periphery. SKELETAL MUSCLE. With maximal exercise testing, the HF patient typically reports leg fatigue. This fatigue is associated with increased lactate release from the legs, evidence supportive of skeletal muscle dysfunction. Lactate levels correlate closely with maximal exercise capacity, suggesting a link between muscle dysfunction and exercise intolerance in HF. Heart failure patients have decreased muscle mass of the lower extremities. Measured as thigh cross-sectional area, a modest correlation with peak exercise capacity has been shown (16). Quantification of capillary density has varied between studies; however, 1 study using cell-specific antibodies to measure capillary density found a significant reduction in microvascular density when compared with control subjects. In addition, capillary density correlated with maximal VO_2 and total exercise time (17).

Muscle biopsies of HF patients demonstrate reduced mitochondrial-based enzymes and mitochondrial size and a shift in fiber type from slow-twitch, oxidative type I fibers to fast-twitch, glycolytic type IIb fibers (18–21). Atrophy of both type IIa and IIb fibers with an increased percentage of type IIb fibers has been shown. A significant inverse relation was reported between the percentage of type IIb fibers and maximal VO_2 (22). Skeletal muscle metabolism is abnormal as well. Magnetic resonance spectroscopy has demonstrated an impairment of high-energy phosphate transfer during exercise in the HF patient (23). Skeletal muscle biopsies performed on HF patients and control subjects matched for age and peak VO_2 showed decreased vascular density and oxidative enzyme activity in the HF patients that could not

Table 1 Pathophysiological Mechanisms of Exercise Intolerance in Heart Failure

Cardiac
Systolic and/or diastolic dysfunction
Reduced stroke volume
Elevated filling pressures
Secondary pulmonary hypertension and RV dysfunction
Mitral regurgitation
Reduced chronotropic reserve
Ventilatory system
Exaggerated minute ventilation relative to CO_2 production
Pulmonary hypertension and resulting pulmonary vascular damage and fibrosis
Ventilation/perfusion mismatch
Alveolar edema
Skeletal muscle
Reduced muscle mass
Reduced Type IIa fibers relative to Type IIb fibers
Reduced enzymes for oxidative metabolism and generation of ATP
Delayed resynthesis of high-energy compounds
Endothelial function
Reduced nitric oxide
Increased reactive oxygen species
Reduced vasodilatory response to shear stress
Neurohumoral system
Increased sympathetic activity
Low vagal activity
Increased levels of pro-inflammatory cytokines

ATP = adenosine triphosphate; CO_2 = carbon dioxide; RV = right ventricular.

Table 2 Exercise Responses in Patients With Dyspnea Due to Heart Failure Compared With Pulmonary Disease

	Heart Failure	Pulmonary Disease
Peak VO_2	Reduced and might plateau	Reduced and does not plateau
Ventilatory threshold	Reduced	Normal or reduced; might not be attained
Breathing reserve, 1 – (peak VE/MVV)	>20%	<15%
Oxygen saturation	Normal	Often reduced >5%
VE/ VCO_2 slope	Might be elevated	Often elevated
Post-exercise FEV_1	Unchanged from rest	Might decrease compared with rest

Reprinted, with permission, from Balady et al. (15).

FEV_1 = forced expiratory volume in 1 s; MVV = maximum voluntary minute ventilation; VE = minute ventilation; VE/VCO_2 = ventilatory equivalent of carbon dioxide; VO_2 = oxygen uptake.

be explained by deconditioning alone (24,25). For a detailed discussion on skeletal myopathy in HF, the reader is referred to a recent review by Middlekauff (26).

ENDOTHELIAL FUNCTION. The vascular endothelium plays an important role in the regulation of arterial tone and, hence, blood flow to exercising muscles. This occurs through complex mechanisms that stimulate and control the release of nitric oxide (NO), a potent vasodilator (27). Release of NO is stimulated by serotonin, thrombin, acetylcholine, and other receptor-dependent agonists (27) and also by increased laminar shear stress, such as occurs during exercise and is associated with acute increases in pulsatile blood flow (28–30). The shear stress in turn stimulates mechanotransducers along the endothelium (including what have been recently termed "endothelial celia") (29,30) to convert the physical stress of flow to generate multiple biochemical signals that ultimately lead to the release of NO. Nitric oxide is counterbalanced by oxidative stress and the release of reactive oxygen species (ROS), which promote local vasoconstriction. The balance or lack thereof (as is present among patients with HF) among these many factors affects the functional state of the endothelium. Many studies have demonstrated evidence of abnormal endothelial function among patients with HF, which can be mitigated by exercise training and will be discussed in the following text. For a detailed discussion regarding exercise and vascular biology, the reader is referred to a recent review by Gielen et al. (31).

NEUROHUMORAL SYSTEM. Other investigative efforts focus on the neurohumoral systems modulating vascular tone that are activated in HF, including the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Vasoconstriction and a redistribution of blood volume with a chronically diminished blood flow to the exercising muscles have long been described. The RAAS activation results in release of angiotensin (Ang) II, which has a potent vasoconstrictive effect via activation of Ang II type 1 receptor. Ang II also stimulates nicotinamide adenine dinucleotide phosphate oxidase (NADPH) activity, which increases local ROS production. The result is a decrease in the half-life of endothelium-derived NO and subsequent endothelial dysfunction (31). Sympathetic activation causes further peripheral vasoconstriction. Catecholamine levels rise with exercise in patients with HF, but it is not clear whether this is a contributor to exercise intolerance or an indication of advanced disease (32).

INFLAMMATION. The role of inflammatory mediators, such as tumor necrosis factor and interleukin-6, in the pathogenesis of skeletal muscle wasting and fatigue in numerous clinical settings—including HF—is an area of active investigation (33–35). Elevated cytokines have been documented in HF patients with reduced lower limb muscle mass and strength (36) and functional class (37). Yet to be defined are possible triggers leading to expression of proinflammatory cytokines, although oxidative stress is felt to play a role (38). Inflammatory cytokines can lead to increased muscle catabolism, loss of muscle protein (39), and apoptosis in skeletal myotubes (40) associated with a decrease in maximal exercise capacity (41).

Impact of Exercise Training

Exercise training is recognized as a valuable adjunct in the therapeutic approach to the stable HF patient and, as such, is recommended by the American College of Cardiology and the American Heart Association (AHA) at a Class 1 level (42). In control subjects, exercise training can positively affect maximal VO_2, central hemodynamic function, autonomic nervous system function, peripheral vascular and muscle function, as well as exercise capacity. These adaptations result in a training effect, allowing an individual to exercise to higher peak workloads at a lower HR with each submaximal level of effort (43). Published studies evaluating the efficacy of exercise training in the HF patient report improvements of 18% to 25% in peak VO_2 and 18% to 34% in peak exercise duration. Subjective symptoms, functional class, and quality of life measures improve after training as well (44). Most exercise training studies in the HF patient employ moderate- to high-intensity exercise (70% to 80% peak HR), although a training effect has also been demonstrated after 8 to 12 weeks of low-intensity training (40% to 50% peak VO_2) (23,45).

The recently published findings of the HF-ACTION (Heart Failure–A Controlled Trial Investigating Outcomes of exercise TraiNing) lend support to a collective body of clinical experience and research findings addressing efficacy and benefits of exercise training in patients with HF (2,44,46–52). This was a multicenter, randomized, controlled trial designed to measure the effects of exercise training on clinical outcomes in medically optimized and stable patients with systolic HF (left ventricular ejection fraction [LVEF] ≤35%). The composite primary endpoint of the study was all-cause mortality or all-cause hospital stay. Subjects with New York Heart Association functional class II to IV symptoms (n = 2,331)

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were randomized to either 36 sessions of supervised, moderate intensity training (60% to 70% HR reserve) followed by home-based training or usual care. All subjects were followed for a median of 30 months. A nonsignificant reduction in the primary combined endpoint of all-cause mortality or hospital stay was found (hazard ratio: 0.93; p = 0.13). However, after adjustment for pre-specified predictors of mortality (duration of the cardiopulmonary exercise test; LVEF; Beck Depression Inventory II score; history of atrial fibrillation), the primary endpoint became modestly significant (hazard ratio: 0.89; p = 0.03). The latter adjustment enabled the analysis to more specifically compare patients of similar risk to increase the statistical power. Additional analysis revealed no significant difference in mortality (16% vs. 17%) between the exercise and control group, respectively. There was a modest but significant improvement in measured peak VO_2 in the exercise group compared with the control group (0.6 ml/kg/min vs. 0.2 ml/kg/min, respectively) at 3 months, which was similar at 1 year. In the exercise training group, the median improvement in measured peak VO_2 was only 4%; a level much lower than that reported in other, smaller training studies. However, these findings must be viewed in the context of the generally low rate of adherence to exercise in the training group, whereby only 30% of subjects exercised at or above the target number of min/week. Moreover, it is estimated that at least 8% of the control patients admitted to exercising throughout the entire study period. These factors might account for the limited improvement in exercise tolerance in the exercise group and attenuate differences in outcomes between the exercise and control groups (2).

The HF-ACTION study provides the largest single study where the safety of exercise in patients with stable HF can be assessed. Exercise training was generally well-tolerated and safe, a finding consistent with earlier, small, single-center studies showing adverse event rates to be low but lacking adequate numbers to evaluate mortality and morbidity as well as control subjects in many cases (46). Details of the reported events are provided in Table 3. Notably, of 490 patients with an implantable cardiac defibrillator in the exercise group, only 1 experienced implantable cardiac defibrillator firing during an exercise session. Overall, the adverse event rates during the entire study period did not differ between the exercise and control groups (2).

Central hemodynamic adaptations. Exercise training does not seem to improve cardiac output during submaximal exercise in patients with HF (21,53,54). Most studies show no change in resting LVEF, although 2 studies have demonstrated a slight increase in cardiac output at peak levels of exercise (53,55), and reductions of resting LV end-diastolic diameter, suggesting a training-induced reverse remodeling (55). Ventilatory threshold, a reproducible, nonvolitional measure of cardiovascular fitness is delayed with training and occurs at a higher VO_2. Pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance are usually unchanged after training either at rest or during exercise (53,56).

Table 3 Summary of Selected Adverse Events in the HF-ACTION Study*

Adverse Events	Usual Care (n = 1,171)†	Exercise Training (n = 1,159)
Pre-specified cardiovascular adverse events		
Worsening HF	340 (29.0)	303 (26.1)
Myocardial infarction	45 (3.8)	41 (3.5)
Unstable angina	88 (7.5)	86 (7.4)
Serious adverse arrhythmia‡	164 (14.0)	167 (14.4)
Stroke	28 (2.4)	33 (2.8)
Transient ischemic attack	23 (2.0)	20 (1.7)
Any of the above events	471 (40.2)	434 (37.4)
General adverse events		
Hospital stay for fracture of hip or pelvis	7 (0.6)	3 (0.3)
Outpatient fracture repair	20 (1.7)	13 (1.1)
ICD firing§	151/644 (23.4)	142/641 (22.2)
Hospital stay after exercise‖	22 (1.9)	37 (3.2)
Died after exercise¶	5 (0.4)	5 (0.4)

Values are n (%). There were no differences in adverse events between the treatment groups. *Unless otherwise indicated. †Follow-up data forms were not available for 1 patient. ‡Defined as sustained ventricular tachycardia lasting longer than 30 s, ventricular fibrillation, supraventricular tachycardia with rapid ventricular response lasting longer than 30 s, cardiac arrest, or bradycardia (heart rate <50 beats/min, symptomatic, and not felt to be related to medication). §Indicates the number fired/number of patients with an implantable cardioverter-defibrillator (ICD) (percentage). ‖Had at least 1 hospital stay due to an event that occurred within 3 h after exercise. ¶Patient died or not known whether patient died during or within 3 h after exercise. Reprinted, with permission, from O'Connor et al. (2).

HF = heart failure; HF-ACTION = Heart Failure–A Controlled Trial Investigating Outcomes of exercise TraiNing.

Effects of exercise training on LV diastolic function in patients with systolic dysfunction have included a significant reduction in LV diastolic wall stress at low work rates (50% peak VO_2). Training at this lower work rate resulted in a 30% increase in peak VO_2 after 2 months (57). In 1 study, 54 HF patients were randomized to 3 months of exercise training or to a control group. Calculations of elastance with Doppler echo diastolic measures showed a 27% reduction with exercise, with no change in ventricular volumes, mean blood pressure, or LVEF (58). In another study that evaluated patients with dilated cardiomyopathy and a Doppler mitral inflow profile suggestive of concomitant abnormal diastolic LV function, only those with delayed relaxation improved their functional capacity after training. In these latter patients, the diastolic filling pattern normalized after training. Those with a restrictive filling pattern, however, were found to have a worse prognosis and did not improve functional capacity or diastolic filling pattern after training (59).

Peripheral adaptations. Abnormalities of both skeletal muscle and vasomotor tone characteristic of HF patients can be reversed with exercise training (20,22). Exercise training can improve the volume density of mitochondria and the volume density of cytochrome c oxidase-positive mitochondria with an increase in expression of oxidative metabolic

enzymes (19–21). A return to type I oxidative fibers (a shift from type II) is seen on muscle biopsy (60). Peak exercise leg blood flow and leg arterio-venous oxygen difference are reported to increase after training (54). A decrease in leg venous lactate levels seems to be inversely related to the changes in mitochondrial volume density and not leg blood flow (60). Studies have documented improvements in endothelial function with exercise training. Endothelial function—evaluated by measuring brachial artery flow-mediated dilation—after handgrip exercise in HF patients normalized. After administration of a NO synthase blocking agent, flow attenuation suggested a NO-mediated training effect (60). Similar improvements in femoral artery flow were found in HF patients randomized to upright cycle exercise or usual activity. Endothelium-dependent change in peripheral blood flow was significantly correlated with a 26% increase in peak VO_2 (61).

NEUROHORMONAL ADAPTATIONS. Activation of RAAS resulting in vasoconstriction is another target of investigation in vascular disease. One study looked at the impact of regular physical activity on Ang II-mediated vasoconstriction mediated by Ang II-induced NADPH oxidase activation and ROS production (62). The messenger ribonucleic acid expression of NADPH oxidase activity and ROS generation were all significantly lower in the training group and associated with an improvement in acetylcholine-mediated vasodilation. Another study demonstrated that exercise training increases the vascular expression of anti-oxidative radical scavenger enzymes, including catalase and glutathione peroxidase (63). Although similar exercise effects remain to be demonstrated in HF patients and correlated with an improvement in functional capacity, it is plausible that similar mechanisms of endothelial dysfunction and regulation exist in both patient groups.

The evaluation of the effects of exercise training on sympathetic nervous activity in HF includes assessment of plasma norepinephrine levels, HR variability, and whole-body norepinephrine spillover. Although results vary among studies, most demonstrate the beneficial effects of enhanced vagal tone and decreased sympathetic tone with exercise training (44,64–66). These findings demonstrate that, when directly measured, there is a decrease in sympathetic nerve activity with exercise training in HF patients. To evaluate the ergoreceptor contribution to exercise in HF, dynamic handgrip and 3-min post-handgrip regional circulatory occlusion was evaluated in HF patients and control subjects. After 6 weeks of forearm training, ergoreflex contributions—as measured by HR variability, changes in diastolic pressure, leg vascular resistance, and ventilation—were reduced more in HF patients (67).

EFFECTS ON INFLAMMATION. Controlled trials of exercise training also demonstrate reduced levels of the inflammatory cytokines tumor necrosis factor-alpha and interleukin-6 after training and a correlation with an improvement in peak VO_2 (27,68). These observations suggest that inflammatory mediators are involved in the skeletal muscle myopathy of HF and the consequent experience of fatigue and exercise intolerance.

Training considerations. The standard recommendations for exercise training in general include aerobic activity performed at least 30 min, 5 or more days/week, with specific parameters that define exercise intensity, duration, and frequency. Exercise intensity in HF training has varied between studies, and some study protocols have used interval or variable intensity training. Practice guidelines (69) promote the development of individual exercise prescription on the basis of an objective measurement of functional capacity. In most clinical settings, an intensity range of 70% to 80% of peak HR determined from a symptom-limited exercise test is used. Exercise training research has examined the additional benefits of high-intensity exercise compared with low- to moderate-intensity exercise in a variety of populations (57,70,71). Recently, a seminal study has evaluated the effect of aerobic interval training (AIT), which involves alternating 3- to 4-min periods of exercise at high intensity (90% to 95% HR_{peak}) with exercise at moderate intensity (60% to 70% HR_{peak}) among patients with post-infarction HF. This comprehensive assessment included measured aerobic capacity, measures of LV remodeling, skeletal muscle mitochondrial function, and endothelial function. Patients were randomized to AIT, moderate continuous training (70% peak HR), or usual activity. The VO_2 increased more with AIT and was associated with reverse LV remodeling (increase in LVEF, decrease in LV volumes, and decrease in pro-brain natriuretic protein). Endothelial function demonstrated greater improvement with AIT, and mitochondrial function increased only with AIT (71). A recent small randomized study has shown that 3 months of progressive training at high exercise intensities of 80% to 90% of peak HR yielded significant additional improvement in peak VO_2, beyond that attained after cardiac resynchronization therapy (5).

Modality of training is another consideration. Although aerobic exercise remains the mainstay of clinical training programs, resistance training has also shown benefits (72), including improved muscle strength, endurance, and blood flow associated with a lower VO_2 at submaximal workloads (73,74). In 2 small studies that randomized HF patients to either resistance exercise or usual activity (75,76), echocardiographically determined LV volumes remained unchanged, and modest improvements in resting LVEF were noted after 8 weeks of training, thus suggesting that resistance exercise has no deleterious effects on LV function or structure. A summary of published resistance training studies in HF is provided in Table 4 (77–82). The beneficial effects of exercise in patients with HF are summarized in Table 5.

ADHERENCE TO TRAINING. Despite ample evidence of benefit, the experience—assuming that exercise is even

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Table 4 Summary of Resistance Training Studies in HF

First Author (Ref. #)	n	Age (yrs)/Sex	Purpose	Findings
McKelvie et al. (81)	10 exercise No control subjects	Age not provided Men only	Examine acute CV response to RT; compare with cycling	Similar SBP, lower RPP, slower HR, higher DBP; no change ESV/EDV with effort
Hare et al. (82)	9 exercise No control subjects	Mean age 63 Men only	Test effects of RT on strength, submax/max aerobic capacity, forearm blood flow	Increase strength, increase basal forearm blood flow, no change aerobic capacity
Oka et al. (79)	20 exercise 20 control subjects	Age 30–76 23 men/ 17 women	Examine safety, efficacy and adherence to at-home AT and RT	Decrease SXS, improve QOL, no AE
Pu et al. (77)	9 exercise 7 control subjects	Mean age 76 Women only	Compare muscle FX with aerobic capacity; test efficacy of high-intensity RT in older pts with HF	No AE, increase strength, increase 6MWD, improve muscle FX/structure
Selig et al. (73)	10 exercise 20 control subjects	Mean age 65 33 men/ 6 women	Reversibility of HF dysfunction with RT	Favorable changes to skeletal muscle strength and endurance, peak VO_2, forearm blood flow, HRV
Levinger et al. (76)	8 exercise 7 control subjects	Mean age 56 Men only	Determine effects of RT on LV structure and FX	No significant effect on LVEDD and LVESD; Improved EF and FS in RT group
Beckers et al. (74)	28 AT/RT 30 AT only	Mean age 58 42 men/ 16 women	Compare AT/RT with AT alone	AT/RT >improvement submaximal exercise capacity, muscle strength and QOL; no difference in LVEDD/LVESD
Palevo et al. (75)	10 exercise 6 control subjects	Mean age 68 Men only	Determine effects of RT on LV FX, exercise capacity, muscle strength, body composition	Modest improvement in EF, SV, muscular strength and 6MWD
Swank et al. (80)	42 exercise No control subjects	Age not provided 27 men/ 15 women	Evaluate AT/RT for differential responses between sex and older individuals with HF	All improved strength; all increased aerobic efficiency
Maiorana et al. (78)	12 RT 12 AT 12 control subjects	Mean age 61 32 men/ 4 women	Evaluate impact of AT vs. RT on arterial remodeling	Decrease brachial artery wall thickness in RT; increase brachial diameter in AT and RT

AE = adverse events; AT = aerobic training; CV = cardiovascular; DBP = diastolic blood pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; FS = fractional shortening; FX = function; HF = heart failure; HRV = heart rate variability; LVEDD = left ventricular end-diastolic dysfunction; LVEDS = left ventricular end-systolic dysfunction; pts = patients; QOL = quality of life; RPP = rate pressure product; RT = resistance training; SBP = systolic blood pressure; 6MWD = 6-min walk distance; SV = stroke volume; SXS = symptoms.

initiated—is that adherence to exercise training is not maintained. The observation that only 30% of the 1,159 subjects in the training group of the HF-ACTION study were adherent to the program as prescribed is sobering in the context of the close monitoring and surveillance provided to these patients by the study investigators.

A Cochrane review of publications since June 2001 evaluating interventions aimed at improving enrollment (uptake) and adherence to cardiac rehabilitation programs and their components found few practice recommendations could be made, although those targeting individual patient barriers might increase success (83). Individual obstacles to exercise that need to be evaluated and possibly mitigated include such things as physical and psychological comorbidities, musculoskeletal limitations of aging, impaired cognition, sleep disturbances, and poor health literacy. Even discounting any recent inactivity due to HF itself, the majority of HF patients referred to a cardiac rehabilitation program for exercise training begin at a completely sedentary baseline of activity (84,85). Exercise is being introduced as a new behavior, and as with all behavior change, many factors are involved in successfully initiating and maintaining it for the long term. In a recent AHA Scientific Statement (84) aimed at improving outcomes from chronic conditions such as HF, the concept of self-care is described. Addressing the necessary knowledge base, behavioral skills, and social supports required of an individual to monitor their health status and make appropriate decisions, self-care addresses some of the challenges experienced in exercise initiation and maintenance. Further emphasis on self-care might serve as a framework for future tailored interventions in this area.

Table 5 Beneficial Effects of Exercise in Heart Failure

Aerobic training	Increased exercise capacity (2,54)
	Lower heart rate response to submaximal exercise (54)
	Improved diastolic function (57–59)
	Improved endothelial function (61,62)
	Increased skeletal muscle oxidative capacity (19,20,60)
	Enhanced vagal tone and lower sympathetic tone (65,66)
	Reduced inflammatory cytokines (27,68)
	Lower all-cause mortality or hospital stay (2,45)
	Improved health status (44,45,47)
Resistance training	Increased muscle strength and endurance (73,75,82)

Challenges other than those related to the individual patient include professional and programmatic ones. Referral rates from practitioners remain low, despite a strong recommendation by both the AHA and American College of Cardiology that exercise be considered a beneficial adjunctive treatment in patients with current or prior symptoms of HF and reduced LVEF (42). Perhaps one of

the greatest obstacles to referral is that HF is still not considered a qualifying diagnosis for cardiac rehabilitation benefits by Medicare, the major provider of healthcare reimbursement for this population in the United States. Although the body of evidence to support such coverage is large, continued advocacy by professional organizations and providers of cardiac rehabilitation to include HF as a qualifying diagnosis is needed. Additional cost-effectiveness studies that evaluate exercise training as a component of a comprehensive multifaceted HF management program will no doubt assist in this effort, especially in this time of increased accountability for care and constrained fiscal resources.

Summary

A preponderance of the evidence supports the benefits and safety of an exercise training program for the stable, systolic HF patient who is receiving optimal medical treatment. Functional capacity improves, symptoms of dyspnea and fatigue diminish, and self-reported quality of life benefits. Several small randomized exercise training trials have demonstrated not only an improvement in peak exercise capacity but a modification of multiple measures of metabolic function, vascular tone, cytokine production, and neural activation. All suggest a positive and important role for exercise in the interruption and improvement in the major limiting symptom of HF, namely exercise intolerance. Although repeat hospital stay rates and mortality are only modestly improved as a combined endpoint, data regarding the latter might be limited because of the high rate of nonadherence to the exercise program in the training group (2). In an effort to extend the benefits of exercise training to a greater number of HF patients, we must address such issues as providing cardiac rehabilitation as a covered insurance benefit for the diagnosis of HF; improving the rate of referral and enrollment of such patients in cardiac rehabilitation programs; further defining training programs with regard to recent data on intensity and modality to optimize functional outcome; and finally, employing methods that optimize adherence to exercise and thus generate the greatest yield of benefits that range from the cellular level to exercise tolerance, the quality and perhaps the length of life.

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Key Words: cardiac rehabilitation ■ exercise ■ heart failure.