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Exercise intolerance and the role of exercise training in heart failure

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Heart failure (HF) often leads to impaired exercise tolerance that incurs significant limitations in patients with this disability and, with the increased prevalence of HF, there are also important and widespread medical, social, and economic implications.[1] In patients with atherosclerotic cardiovascular disease, exercise training has been demonstrated to improve functional capacity and quality of life, reduce ischemia, and lower subsequent mortality.[2,3] Previously, exercise was proscribed in patients with HF; however, seminal data first published in the late 1980s sparked a remarkable interest in the application of exercise training to HF patients.[4,5] Recent studies demonstrating an improvement in functional capacity with exercise training in HF patients have led to the recognition that regular exercise can be a valuable adjunctive treatment strategy for stable HF patients. The application of exercise training as a therapeutic intervention has also yielded novel insights into the central and peripheral mechanisms of exercise intolerance. Accordingly, the American Heart Association recently published a comprehensive scientific statement on the topic of exercise and HF[6] that aims to stimulate the appropriate use of exercise training in HF patients and promote further research examining the many questions in this area that remain unanswered. The multicenter Heart Failure ACTION (A Controlled Trial Investigating Outcomes of exercise traiNing) trial, recently funded by the National Institutes of Health, promises to provide information regarding the effect of exercise training on morbidity and mortality in HF patients. Since the bulk of the clinical data to date have included only patients with left ventricular systolic dysfunction, this issue of *Cardiology Rounds* will not discuss the topic of diastolic or preserved systolic function HF.

Factors affecting exercise intolerance in heart failure

Exercise intolerance is often the initial presenting symptom in patients with left ventricular (LV) dysfunction and is a clinical hallmark of this condition. However, the pathophysiological basis for the development of limiting symptoms (eg, fatigue and dyspnea) remains somewhat controversial.[7-12] It is interesting (and somewhat surprising) that measures of the degree of LV systolic function (eg, ejection fraction) are only poorly correlated with exercise capacity.[13,14] Oxygen uptake (VO_2) is considered to be the best measure of cardiovascular fitness and exercise capacity. Maximal oxygen consumption (VO_{2max}) is the greatest amount of oxygen consumed from inspired air while performing dynamic exercise involving a large part of total muscle mass (from the Fick equation: VO_2 = cardiac output x arterio-venous oxygen difference).[15]

Each of the 3 systems participating in the exercise response – the central circulation, the peripheral vessels and skeletal muscles, and the ventilatory system – has been studied extensively.

The central circulation

The central circulation in LV systolic dysfunction is characterized by inadequate LV shortening, increases in end-systolic and end-diastolic volume, and a decrease in ejection fraction. Secondary

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Figure 1: Comparison of cardiac output (C.O.) and arteriovenous oxygen difference (AVOD) during graded exercise in normal subjects (NL) and those with heart failure (HF)[16]

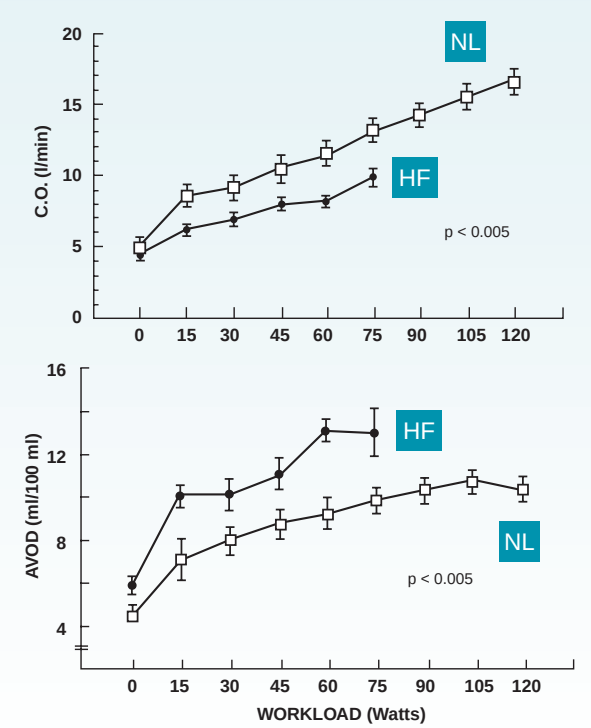
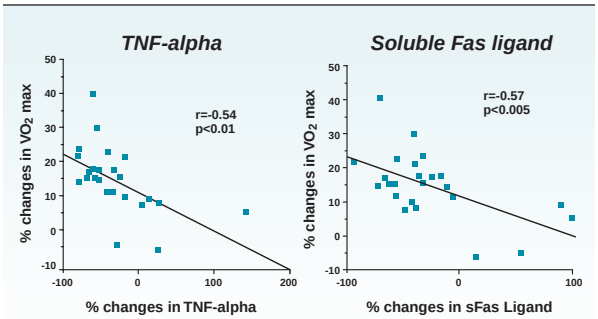


Figure 2: Changes in TNF-alpha and soluble Fas ligand are inversely related to changes in exercise capacity in subjects with heart failure. These markers are reduced as exercise capacity increases.[27]



pulmonary hypertension may result in right ventricular dysfunction and mitral regurgitation may arise from annular dilatation or papillary muscle dysfunction. Reduction in forward stroke volume coupled with a lower heart rate reserve (difference between resting and peak heart rate),[4] yield a lower cardiac output at submaximal and peak levels of effort (Figure 1).[16] In addition, diastolic dysfunction often accompanies systolic dysfunction and is characterized by an increased resistance to filling of one or both ventricular chambers. LV diastolic filling is governed by the pressure in the ventricular chamber, the LV compliance, and the duration of diastole. The normal left ventricle accomplishes a higher diastolic filling rate during exercise by increasing its distensibility, thus increasing LV diastolic volume without raising its pressure. Patients with LV diastolic dysfunction have an impaired ability to increase ventricular distensibility with exercise, thus leading to a rapid rise in LV diastolic pressure and pulmonary capillary wedge pressure, and hence, exercise-limiting dyspnea.

The periphery

The "periphery" is abnormal in patients with LV systolic dysfunction with changes observed in peripheral vascular tone, as well as in the structure and function of skeletal muscle. During maximal exercise testing, patients typically report leg fatigue. This fatigue is associated with a greater release of lactate from the legs, thus providing objective evidence of muscle dysfunction. The degree of abnormality in lactate relates closely to maximal exercise capacity, suggesting a close link between muscle dysfunction and exercise intolerance in HF. Duscha et al noted that skeletal muscle abnormalities in heart failure patients are beyond that which would ordinarily exist in sedentary individuals and they defined this as a state of "ultradeconditioning."[17] This skeletal muscle dysfunction may be due, in part, to inadequate blood flow, since 50% to 60% of HF patients have lower than normal blood flow to the legs during exercise. In the remaining patients, blood flow during exercise is within the normal range, although muscle lactic acid release is impaired.[18] Intrinsic skeletal muscle abnormalities have been described in HF patients despite normal limb blood flow and oxygenation. Muscle biopsy studies have demonstrated reduced mitochondrial-based enzymes, reduced mitochondrial size, decreased Type II muscle fiber size, and an increase in the percentage of type II fibers.[18-22] Using phosphorus nuclear magnetic resonance spectroscopy, a number of investigators have demonstrated that the metabolic responses of both the forearm and calf muscles to exercise are altered in HF patients. Phosphocreatinine depletion is more rapid, resynthesis of high-energy compounds (phosphocreatine and ATP) is delayed, and there is an earlier development of acidosis in these patients.[23] These abnormalities may be attributed to higher levels of inducible nitric oxide synthase (iNOS) in the skeletal muscles of HF patients. iNOS appears to attenuate mitochondrial energy transfer by reducing muscle creatine kinase. It has been demonstrated that exercise capacity is inversely related to iNOS levels and positively related to creatine kinase levels.[24]

Skeletal muscle mass of the lower extremities, measured using thigh cross-sectional area, has a modest correlation with peak exercise capacity.[25] Reduced skeletal muscle mass has been demonstrated in HF patients and becomes more apparent as the severity of HF increases.[26] Although this finding may be attributed, in part, to the disuse atrophy of a sedentary lifestyle, emerging data provide further explanations. Higher levels of apoptotic mediators[27] and lower levels of insulin-like growth factors (IGF-1)[28] in the skeletal muscles of HF patients may further contribute to their observed reduced muscle mass and ultradeconditioned state (Figure 2). Notably, HF patients with reduced lower limb muscle mass also have lower IGF-1 levels.[28]

The ventilatory system

The ventilatory system also demonstrates a wide range of changes in patients with LV systolic dysfunction, including structural abnormalities (pulmonary damage and fibrosis) and dynamic changes (eg, skeletal muscle fatigue).[29] However, it appears clear that ventilatory abnormalities do not limit peak exercise performance in most HF patients. Ventilatory reserve is high,[30] arterial O_2 and CO_2 concentrations remain normal,[5] the anaerobic threshold occurs early during progressive exercise testing,[31] systemic and regional venous oxygen desaturation are maximal,[4] and VO_2 often plateaus — all suggesting circulatory rather than pulmonary limitations.

The role of exercise training

Central effects

Although pharmacologic therapy is the cornerstone in the treatment of HF, exercise training can be an important adjunctive therapeutic modality in stable patients. Exercise training in apparently healthy persons alters maximal oxygen uptake, central hemodynamic function, autonomic nervous system function, peripheral vascular and muscular function, as well as submaximal exercise capacity. Collectively, these adaptations result in an exercise *training effect* that allows an individual to exercise to higher peak workloads with lower heart rates at each submaximal level of exercise.[15] To date, there are more than 30 published studies collectively involving several hundred HF patients that have evaluated the efficacy of exercise training. Improvements of 18%-25% in peak oxygen uptake and 18%-34% in peak exercise duration have been attained (Table 1). Subjective symptoms, activity profile, and quality of life scores have also improved after training.[32] Most exercise-training studies in patients with HF have generally employed moderate to high intensity exercise (70%-80% peak heart rate). However, two studies have demonstrated significant improvements in peak oxygen uptake and peak work rate after 8-12 weeks of lower intensity training (40%-50% of peak VO_2).[22,23]

Exercise training does not appear to improve cardiac output during submaximal exercise in patients with LV dysfunction.[22,34,35] Most studies show no change in resting ejection fraction, although one study demonstrated that with peak levels of exercise, cardiac output is slightly increased.[34] The ventilatory anaerobic threshold, an objective, non-volitional measure of cardiovascular fitness, is delayed after training and occurs at a higher O_2 consumption.[32,34] Pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance are usually unchanged after training either at rest or during exercise.[32,34] One study has demonstrated that HF patients with an impaired cardiac output response to exercise, usually do not improve their functional capacity with exercise training.[36] Although the use of invasive hemodynamic assessment in the large number of patients with LV dysfunction precludes broad screening of these patients prior to exercise training, further research in this area, perhaps using non-invasive determinants of exercise cardiac output, may offer additional insight into this potentially important observation.

Table 1: Studies on exercise training in chronic heart failure

Author	Year	N	EF (%)	Intensity
Conn, et al[51]	1982	10	29	70%-80% HR
Sullivan, et al[5]	1988	12	24	75% VO_2
Jette, et al[52]	1991	7	24	70%-80% HR
Meyer, et al[53]	1991	12	23	70 – 80% HR
Coats, et al[32]	1992	17	19	70%-80% HR
Koch, et al[54]	1992	12	26	Individualized protocol
Belardinelli, et al[22]	1995	16	31	40% VO_2
Belardinelli, et a[37]	1995	36	28	60% VO_2
Hambrecht, et al[19]	1995	12	26	70% VO_2
Keteyan, et al[55]	1996	15	21	60%-80% HR
Kavanaugh, et al[56]	1996	15	22	50%-60% VO_2
Kilavuori, et al[57]	1996	12	24	50%-60% VO_2
Wilson, et al[36]	1996	32	23	60-70% HR
Demopoulos, et al[33]	1997	16	21	50%-80% VO_2
Dubach, et al[35]	1997	12	32	70%-80% VO_2
Meyer, et al[58]	1997	18	21	50% VO_2
European Heart Failure Training Group[59]	1998	134	25	70%-80% HR
Hambrecht, et al[39]	1998	10	24	70% VO_2
Benardinelli, et al[60]	1999	50	28	60% VO_2
Braith, et al[43]	1999	10	30	70%-80% VO_2
Hambrecht, et al[61]	2000	73	27	70% VO_2
McKelvie, et al[62]	2002	181	<40	70% VO_2 and resistance training
Adamopoulos,et al[27]	2002	24	23	60%-80% HR

The effects of exercise training on LV diastolic function have not been well studied. In patients with systolic dysfunction, LV diastolic wall stress has been shown to be significantly lower during exercise at low work rates (50% peak VO_2), than that during conventional work rates (70%-80% peak VO_2). Such training at the lower work rate yielded a 30% increase in peak VO_2 after 2 months.[33] Another study demonstrated that among 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. In contrast, those with a restrictive filling pattern were found to have a worse prognosis and did not improve functional capacity or diastolic filling pattern after training.[37]

Peripheral effects

Skeletal muscle abnormalities found in HF patients can be reversed with exercise training.[20,21,32] Exercise training can improve the volume density of mitochondria and the volume density of cytochrome-c oxidase-positive mitochondria with an increase expression of enzymes for oxidative metabolism.[19,20,22,32] Peak exercise leg blood flow and leg arteriovenous oxygen difference appear to increase after training.[34]

Figure 3: Brachial artery flow-mediated dilation (blue bars) is impaired in subjects with heart failure (CHF) compared to normal subjects, and improved after training (CHF trained). Flow-mediated dilation (gray bars) is attenuated after administration of L-NMMA in all subjects.[38]

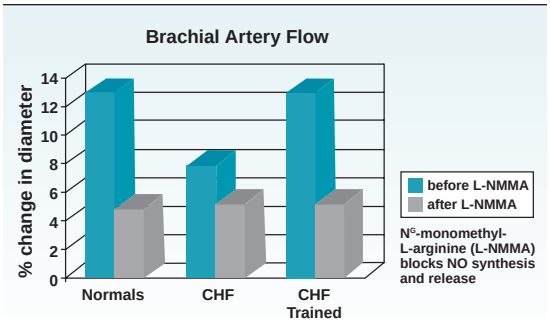
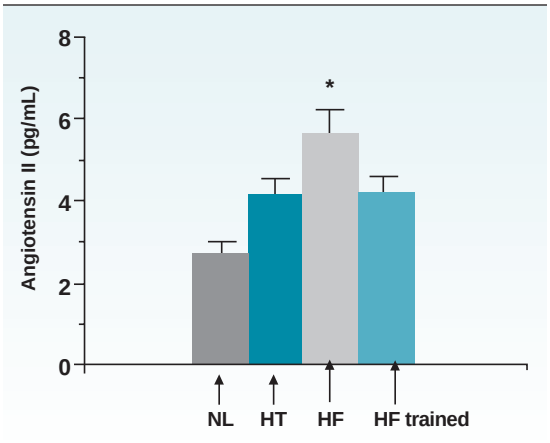


Figure 4: Angiotensin II levels are increased in subjects with heart failure (HF) compared to normal subjects (NL), and are reduced in heart failure subjects after exercise training (HF trained).[43]



HT = heart transplant patients

Improvement in endothelial function has been suggested as a possible mechanism for these findings and is an area of great research interest. Using measures of brachial artery flow-mediated dilation to assess endothelial function, forearm blood flow has been shown to normalize after local forearm muscle training in HF patients. This improvement is attenuated by local administration of N^G-monomethyl-L-arginine (L-NMMA) that blocks nitric oxide synthesis, thus indicating that the positive effects of exercise training on vascular function are at least, in part, mediated by nitric oxide (Figure 3).[38] Similarly, femoral artery flow responses to acetylcholine have been shown to improve in patients with HF after cycle exercise training, compared to sedentary control subjects. These improvements in flow responses show a modest positive correlation with improvements in peak VO_2 after training.[39] Further, exercise studies in patients without HF indicate that systemic improvements in endothelial function occur after training, as improved flow responses to acetylcholine are seen in non-trained limbs[40] and in diseased coronary arteries.[41]

Increased plasma catecholamines have been associated with a poor prognosis in patients with HF. Although results are variable, most studies demonstrate the beneficial effects of enhanced vagal tone and decreased sympathetic tone after exercise training.[32,42] Baroreflex dysfunction and renal hypoperfusion in HF patients lead to increased levels of the neurohormones (angiotensin, aldosterone, vasopressin, and atrial naturetic peptide). One study demonstrated that dynamic exercise training buffers this neurohormonal hyperactivity (Figure 4).[43] Controlled trials of exercise training also demonstrate reduced levels of the inflammatory cytokines (eg, tumor necrosis factor alpha [TNF-α] and interlukin-6 [IL-6]), in HF patients after training.[27] Whether these positive effects of exercise training on autonomic tone, neurohormones, and inflammatory cytokine levels actually yield benefits for the HF patient is not yet known. These results signal that the beneficial effects of exercise training may likely extend beyond improvements in exercise tolerance.

Risks of exercise training in patients with heart failure

Individuals with cardiac disease appear to be at an increased risk for sudden cardiac arrest during vigorous exercise (eg, jogging) than healthy individuals.[15] The incidence of major cardiovascular complications during outpatient cardiac rehabilitation exercise programs has been estimated to be 1 in 60,000 participant-hours.[44] Patients with chronic HF have a greater overall morbidity and mortality than that of healthy persons and those with other forms of heart disease. Thus, current practice guidelines stratify HF patients at the highest level of risk.[15,45,46] However, exercise-training studies of patients with HF (Table 1) demonstrate that the overall adverse event rate appears to be low. Hypotension after exercise, atrial and ventricular arrhythmias, and worsening of HF symptoms are the most commonly reported adverse events. Remarkably, the adverse event rates in studies of HF patients who performed home exercise is also low.[19,32,39] The Heart Failure ACTION trial promises to provide important information regarding the risks of moderate-intensity exercise in HF patients, and adverse event rates relative to the level of supervision during training.

LV remodeling is a dynamic process that occurs after acute myocardial infarction (MI), and can affect the size and shape of the left ventricle. Concerns have been raised about the possible detrimental effects of exercise training on LV remodeling in patients after MI. Although no studies have specifically addressed this issue in HF patients, a single, small, non-randomized study has shown that patients after first anterior Q wave infarction with >18% asynergy, experienced a further increase in asynergy and a decrease in ejection fraction after

12 weeks of exercise training when compared to non-exercising controls.[47] However, 2 subsequent randomized controlled trials of moderate- to high-intensity exercise-training patients after a large MI have not demonstrated adverse effects on regional wall motion, LV systolic function, or LV chamber dimensions after several months of exercise.[48,49] The Exercise in Anterior MI (EAMI) trial showed that among patients with ejection fraction <40%, spontaneous global and regional LV dilatation occurred similarly in both the exercise and control groups, but was not influenced by exercise training.[48] In another study[49] of 25 patients with an average ejection fraction of 32%, using serial LV measurements obtained from magnetic resonance imaging, no detrimental effects on LV volumes or ejection fraction were seen after 2 months of moderate-intensity cycle exercise training.

Conclusion

The American Heart Association[6,50] and the American College of Cardiology[50] conclude that the data regarding exercise in HF offer important evidence for encouraging its broader application among this rapidly enlarging population of patients. However, further studies are needed to evaluate the safety and effectiveness of exercise-training prescriptions. More information is needed concerning the role and efficacy of resistance training, the effects of exercise on prognosis, as well as the efficacy of exercise programs in patients with HF from causes other than coronary artery disease (ie, valvular regurgitation and other cardiomyopathies). The Heart Failure ACTION trial is designed to provide important information regarding the effect of exercise on morbidity and mortality, as well as the risks of supervised and unsupervised exercise in HF patients. Substudies of this trial will provide further insights into the mechanisms of exercise intolerance in HF and the effects of exercise training in modulating these responses.

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***Dr. Gary Balady** has no disclosures to announce related to the enclosed CME program.*