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Skeletal Muscle Changes in Chronic Cardiac Disease and Failure

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Abstract

Peak exercise performance in healthy man is limited not only by pulmonary or skeletal muscle function but also by cardiac function. Thus, abnormalities in cardiac function will have a major impact on exercise performance. Many cardiac diseases affect exercise performance and indeed for some cardiac conditions such as atherosclerotic heart disease, exercise testing is frequently used not only to measure functional capacity but also to make a diagnosis of heart disease, evaluate the efficacy of treatment, and predict prognosis. Early in the course of cardiac diseases, exercise performance will be minimally affected but with disease progression impairment in exercise capacity will become apparent. Ejection fraction, that is, the percent of blood volume ejected with each cardiac cycle is often used as a measure of cardiac performance but frequently there is a dissociation between the ejection fraction and exercise capacity in patients with heart disease. How abnormalities in cardiac function impacts the muscles, vasculature, and lungs to impact exercise performance will here be reviewed. The focus of this work will be on patients with systolic heart failure as the incidence and prevalence of heart failure is reaching epidemic proportions and heart failure is the end result of many other chronic cardiac diseases. The prognostic role of exercise and benefits of exercise training will also be discussed.

Introduction

Cardiac function is a major determinant of peak exercise performance in normal man in addition to pulmonary and skeletal muscle function. Abnormal cardiac function has, therefore, a major impact on exercise performance. Exercise performance is affected by many cardiac disease states and for some cardiac conditions such as atherosclerotic heart disease, exercise testing is frequently used both as a prognostic and diagnostic test to assess both functional capacity and diagnose heart disease. The results of these assessments have impact on the efficacy of treatment and predict prognosis. Early in cardiac diseases, exercise performance will be minimally affected but with disease progression impairment in exercise capacity will become apparent. Ejection fraction, that is, the percent of blood volume ejected with each cardiac cycle is often used as a measure of cardiac performance but frequently there is a dissociation between the ejection fraction and exercise capacity in patients with heart disease.

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The cardiovascular system is a continuous vascular circuit that includes a muscular pump and the vasculature to deliver oxygen and nutrients to all organs. As such, the ability of the heart to augment its output in response to the energy demands of exercise makes it an integral part of any discussion of exercise physiology. Maximum oxygen uptake during exercise is derived from the Fick equation, that is, the product of maximum cardiac output times the arteriovenous oxygen difference. Resting cardiac output averages 4 to 6 L/min and can increase by a factor of 4 to 6 during maximal upright exercise. The distribution of blood secondary to the increased cardiac output during exercise is primarily to the working muscle, that is, skeletal and cardiac muscle with the vast majority of the blood flow redirected to the skeletal muscle. The heart generates this response primarily by not only an increase in heart rate, but also by augmentation of stroke volume. This increase of stroke volume results from increased venous return and the Frank Starling principle as well as increased contractility from sympathetic stimulation and peripheral vasodilation. End-diastolic volume increases with exercise and end-systolic volume decreases during upright but not supine exercise as a consequence of the difference in venous return affected by gravity. In patients with cardiac disease, failure to increase cardiac output can be derived from a variety of mechanisms including cardiomyopathies, coronary artery disease with active ischemia, valvular heart disease, and pulmonary hypertension. Additionally, the reduced cardiac output can over time affect the peripheral vasculature as well as the skeletal muscle. In this article, we will review the effect of chronic heart failure (CHF) on exercise performance. The use of exercise to risk-stratify patients with heart failure (HF) will be discussed as well as the use of exercise as therapy for cardiac diseases.

Abnormalities in Exercise Performance in Chronic HF

The exercise response in patients with HF

HF is defined as the inability of the heart to adequately perfuse the metabolizing tissue. The clinical syndrome of congestive HF (HF) involves a complex interplay of skeletal muscle and peripheral vascular adaptations resulting from decreased myocardial performance. The classic symptoms of HF are exertional fatigue and dyspnea. Traditionally, it has been hypothesized that the major limitation to exercise performance in these patients results from a reduced cardiac output response to exercise leading to skeletal muscle hypoperfusion and lactic acidosis (120). However, secondary changes in other organ systems such as skeletal muscle, the vasculature, and the lungs play an important role in the genesis of both fatigue and dyspnea (33). Later in this review, we will review in detail the numerous peripheral changes that are observed in the vasculature, respiratory tract, and skeletal muscles of HF patients and discuss how these changes impact exercise performance.

In the presence of a reduced cardiac output, the heart is dependent on three principle compensatory mechanisms to maintain normal function. First, the Frank-Starling mechanism which increases preload to sustain cardiac stroke volume. Second, myocardial hypertrophy occurs, to increase the mass of contractile tissue. Third, the sympathetic nervous system is activated to augment myocardial contractility. These compensatory mechanisms are limited and with persistent stimulation ultimately become detrimental, contributing to the progression of the disease process. The heart rate response which is critical in increasing

cardiac output frequently is blunted in HF patients due to both chronotropic incompetence as well as the widespread use of beta blockers which have become a cornerstone of treatment for this disease (151).

In the short term, these compensatory mechanisms serve to preserve cardiac output which is the primary limitation to maximal physical performance in normal subjects. In HF patients, decreased exercise capacity has similarly been attributed to a decreased cardiac output response which leads to skeletal muscle underperfusion and intramuscular lactic acidosis (48, 64). This is based on observations that patients with HF exhibit reduced cardiac output responses to exercise compared to normal subjects. Additionally, there is a pronounced increase in filling pressures with the development of marked pulmonary hypertension with pulmonary capillary wedge pressures reaching as high as 50 to 60 mmHg.

Exercise hemodynamic measurements and ventilatory gas measurements during progressive treadmill exercise in patients with HF have first been described by Karl Weber in 1981 (204). This report demonstrated the usefulness of this technique as a noninvasive method for characterizing cardiac reserve and functional status. Weber demonstrated a significant correlation between cardiac output response and oxygen consumption and was able to classify patients into groups of worsening severity on the basis of this noninvasive technique. He found that with worsening HF the cardiac output response is markedly diminished. Several other studies have shown a significant correlation between the peak VO_2 and cardiac output (99,188). It is this correlation between peak VO_2 and cardiac output which underlies the prognostic value of exercise variables in HF leading to the widespread use of cardiopulmonary exercise testing in the evaluation of patients with HF. Use of metabolic carts equipped with rapidly responding carbon dioxide and oxygen sensors have not only provided a means of better understanding the exercise response of patients but also in providing important clinical information on prognosis and how to direct medical therapy.

Peripheral Factors Limiting Exercise Performance in HF

Skeletal muscle abnormalities

Though peak exercise capacity is clearly dependent on the cardiac output response to exercise, this is not the sole determinant of exercise performance in patients with HF. Patients with similar reductions in left ventricular function have a wide range of exercise capacity. Furthermore, therapeutic interventions aimed at acutely increasing cardiac output such as inotropic drugs like dobutamine and milrinone, do not significantly increase exercise capacity or peak VO_2 (130,134,210). This discrepancy between enhanced cardiac output and fixed peak VO_2 can be explained on the basis of the peripheral vascular and skeletal muscle derangements in CHF. Due to regional vascular or skeletal abnormalities, the augmented cardiac output cannot be utilized by the exercising muscle beds and therefore peak VO_2 is not altered. Evidence for a peripheral abnormality in CHF was first described in the 1970s by Zelis (214,215).

Skeletal muscles are not simply a mechanical system, but sensory organs that sense effort, tension, displacement, and fatigue via tendon organs, muscle spindles, joint receptors, and

small nerve endings. It is the sensory aspect of skeletal muscles that mediates the symptoms of exercise intolerance in both healthy and disease states (111,142,164,180).

Alterations of skeletal muscle metabolism and mass also play an important role in limiting peak functional capacity in patients with HF (82,133,200). Metabolic and atrophic alterations have been shown in skeletal and diaphragmatic muscle of patients with HF (45,108,131,145,184). It is well established that muscle wasting is a strong independent risk factor for mortality in HF (4). However, the etiology underlying the muscle changes remain unclear. Most investigators agree that reduced physical activity (disuse and immobilization in advanced stages) plays some part in the muscle alterations in HF but cannot explain the full extent of changes in muscle structure, function, and metabolism (28,29,139,179). Of note, HF-related muscle abnormalities are not substantially different from those observed in other chronic conditions such as chronic pulmonary or renal disease (197). Chronic low-level systemic inflammation characteristic of the HF state effect changes in skeletal muscle (132) and with the progression of HF, inflammatory mediators released into the circulation further activate systemic inflammation and promote muscle atrophy.

Skeletal muscle alterations develop and worsen as symptoms in patients with HF intensify. Severity of HF due to LV systolic dysfunction is currently categorized in four stages: Stage A includes those patients with risk factors for developing HF; Stage B includes patients with LV remodeling in the absence of symptoms (61); Stage C is defined by the occurrence and progression of symptoms; and Stage D includes patients with symptoms refractory to medical therapy.

Histologic changes of skeletal muscle in HF—Histomorphologic and metabolic changes of skeletal muscle in HF include changes in the fiber composition of muscle, fiber atrophy, fatty infiltration, and decrease in oxidative enzymes. Adult human muscle is composed various fiber types: Types I, IIa, and IIx. The fiber types are defined by their myosin heavy-chain isoforms, and can be identified by ATPase staining or immunohistochemistry (9, 175) (Table 1).

Several investigators have reported that patients with HF develop a characteristic shift in muscle fiber distribution with an increased number of Type II fibers (anaerobic, gylcolytic) as compared to Type I (aerobic, oxidative) (174, 187). In muscle biopsies, an increase in glycolytic, fast-twitch type IIa/x fibers, type II fiber atrophy, and a reduction in lipolytic and oxidative enzymes was described (157,179). Nevertheless, although conventional wisdom suggests that fiber type is shifted by HF, this could be due to muscle disuse. Excellent work by Mettauer et al. (140), which controlled for deconditioning in the HF population, found no fiber type shift compared to controls with similar VO_2 max. These findings have recently been substantiated (144). Drexler et al. further described decreased volume density of the mitochondria and surface density of the mitochondrial cristae, implying that oxidative transport coupling was compromised (45). The decreased mitochondrial volume correlated with peak aerobic capacity, suggesting a major contribution of altered skeletal muscle metabolism to exercise intolerance. The content of intramitochondrial Krebs cycle citrate synthase, total cytosolic creatine kinase (CK), skeletal muscle-specific CK (MM-CK) and lactate dehydrogenase (LDH) decreases in HF patients (139). Notably, angiotensin-

converting enzyme inhibition seems to prevent the fiber switch from Type I to II in the skeletal muscle (172,176,202).

Abnormal skeletal muscle metabolism in HF—Muscle metabolism in various muscle groups has been studied in patients with HF. Abnormal skeletal muscle metabolism, that is, reduced oxidative metabolism with earlier shift to glycolytic metabolism, has been demonstrated in patients with HF using ^{31}P magnetic resonance spectroscopy (29,55,114,123,136,155). These studies consistently show an accelerated rate of phosphocreatine utilization (PCr, a high-energy phosphate), accumulation of inorganic phosphate (Pi, a by-product of ATP utilization), early intracellular acidification (low Ph) and delayed PCr recovery after exercise. These abnormalities appear to be independent of total limb perfusion (55,114,135,206), histochemical changes (184), muscle mass (98), or severe tissue hypoxia (87). Venous plethysmography to measure limb blood flow demonstrated that metabolic changes during exercise in HF occurs in the absence of associated decrease in limb perfusion (206). Persistent metabolic abnormalities in patients with CHF compared to normal subjects was also demonstrated during ischemic exercise, that is, exercise performed during arterial occlusion. Moreover, acutely increasing cardiac output with therapeutic agents such as dobutamine did not improve the metabolic abnormalities observed in these patients (134).

Simultaneous monitoring of cellular metabolism and oxygenation during leg exercise in HF patients by coupling ^{31}P magnetic resonance spectroscopy to near infrared spectroscopy revealed that metabolic abnormalities observed in patients with HF occurred despite what appears to be adequate muscle oxygenation. This again supports an intrinsic skeletal muscle metabolic change in these patients. Overall, patients with HF experience metabolic alterations that are similar to those reported after deconditioning. To what extent muscle atrophy, fibrosis and inflammation underlie 31P-MRS metabolic alterations remains unclear.

Adamopoulos (2) showed that physical conditioning substantially improve the muscle metabolic alterations in patients with HF but did not normalize it. After 8 weeks of home-based bicycle exercise training in a randomized-crossover trial, patients with HF exhibited less PCr depletion and faster PCr recovery. However, exercise-induced acidification was unaffected by physical conditioning.

Impaired skeletal muscle excitation contraction coupling in HF—Excitation contraction coupling of the skeletal muscle sarcomere is abnormal in HF and is in part related to abnormalities in intracellular calcium handling leading to an intracellular calcium overload state.

In the myocardium, calcium cycling mediated by the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) 2a is a critical control mechanism in regard to cardiac contraction. During the action potential, calcium enters the cell through L-type calcium channels as inward calcium current. Calcium entry triggers further calcium release from the sarcoplasmic reticulum into the cytosol by activation of the ryanodine receptor. The increase in cytoplasmic free calcium allows calcium to bind to troponin C triggering contraction. Relaxation depends on the release and decline of cytosolic calcium. This requires calcium transport out of the cytosol

by multiple pathways including SERCA 2a at the sarcoplasmic reticulum, the membrane-bound sodium-calcium exchange pump, mitochondrial transport, and ryanodine receptors. SERCA 2a removes up to 90% of intracellular calcium in rodents and 70% in humans and large animals. Abnormal cellular calcium handling is observed in the failing heart (18,119,162). Increased sodium/calcium exchange mechanism, reduction in SERCA2a activity, decreased phospholamban/SERCA 2a ratios and increased phosphorylation of ryanodine receptor producing “leakiness” altogether result in decreased sarcoplasmic reticulum calcium content and a prolonged calcium transient flux (Fig. 1).

Skeletal muscles from animals with HF exhibit increased Ca^{2+} spark frequency, decreased Ca^{2+} spark amplitude, and increased Ca^{2+} spark duration consistent with leaky sarcoplasmic reticulum Ca^{2+} release and with decreased sarcoplasmic reticulum Ca^{2+} content (162). Comparable to the failing myocardium, the muscle-specific Type 1 ryanodine receptor (RyR1) becomes leaky in HF as chronic adrenergic stimulation results in hyperphosphorylation of the channel. This change dissociates calstabin-1, the stabilizing protein that keeps the RyR1 channel in a closed state (18). Data regarding sarcoplasmic reticulum Ca^{2+} pumping in HF differ in fast and slow twitch muscles and according the level of fatigue (119). In agreement with data in aging, sarcoplasmic reticulum Ca^{2+} pumping appears to be most impaired in slow twitch muscles of animals with HF. Data regarding skeletal muscle protein and mRNA expression of SERCA 1a, the skeletal muscle specific isoform of SERCA, are divergent in HF (120,162) Predominant muscle fiber composition, degree functional impairment, and nature of the HF model may in part account for the disparate findings that have been occasionally correlated with early muscle fatigue.

Another recently investigated target in Ca^{2+} signaling pathomechanisms in HF are calpains. These Ca^{2+}-activated proteases appear to have pleiotropic effects on various aspects of skeletal and cardiac muscle homeostasis such as cardiac remodeling, inflammation, and fibrosis as well as skeletal muscle atrophy (16,43,110).

Muscle fiber atrophy and changes in total muscle mass—In addition to fiber atrophy noted on muscle biopsy, HF patients also exhibit generalized muscle atrophy (131). Analysis of skinfold fat thickness, arm circumference, and 24 h urine collections for creatinine to estimate total muscle mass showed that patients with HF have adequate fat stores but in 60% of patients significant muscle loss develops. In another study, calf muscle volume assessed by magnetic resonance imaging showed reduced muscle volume in patients with HF and significant water and fat infiltration was also noted in the muscle sections of these patients (126). Calf muscle mass was reported to be significantly lower in patients with severe HF as evidenced by a peak VO_2 of 13 mL/min/kg when compared to age and gender matched controls. However, some investigators have reported normal muscle mass in patients with HF (98).

The assessment of muscle function in patients with HF consistently showed decreased muscle strength and increased fatigability when normalized to fiber cross-sectional area in patients with HF (48). Slowing of relaxation and steady decline in strength has been reported during low-frequency stimulation of slow twitch muscles in rats with congestive HF (119). While still controversial, reduced isometric force and calcium-activated actomyosin ATPase

activity in patients with HF may be due to a decline in density of contractile proteins and the specific rate of cross-bridge attachment or in both (143,144,187). A reduction in contractile proteins contents appears to be the most likely explanation of reduced muscle strength since single fiber muscle contractile protein function has been reported to unaltered in patients with HF (156) (Fig. 1).

The impact of muscle mass on peak VO_2 has been investigated by several groups and a weak but significant correlation with total skeletal muscle mass derived from equations using 24 h urinary protein measurements have been reported (131, 162). LeJemtel contrasted peak oxygen consumption during combined upper arm and maximal leg exercise (103). In normal subjects, the addition of more muscle mass via arm exercise did not increase peak exercise performance and VO_2 remains unchanged suggesting that under normal conditions, cardiac output response to exercise rather than amount of exercising muscle determines peak VO_2. However, in patients with severe HF, the addition of upper arm exercise significantly increases peak VO_2 suggesting the importance of skeletal muscle mass in limiting peak VO_2 in patients with HF. An alternative hypothesis is that the peripheral vasodila-tory abnormalities in these patients resulted in a physiologic shunt to the upper arm musculature resulting in higher peak VO_2 with combined arm and leg exercise.

Mechanisms of skeletal muscle atrophy—The mechanisms that mediate skeletal muscle wasting and atrophy have only recently been studied in patients with HF and animal models of cardiac dysfunction. Generally, muscle atrophy may result from a decrease of anabolic mechanisms, increased protein degradation or both. The impact of the clinical compensatory status and acute disease exacerbations on muscle atrophy in HF is controversially discussed. The majority of studies have shown no alterations in either muscle protein synthesis or breakdown in clinically stable HF patients which indicates that the onset and progression of muscle atrophy is linked to disease exacerbation. To date, no studies investigated possible metabolic derangements in skeletal muscle during acute disease exacerbation. Below, we will review the known pivotal signaling pathways that are involved in protein metabolism.

Enhanced protein degradation.: Experimental data in a murine model of chronic HF indicate that the ubiquitinproteasome pathway plays an important role in HF induced skeletal muscle atrophy (46). Through this central pathway of protein degradation, proteins are marked by ubiquitin for rapid degradation through the 26S proteasome in an ATP-dependent pathway that yields peptides and intact ubiquitin. Two pivotal enzymes of this pathway are ubiquitin-ligases MuRF1 and Atrogin-1 (63,69). MuRF1 and Atrogin-1 are a downstream part of a signal cascade involving p38 MAPK/FoxO which is parallel to the myostatin signaling mechanism (69) (see below). Skeletal muscle from mice with left ventricular dysfunction revealed activation of the ubiquitin-proteasome pathway with increased protein ubiquitination, FoxO transcription factor activation, increased expression of muscle-specific atrogenes, and overall muscle atrophy. In the pathway mentioned above, IGF-1 is a major upstream signaling molecule. Transgenic overexpression of a local isoform of IGF-1 prevents proteasome activation, breakdown of skeletal muscle structural proteins, and atrophy (177). Further experimental data regarding the critical inhibitory role of IGF-1

in the development of skeletal muscle atrophy have been provided in a model of skeletal muscle wasting induced by chronic administration of angiotensin II (AII) (181). Chronic administration of AngII suppresses IGF-1 signaling via the Akt/mTOR/p70S6k pathway that is critical for caspase-3 activation, actin cleavage, ubiquitination, and apoptosis. Caspase-3 activation is another important mechanism in muscle protein degradation. Muscle-specific expression of IGF-1 blocks the AngII-induced muscle atrophy. Whether the beneficial effects of ACE inhibition on skeletal muscle in HF patients are mediated though the IGF-1 pathway or result from direct effect on skeletal muscle vasculature via improvement of vascular endothelial function remains to be determined. In addition to AngII, elevated cytokines can directly activate the ubiquitinproteasome pathway and thereby result in skeletal muscle protein degradation (161).

Impaired growth factor signaling and protein synthesis.: HF is a catabolic state with deficiencies in several anabolic hormones (25, 77, 173). In male HF patients, a decrease of circulating total testosterone, dehydroepiandrosterone and IGF-1 levels have been described which correlate with a poor prognosis (13). Testosterone has anabolic effects on skeletal muscle by increasing fractional muscle protein synthesis (20) and appears to stimulate IGF- expression. In a placebo-controlled trial of 70 elderly patients with moderately severe HF, testosterone application improved exercise capacity, muscle strength, glucose metabolisms, and baroreflex sensitivity (25). Despite beneficial effects on insulin resistance, testosterone had no apparent effects on myocardial performance and left ventricular function. Long-standing therapy seems to be well tolerated by elderly patients with moderately severe HF.

Growth hormone (GH) resistance and reduction in skeletal muscle IGF-1 concentration contribute to skeletal muscle atrophy in HF by directly reducing protein synthesis and by decreasing muscle satellite cell recruitment and differentiation (181). Exercise training has been shown to increase local expression of IGF-1 in normal subjects and patients with HF (178). Ghrelin, a novel GH-releasing peptide stimulates physiological release of IGF-1 through a mechanism that is independent from hypothalamic GH releasing hormone (150). Administration of Ghrelin for 3 weeks improves functional capacity and alleviates skeletal muscle atrophy in patients with chronic HF and COPD (149).

Recently, the possible role of myostatin in muscle atrophy in advanced HF has been investigated (74). Myostatin is secreted from skeletal muscle and is a local and circulating factor with antianabolic and antihypertrophic effects. It has been shown in a murine model that myostatin activation leads to profound muscle wasting (217) through a p38-MAPK/ SMAD 2/3-mediated pathway (69). Furthermore, there is evidence from animal experiments that circulating myostatin released from cardiomyocytes during myocardial injury induces skeletal muscle atrophy (74). However, skeletal muscle-derived myostatin provides the abundance of systemic myostatin (24). In conclusion, Myostatin could be an attractive therapeutic target since circulating levels of myostatin (57), and other TGF receptor ligands, such as activin (212), are increased in HF patients. Consequently, it has been proposed to use these circulating members of the TGF family such as myostatin as biomarkers assessing for cachexia in HF patients (62). However, this approach is controversially discussed (67,213).

Patients with HF develop worsening insulin resistance that is related to clinical events and mortality (42). Impaired insulin signaling in skeletal muscle has been linked to muscle atrophy and impaired metabolism with accumulation of toxic metabolic molecules.

Skeletal muscle inflammation.: HF induces a chronic low level inflammatory state as evidenced by modest elevation of circulating IL-1 and −6 and TNF-*a* (51, 191). The initiating factors of skeletal muscle inflammation are incompletely understood. Disuse induced atrophy promotes skeletal muscle inflammation through activation of several signaling pathways.

Increased skeletal muscle inflammation relates to reduced O_2 delivery and local IGF-1 concentration as well as increasing oxidative stress. In turn, muscle inflammation induces cytokines especially IL-6 and TNF-*a* and expression of inducible nitric oxide (NO) synthase (59). There is experimental evidence that oxidative stress causes changes in muscle fiber elasticity via titin modification and activation of Calpain-1, a protease degrading titin, as well as other mechanisms (16). Elevated IL-6 and TNF-*a* concentrations activate the NFκB signaling pathway that modulates immune and inflammatory skeletal muscle responses and thereby exacerbating muscle wasting (146). Increased IL-6 concentration has been associated with skeletal muscle and diaphragmatic atrophy in rats and the Janus activated kinase, activator of transcription, and cAMP-activated protein kinase signaling pathways (78). As previously mentioned, increased FoxO activity precipitates muscle protein degradation and muscle atrophy through the ubiquitin-proteasome pathway in HF. In summary, SM inflammation exacerbates SM atrophy through stimulation of multiple cytokines activated signaling pathways.

The activation of the renin-angiotensin system results in vasoconstriction and elevated skeletal muscle concentrations of AngII which increases local oxidative stress and lowers skeletal muscle concentration of IGF-1. Consequently, these mechanisms may accelerate protein degradation while decreasing protein anabolism. In HF, muscle reflex alterations have been reported (200) which are explained by the interplay of loss of skeletal muscle mass, reduction in muscle perfusion and blood flow distribution and altered fiber-type composition. Physiologically, muscle reflex activation increases systemic blood pressure and thereby maintains muscle perfusion during muscle acidosis. However in the failing heart, muscle reflex activation occurs at the onset of exercise resulting in vasoconstriction and limited skeletal muscle perfusion.

In summary, chronic disease states and particularly chronic HF are associated with reduced physical activity resulting in disuse and low level systemic inflammation. Both disuse and systemic inflammation promote loss of muscle mass and ultimately atrophy. Continuous loss of skeletal muscle mass activates multiple signaling pathways that mediate muscle inflammation. In turn, local inflammation activates signaling pathways that promote further loss of muscle mass and exacerbates local inflammation. The circulus vitiosus between atrophy and inflammation within the skeletal muscle appears to progress independently from the initial event and may be related to the presence of comorbidities including hormonal deficiencies, diabetes mellitus, and obesity/sleep disorder. An important goal of therapy in

HF patients is to reverse or optimally prevent the development of skeletal muscle alterations to restore a normal functional capacity.

Vascular dysfunction

Experimental and clinical evidence suggests that the peripheral circulation undergoes substantial transformations during the progression of HF with an alteration of regional vascular control. These changes occur both at the level of the vascular endothelium, an important modulator of vascular tone, and at the level of the vascular smooth muscle. Furthermore, changes in capillary density have been reported in skeletal muscle of patients with HF.

Changes in capillary density in HF

At stage C of HF, muscle perfusion during exercise is primarily limited by an impaired vasodilatory response of lower limb skeletal muscle beds in addition to the impaired cardiac output response to exercise. At stage D of HF, skeletal muscle perfusion during exercise is limited by the cardiac output response as it is in normal subjects (174). The findings regarding muscle microcirculation are controversial in severe HF (48). Capillary density has been reported to be normal or decreased depending on normalization to muscle fibers number and size. Duscha et al. (47) measured vascular density in the skeletal muscle of patients with HF. Using cell-specific antibodies to measure vascular density, these investigators found decreased numbers of endothelial cells per fiber, which indicates a reduced capillary density. However, since capillary density varies with fiber type, and fiber-type switching is a dynamic process in patients with HF, studies on capillary density ratio should be interpreted with caution. Other investigators have reported a normal skeletal muscle capillary density in patients with HF (121). Thickness of the capillary basement membrane is increased in the pronator teres muscle of patients with HF (115). Finally, the resistance of the microvasculature is only minimally increased in the cutaneous tissue in patients with HF (115,121). Of note, although vascular endothelial dysfunction (an important determinant of capillary behavior during exercise) is impaired in HF, oxygen extraction by exercising SM is nearly complete in severely symptomatic patients (87). Similarly, reduced muscle oxidative capacity does not limit oxygen extraction by exercising muscles in HF (201). The oxygen content of the deep femoral vein that exclusively drains skeletal muscle is less than 1 to 2 mL/100 mL in patients with severe HF (87). In summary, while skeletal muscle capillary density is likely to be altered in HF and oxidative capacity is reduced, they do not limit oxygen extraction by exercising muscles.

Abnormal endothelial function in HF

The mechanisms of vascular alterations are incompletely understood in HF. A number of studies have systemically studied vascular endothelial function, and particularly NO-mediated control of vasomotor tone has been extensively studied in HF (85,86,95,190). In both animal and human models of HF, the responses to endothelium-mediated vasodilation are blunted. Endothelial dependent dilation in the aorta of rats with ischemic cardiomyopathy is reduced (44). Kubo et al. demonstrated that endothelium-dependent vasodilation is attenuated in patients with HF (94). Changes in sheer stress is an important

determinate of endothelial function. In normal vasculature, changes in sheer stress on the endothelial cell that accompany alterations in blood flow serve to enhance vasodilation via release of NO and prostaglandins (15,70). Of note, aerobic training normalizes endothelial function in patients with HF probably via a mechanism of increased shear stress. In canine models of HF, the vascular responses to low-dose acetylcholine are amplified by pretreatment with indomethacin (192). These alterations in vascular reactivity in CHF have been postulated to be adaptive in that they function to maintain shear stress close to control levels (75).

In the rat model, HF induced by ligation of the left anterior descending artery causes progressive peripheral vascular endothelial dysfunction (190). The systemic vascular response to acetylcholine was not decreased until four weeks after coronary ligation and progressively worsened through week 16. Similar data are not available in human subjects. The mechanisms that mediate vascular endothelial dysfunction early in the course of HF are likely to be different than those responsible at later stages. In patients with symptomatic HF, the improvement induced by vitamin C administration and subsequent decreased extra-cellular SOD (superoxide dismutase) activity implies that increased oxidative stress may accelerate NO degradation, and may be partially responsible for vascular endothelial dysfunction (15). Additional data suggest that there is increased expression of endothelial NO synthase (eNOS) when normalized to von Wille-brand factor in the vastus lateralis muscle of patients with HF (192). Increased eNOS endothelial expression implies the development of an adaptive mechanism to compensate for accelerated NO degradation. Nevertheless, it is unclear whether uncoupling of eNOS with conversion of bioactive NO to reactive nitrate species develops in the vascular bed of patients with HF as it is known in patients with diabetes mellitus.

Using a canine model of HF produced by rapid ventricular pacing, Zelis also measured the arterial sodium content in the aorta and femoral artery in control and HF animals (214). A significant increase in the arterial sodium content in the HF animals was demonstrated. Zelis postulated that arteriolar stiffness from increased salt and water content resulted in an abnormal vasodilatory response in HF. Longhurst et al. showed a similar deficiency in the forearm vasculature responses to static exercise.

Endothelial function in patients with HF was first evaluated in the upper limb vasculature by measuring forearm blood flow in response to methacholine, an endothelium-dependent dilator, and nitroprusside, an endothelium-independent dilator (95). Blood flow was measured by venous plethysmography. The response to methacholine was significantly lower in patients with HF, when compared to age-matched controls, while the response to nitroprusside tended to be lower, although it did not reach statistical significance. The blunted response to methacholine implies that patients with HF have an impaired reserve of vascular endothelium. Endothelial function was also studied in the lower limb vasculature of patients with HF using Doppler ultrasonography of the superficial femoral artery (44). Patients did not have comorbid vascular disease that could have contributed to endothelial dysfunction. The maximal velocity of blood using a volume sampler positioned in the center of the vessel was evaluated during intra-arterial administration of acetylcholine, an endothelial-dependent dilator, and nitroglycerin, an endothelial-independent dilator.

Maximal blood flow velocity did not increase in response to acetylcholine at concentrations of 10–5 M, while it increased by fivefold in healthy subjects. Maximal blood flow velocity in response to nitroglycerin at 10–7 M was substantially reduced in patients when compared to the response elicited in healthy subjects. Following administration of a dose of nitroglycerin at 10–5 M, patients with HF experienced an increase in maximal blood flow velocity similar to that produced by nitroglycerin at 10–7 M in healthy subjects.

The lack of response to acetylcholine clearly demonstrates the absence of functional reserve of the vascular endothelium in patients with HF. However, reduced vascular endothelial function in patients with HF may, in part, be due to reduced functional integrity of the cyclic GMP pathway that is evidenced by the depressed response to nitroglycerin. The mechanisms that are responsible and mediate the progression of vascular endothelial function in patients with HF are still poorly understood. Furthermore, the state of vascular function under basal conditions in patients with CHF is still debated. Administration of L-NMMA (N-monomethyl-L-arginine), a selective inhibitor of the production of NO from arginine, yielded similar forearm blood flow decreases in patients with CHF and in healthy subjects (85;86). However, others observed the expected decrease in blood flow following administration of L-NMMA in healthy subjects, but did not observe a decrease in patients with HF (70). Experimental data indicate that increases in oxidative stress associated with HF may accelerate NO degradation, and thus may impact on NO availability (15).

Endothelial dysfunction appears to be a time-dependent alteration. With increasing severity of HF, there is a deterioration of endothelial vascular function. In rats with early stages of HF, vascular endothelial function was preserved, whereas in more severe stages, an impairment was noted (190). Circulating cytokines such as TNF*a* are elevated in severe HF and TNF*a* impairs the release of NO. Plasma levels of TNF*a* in patients with HF are correlated with the degree of endothelial dysfunction assessed by infusion of acetylcholine (132). Chronically decreased skeletal muscle perfusion, increased tissue ACE activity, increased oxygen free radical formation, and increased endothelial vasoconstriction agents are other potential mechanisms which are involved in the development of endothelial dysfunction in these patients.

The impaired vascular response to exercise in HF

A fixed vasodilatory capacity of the skeletal bed during exercise exists in CHF. This was demonstrated in a study comparing one versus two-leg bicycle exercise. In contrast to normal controls, patients with severe HF were unable to augment maximal limb blood flow during one-leg bicycle over that reached during two-leg bicycle exercise (103). Furthermore, regional differences exist in abnormal peripheral circulatory abnormalities and a comparison of peak reactive hyperemia between the forearms and calves of HF patients demonstrated abnormal calf flow only (81). Furthermore, only calf peak reactive hyperemia correlated to peak VO_2. Selective deconditioning may be responsible for these regional differences. As HF progresses, decreased use of lower extremities but upper extremity use remains relatively preserved which might explain these regional differences in blood flow.

During exercise, peripheral vasoconstriction is increased to prevent systemic hypotension in patients given the blunted rise in cardiac output (192). Tissue hypoxia and enhanced

sympathetic and angiotensin activation are two proposed mechanisms mediating abnormal peripheral vasoconstriction in HF. Institution of sympathetic and renin-angiotensin blockade do not completely reverse the peripheral derangements seen in CHF though they modify it.

While lower limb blood flow may increase up to 20 times from rest to peak exercise in healthy subjects, lower limb flow can increase only two to three times in patients with advanced HF due to LV systolic dysfunction (108,215). Thus, the vasodilatory response of the lower limb skeletal muscle beds to exercise is relatively much more impaired than that of the cardiac output in severe HF. Some investigators have failed to observe a limited vasodilatory response of skeletal muscle vascular beds to exercise in patients with severe HF (10,76,210). Etiology of HF (primarily due to valvular disease rather than end stage cardiomyopathy), and technical issues in the measurement of skeletal muscle blood flow (use of single thermistor for the thermodilution technique and measurement of blood flow draining other tissues than skeletal muscles) may in part explain the disparate findings.

Changes in respiratory muscle function

General mechanisms of dyspnea

A unified mechanism for dyspnea based on respiratory muscle function is that breathlessness occurs when the activity of the respiratory muscles is increased and/or the respiratory muscles are weak (89). Varying respiratory muscle strength and workload will result in differences in perception of load and dyspnea (26,27,83,171,183). Dyspnea is a conscious sensation that results from an unusual perception of discomfort during breathing (52,203). As it is a sensation, it has a significant affective component that can be modified by cognitive and contextual influences. Dyspnea occurs in both normal and diseased states and originates from the stimulation of mechano-, chemo-, or proprioreceptors. The magnitude of a stimulus to the peripheral receptor is transduced by the firing frequency in afferent nerves to the central nervous system. The central impression constructed is interpreted based on past experience to generate a conscious sensation (52).

Respiratory muscle fatigue may also contribute to dyspnea via biochemical changes in the muscles (80). Dempsey et al. have shown fatiguing contractions of the inspiratory muscles result in an accumulation of metabolites that activate Type IV phrenic afferents resulting in an increase in sympathetic vasoconstrictor activity via a supraspinal reflex, that is, inspiratory muscle metaboreflex (80). This reflex is important during heavy sustained exercise and modulates the competition for blood flow between the respiratory and locomotor muscles. Activation of this reflex redirects blood flow from the periphery to the ventilatory muscles.

Additionally, increased respiratory drive during exercise may be due to metabolic stimuli arising from limb skeletal muscle (55, 136). To proof that metabolic changes in skeletal muscle stimulate respiration, Oelberg et al. (155) used magnetic resonance spectroscopy to demonstrate that skeletal muscle pH correlates with minute ventilation. However, it is not clear whether such stimulation occurs through central or peripheral pathways (136).

Abnormal respiratory muscle function in HF

Respiratory muscle function is assessed by measurement of respiratory muscle strength (166). Maximal inspiratory pressure is measured with the subject inhaling against resistance at functional residual volume to maximize the force length relationship of the muscles. This measurement is volitional and as such may overestimate the degree of muscle weakness but this measurement has been shown to be reproducible. Inspiratory muscle weakness is arbitrarily defined as a Pi_{max} <70% of predicted value. A reduction in inspiratory and expiratory respiratory muscle strength in patients with HF from both systolic and diastolic dysfunction has been shown in many studies (3,72, 137, 152). Studies measuring diaphragmatic strength using esophageal and transdiaphragmatic pressure during maximal sniffs and phrenic nerve stimulation have also demonstrated reduction in diaphragmatic strength in HF patients.

When both respiratory muscle and limb muscle strength are measured in HF patients, a more marked reduction in respiratory rather than peripheral muscle strength has been observed. Chua et al. failed to find a correlation between Pi_{max} and quadriceps strength (32). Ambrosino (3) reported reductions in maximal inspiratory and expiratory pressures that paralleled the severity of HF. HF patients with relatively preserved exercise capacity had reduced Pi_{max}.

Pi_{max} has been shown to have prognostic value independent of peak VO_2. Meyer et al. (141) measured Pi_{max} in 244 consecutive HF patients and found this measurement to be a strong univariate and multivariate predictor of survival. Improvement in Pi_{max} has been found in patients with HF following initiation of angiotensin converting enzyme inhibitor therapy, CPAP and respiratory muscle training. However, serial changes in inspiratory strength was not predictive of prognosis (54).

Increased activity of the respiratory muscles and/or respiratory muscle weakness rather than fatigue may be sufficient to evoke the sensation of dyspnea. Measurement of the tension-time index and thus the work of the diaphragm per breath demonstrated dramatic increases in patients with HF at rest and during exercise (129). The tension time index is calculated for each breath and is the product of the ratio of the time in inspiration divided by the time per breath ($Ti/Ttot$), and the ratio of the mean transdiaphragmatic pressure to maximal transdiaphragmatic pressure. It approximates oxygen consumption of the diaphragm. Fatigue of the diaphragm is thought to occur when the tension time index reaches a ratio of 0.15 or greater (12). However, this fatiguing ratio may be lower in ischemic muscle, or with high tidal volumes, breathing frequency, and minute ventilation. In the majority of the patients studied, the tension time index at end exercise was ≥0.1 and thus approached fatiguing levels.

The relationship between parameters of respiratory muscle function and ratings of perceived dyspnea during sub-maximal exercise was also examined (129). Significant linear correlations were observed between a rating of perceived dyspnea (i.e., the Borg Scale) at a fixed exercise workload (25 watts) and parameters of respiratory muscle strength (maximal inspiratory and expiratory pressures), and work (tension-time index), but not with lung volumes (tidal volume, minute ventilation). McParland also demonstrated a strong

correlation between inspiratory muscle weakness and dyspnea during daily activities in stable ambulatory HF patients, as quantitated by the Dyspnea Index (137).

The endurance of the respiratory muscles in HF patients is also diminished. Respiratory muscle endurance can be assessed by progressive isocapnic hyperpnea using a rebreathing circuit to measure maximal sustainable ventilatory capacity (128). Both maximal voluntary ventilation and maximal sustainable ventilatory capacity are significantly reduced in HF patients compared to normal subjects consistent with lowered respiratory muscle endurance.

Impaired respiratory muscle perfusion in HF

As described above, limb skeletal muscle hypoperfusion has been described in patients with HF (216). Animal and human studies suggest that with HF, respiratory muscle hypoperfusion may also occur. The diaphragm, the major respiratory muscle, has a complex and generous blood supply provided by the internal mammary, intercostal, and phrenic arteries and the costophrenic arcades. Because of its rich perfusion, the diaphragm is relatively resistant to ischemia, even during exercise, when large increases in perfusion of the diaphragm are needed. Examination of regional muscle perfusion in the dog during exercise has demonstrated that the muscle group with the largest increase in perfusion is the diaphragm (53). In animal models of HF, the increase in diaphragmatic blood flow during submaximal exercise (147) was greatest in those animals with the most severe HF. Presumably the increased blood flow was required for increased work of breathing. During exercise, dramatic increases in blood flow occur in the diaphragm and this response is accentuated in HF.

Application of near-infrared spectroscopy during maximal exercise has demonstrated accessory respiratory muscle deoxygenation in HF but not in normal subjects (125). Whether this respiratory muscle deoxygenation represents underperfusion, ischemia, and/or fatigue was investigated by measuring the development of low-frequency muscle fatigue following exercise in HF patients. Davies et al. (39) demonstrated a decrease in maximum inspiratory and expiratory pressure following bicycle exercise in HF patients consistent with respiratory muscle fatigue. However, measurements of maximal inspiratory and expiratory pressures are motivation dependent, and the observed reduction may have occurred from central mechanisms. To investigate objectively whether low frequency diaphragmatic fatigue occurs in HF patients, supramaximal bilateral transcutaneous phrenic nerve stimulation before and after maximal bicycle exercise has been performed (129). Maximal transdiaphragmatic pressure was derived before and after exercise using the twitch interpolation technique. In both normal and HF subjects, maximal inspiratory and expiratory pressures decreased significantly with peak exercise. However, the maximal transdiaphragmatic pressure derived from the twitch interpolation technique was unchanged in both normal and HF subjects. Thus, low-frequency diaphragmatic muscle fatigue did not occur in patients with HF despite accessory respiratory muscle deoxygenation during exercise.

Changes in diaphragmatic histochemistry in HF

Histochemical and metabolic changes that occur in respiratory muscles may serve to accentuate the sensation of dyspnea in HF patients. A diaphragmatic myopathy has been demonstrated in an animal model of chronic HF (105) with decreased contractile and relaxation parameters (106). Other studies have also characterized these fundamental molecular defects (165,199) and linked the molecular abnormalities to mechanisms operable in other chronic diseases in humans (159). Impaired diaphragmatic performance was correlated to total cross-bridge number and altered calcium regulation (104). Cytokine activation has been suggested to explain the diaphragmatic dysfunction (78, 112, 165) and malnutrition have been shown to affect diaphragmatic weight and histochemistry (11,193).

Various histologic abnormalities in the diaphragm of patients undergoing cardiac transplantation have been described (40,113,194). In one study, costal diaphragmatic biopsies were obtained from 7 normal subjects and 10 patients at the time of transplant or left ventricular assist placement (194). The distribution of myosin heavy chain isoforms I, IIa, and IIb (MHC) by SDS gel electrophoresis was measured along with the activities of the oxidative (citrate synthase), lipolytic (beta hydroxyacyl CoA dehydrogenase) and glycolytic (LDH) enzymes. In normal subjects the distribution of MHC isoforms I, IIa, IIb was 35%, 49%, and 17% respectively versus was 54%, 40%, and 6% in the HF subjects. Therefore in the patients with HF, slow myosin heavy chains were significantly increased and glycolytic fast twitch fibers significantly reduced compared to normal subjects. Additionally, oxidative and lipolytic enzymatic activities were greater and glycolytic enzyme activity was significantly less in HF than normal subjects. Thus in the diaphragm in HF, there is a shift from fast to slow myosin isoforms with an increase in oxidative capacity and a decrease in glycolytic capacity. These changes are consistent with those elicited by endurance training. The endurance changes described in the diaphragm probably are the consequence of the increased work of breathing that occurs in this patient population. These findings were subsequently found in animal models (105,106).

However despite the shift to more oxidative metabolism, evidence of decreased contractility and strength were described in animal models. A rat model of HF demonstrated similar histochemical changes as described in HF patients (198). However, the mitochondrial function of the rat costal diaphragmatic muscle was reduced as measured in skinned muscle fibers using an oxygen electrode. ADP sensitivity of the mitochondria was increased but returned to normal in the presence of creatine. Decreased concentration of the mitochondrial isoform of CK has been previously demonstrated in HF. Thus, though the diaphragmatic muscle had an appropriate training response to the heightened work of breathing, the performance of the muscle was still attenuated due to the altered mitochondrial function.

Myogenic regulatory factors regulate the expression of myosin heavy chains. In a rat model of HF, the expression of Myo D, myogenin, and MRF4 were examined in the diaphragm of HF and control rats. Myogenin is expressed at higher concentrations in slow twitch muscle whereas Myo D expression is increased in fast twitch fibers. In the HF rats, selective suppression of Myo D associated with a lower percentage of fast twitch fibers was observed. The trigger for the downregulation of the Myo D is unknown but also thought to be due to neurohormonal and cytokine activation (116).

In conclusion, dyspnea is an extremely common symptom in patients with HF. In these patients, an increased work of breathing results from a combination of factors, including excessive ventilatory response during exercise from increased dead space ventilation from ventilation perfusion mismatching; an increased impedance to breathing from bronchial hyperreactivity due to venous engorgement; and decreased lung compliance from elevated filling pressures and subsequent chronic fibrotic changes. This increased work of breathing is transduced into the sensation of dyspnea by stimulation of receptors in weak, atrophic, underperfused, and metabolically abnormal respiratory muscles. Furthermore, the atrophic and metabolically abnormal limb skeletal muscles may also exacerbate this sensation through an excessive muscle reflex activity.

The prognostic role of exercise testing

Exercise testing as a widely applicable form of stress-testing, the cardiovascular system is the most established form of assessing peak functional capacity, analysis of the cardiovascular reserve as well as to define margins and limitations for exercise training protocols. The following section will highlight several of the most commonly used modes of exercise testing in patients with HF and also discuss the specific advantages and limitations of these forms of exercise testing.

The 6-min-walk test in patients with HF

Reduced functional capacity is the cardinal symptom of HF. Functional capacity has been traditionally assessed by the New York Heart Association (NYHA) criteria. Such assessment is both subjective and insensitive. The 6-min-walk test, that is, the distance walked over a period of 6 min, is less subjective than the NYHA functional class, but still can be heavily influenced by the patient's and/or tester's motivation. Additionally, the 6-min-walk test results cannot estimate how close the patient was to his or her maximal capacity and in patients with severe HF this submaximal test approaches maximal effort (168). Despite these caveats, the 6-min-walk test has been shown to provide prognostic information by the Study of Left Ventricular Dysfunction investigators who demonstrated in a substudy of 898 HF patients in their registry that mortality risk was 3.7 times higher in those patients with a 6-min-walk distance <350 m compared to those who walked >450 m. Similarly, the risk of HF hospitalization was 1.4 times higher in those with reduced walk distance (21). Subsequently, in some cohorts, investigators have shown the prognostic value of the 6-min-walk test but the prognostic significance of this test diminishes (168,169).

Peak oxygen uptake during maximal symptom limited exercise in HF

Determination of peak oxygen uptake during a symptom limited treadmill or bicycle exercise test is the most objective method to assess maximal functional capacity in HF patients. By identifying the ventilatory threshold, the physician can determine the adequacy of the patient's effort, and if not maximal, how close the patient was to achieving his or her maximal effort. Thus, noninvasive cardiopulmonary exercise testing has gained widespread application in the functional assessment of patients with congestive HF. It is a useful test to determine the severity of the disease, provide important prognostic information, and assess the efficacy of new drugs and devices.

Peak oxygen consumption is derived from the Fick Principle: peak oxygen consumption (VO_2) is the product of peak cardiac output and maximal arteriovenous oxygen difference. As most sedentary individuals will achieve comparable maximal arteriovenous difference, peak VO_2 provides an indirect assessment of cardiac output reserve and this largely underlies the effectiveness of peak VO_2 in risk stratification. Moreover, several peripheral factors may also impact peak oxygen consumption, such as the metabolic activity of skeletal muscle mass and endothelial function, as well as age, gender, and conditioning status. Since skeletal muscle mass and its metabolic activity both decrease and endothelial function is progressively impaired as HF severity increases, the prognostic utility of peak VO_2 is enhanced.

Analysis of the ventilatory data obtained during cardiopulmonary testing enables the clinician investigator to determine if a maximal test has been performed and thus whether an accurate peak VO_2 has been measured. Identification of the anaerobic threshold at 50% to 80% of peak VO_2 generally indicates a maximal effort. Peak VO_2 is a continuous variable. Use of statistical methods such as stratum specific ratios to identify a clear threshold below of which the relative risk of death will precipitously increase, have yielded a linear relationship of VO_2 to outcome without clear thresholds (1,138). Peak exercise VO_2 can be influenced by noncardiac factors such as muscle mass and deconditioning, age, gender, and obesity. Analysis of peak VO_2 normalized by a predicted maximum based on age, obesity, and gender has been performed to determine if better prognostication can be achieved by using a percentage of predicted peak VO_2. Some investigators have suggested the superiority of this approach, though others have shown no clear benefit (31,170). Likely, the additional value of adjusting for sex, age, and body composition in any study cohort is a function of how these characteristics are distributed across the cohort; in studies of largely middle age men of average weight, the methods give similar results while cohorts with greater heterogeneity would likely be better served by reference to sex and age specific prediction equations with adjustment for weight extremes.

Prognosis of patients with HF based on exercise perform ance and peak VO_2

The use of peak VO_2 to predict prognosis of patients with HF was first described by Szlachcic (188). In 27 patients, she reported a 77% 1-year mortality rate for patients with a VO_2 of less than 10 mL/kg/min and a 21% mortality rate for those with a VO_2 of 10 to 18 mL/kg/min. In a prospective study of 114 ambulatory patients with CHF referred for cardiac transplantation, a VO_2 of less than 14 mL/kg/min was used as a criterion for acceptance for cardiac transplantation (124). Patients were divided into three groups based on the results of their cardiopulmonary stress tests. Patients with a peak VO_2 below 14 mL/kg/min were accepted as transplant candidates (group 1); transplant was deferred for patients with a peak VO_2 above 14 mL/kg/min (group 2) and patients with a peak VO_2 below 14 mL/kg/min who had a significant comorbidity that precluded transplant (group 3). One-year survival was 94% in patients with a VO_2 above 14 mL/kg/min. Accepted transplant candidates with a VO_2 below 14 mL/kg/min had a 1-year survival of 70%, whereas the patients with a

significant comorbidity and reduced VO_2 had a 1-year survival of 47%. This approach permitted the identification of candidates whose transplant could be safely deferred.

Use of serial measurements of peak VO_2 has also been shown to effectively identify patients in a low-risk category over time (118), and conversely, a significant decline usually parallels clinical worsening and a worse prognosis. This is particularly important as the therapy for cardiac diseases continue to evolve and improve. Since the initial report of the value of peak VO_2 in guiding transplant candidate selection in 1991, there have been many advances in the treatment of HF. In particular, the use of beta blockade has significant impact on the long-term survival without significantly improving peak VO_2. Whether VO_2 retains its predictive power in the beta-blocker era has been the subject of several reports (92, 117, 154). Consistent across the reports was the sustained utility of this parameter in predicting survival. Cohorts dichotomized by threshold values of above and below 14 mL/kg/min, or above and below 10 mL/kg/min in patients on beta blockers, demonstrated that VO_2 retained its predictive value. The survival for patients on beta blocking agents shifted up but nevertheless diverged according to peak VO_2. With the improved survival, a lower cut point than 14 mL/kg/min for referral or listing for cardiac transplant has generally been accepted, with the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines now selecting a peak VO_2 below 10 mL/kg/min with achievement of anaerobic threshold as an absolute indication for transplant (in the absence of significant contraindications). A peak VO_2 of 11 to 14 mL/kg/min or 55% of predicted peak VO_2 resulting in major limitation of the patient's daily activities is considered a relative indication for transplant listing (14, 79).

VE/VCO_2 ratio during maximal symptom limited exercise in HF

During cardiopulmonary exercise testing many variables are collected that also confer prognostic information. The ventilatory response to exercise, most frequently measured by the VE/VCO_2 ratio or slope, has been found by several investigators to be even more predictive of outcome than peak VO_2 (91,158,167). The abnormal VE/VCO_2 response results from increased ventilation-perfusion mismatching and heightened chemosensitivity and ergoreflex responses. This heightened ventilatory response occurs from the onset of exercise and thus unlike peak VO_2, the VE/VCO_2 relation does not require a maximal effort. However, there has been no consensus on how best to derive this parameter. Both VE/VCO_2 ratios and slopes have been reported (i.e., VE/VCO_2 ratio at anaerobic threshold or at peak exercise) and the VE/VCO_2 slope from onset of exercise to the anaerobic threshold or throughout the total exercise period. VE/VCO_2 slope derived throughout exercise testing appears to have the greatest prognostic power. VE/VCO_2 > 34 has been the cut-point selected in many studies but similar to peak VO_2, this parameter is a continuous variable with no absolute cut-point. Published studies have shown a VE/VCO_2 ratio of >30 conferring increased risk with worst prognosis associated with VE/VCO_2 >40.

VE/VCO_2 correlates more strongly with pulmonary pressures measured during exercise than does peak VO_2. Frequently in studies, both peak VO_2 and VE/VCO_2 are found to have independent prognostic power. Therefore the combination of both VE/VCO_2 and peak VO_2 may provide the strongest way to determine risk. For example a patient with a preserved

peak VO_2 yet an abnormal VE/VCO_2 remains at greater risk than if the ventilatory response was normal. Similarly, with the converse situation where peak VO_2 is severely reduced but VE/VCO_2 normal, that patient remains at increased risk despite the normal ventilatory response. Accordingly, those with severely reduced VO_2 (<10 mL/kg/min) and excessive VE/VCO_2 (>40) fall into the poorest survival group. Thus both peak VO_2 and VE/VCO_2 slope provide independent and complementary data on prognosis and should be used together to assess risk (6,8).

Other markers of prognosis related to exercise performance in HF

Exercise oscillatory breathing is associated with a poor prognosis in both patients with diastolic and systolic dysfunction. There is no uniform definition of this type of breathing but it is a periodic cycling of hyper and hypopnea with appropriate changes in PET O_2 and PET CO_2. This breathing pattern is observed in about 12% to 30% of HF patients during exercise and most patients with exercise oscillatory breathing will have central sleep apnea. A definition for this breathing pattern is not established but a persistence of periodic breathing for 60% of exercise with amplitude of oscillations >15% over rest has been suggested. Presence of periodic breathing can predict mortality by itself or when combined with the ventilatory slope. In 156 patients with HF, this breathing pattern was strongly correlated with sudden death (68, 186).

Other parameters measured during cardiopulmonary exercise testing that also have been shown to have prognostic power in chronic HF include: blood pressure response to exercise (i.e., blunted or failure to increase BP with exercise associated with poor prognosis), the heart rate response to exercise (i.e., chronotropic incompetence), the ventilatory threshold, circulatory power (Peak VO_2 × systolic BP), oxygen kinetics, end tidal PCO_2, and oxygen recovery postexercise (5,7,36,60,151).

Invasive versus noninvasive assessm ent of hemodynamic changes during exercise in HF

As the therapy of HF has advanced with time so has the technology of metabolic carts. Advances in technology now permit noninvasive measurement of cardiac output using inert gas rebreathing techniques (97, 99). Also bioreactance technology can be used at rest and during exercise to derive cardiac output measurements. The prognostic value of peak VO_2 has been demonstrated as a noninvasive indicator of peak cardiac output response to exercise. Prior to the availability of the newer noninvasive methodologies, several studies suggested that hemodynamically derived variables from Swan Ganz catheters may enhance risk stratification over peak VO_2 (97).

The prognostic superiority of hemodynamically derived exercise variables over peak VO_2 was first shown by Griffin (66) who reported data on 49 HF patients. In this study, left ventricular stroke work index (LVSWI) at peak exercise dichotomized at 20 gm/m^2, identified patients with a threefold to fivefold higher mortality compared with the remaining patients. Exercise duration and peak VO_2 were not able to discriminate survivors from nonsurvivors. This was followed by the study of Roul (170) who measured hemodynamic

variables during exercise in 50 patients with NYHA class III CHF. This study population had 26% mortality over 21.2 ± 1.2 months. Cardiac power output (CPO) and LVSWI measured at peak exercise were strong mortality predictors. The authors also showed that, as a survival predictor, peak VO_2 was almost as powerful as CPO. Since, the measurement of CPO at their center required right heart catheterization with the patients supine, which was not always tolerated well, they recommended peak VO_2 as an alternative to the hemodynamic measurements.

Wilson (211) investigated the relationship between hemodynamic data and peak VO_2 in 64 patients with stable heart CHF referred for cardiac transplant. Forty-four percent of patients had only mild or moderate hemodynamic dysfunction despite a peak VO_2 value less than the recommended limit for transplantation (<14 mL/kg/min). Conversely, 33% of patients with a peak VO_2 > 14 had severely impaired cardiac output at peak exercise. His conclusions were that invasive hemodynamic information should be used in combination with VO_2 to determine transplant eligibility, and that patients with a low VO_2 who can demonstrate appropriate cardiac function at peak exercise not be listed (hypothesizing that the low peak VO_2 in such patients likely resulted from deconditioning, obesity or other peripheral factors). The same researchers (31) studied a larger group of 185 patients in NYHA class II-IV HF, and found the CO response to exercise the most powerful predictor of survival by both univariable and multivariable analyses. The additional finding of a peak VO_2 of ≤ 10 mL/min/kg in such patients identified a group with a particularly unfavorable prognosis (38% were alive at 1 year).

The findings by Wilson (211) required further confirmation. Other investigators (122,138) reported that LVSWI appeared to be a better prognostic indicator than peak VO_2 but it was unclear whether the risk of the catheter placement was acceptable, particularly for serial assessment, given the small enhancement in risk prognostication.

In 2001, Williams et al. (208) published the first study on the correlation between survival and hemodynamic data obtained by noninvasive measurement of CO using CO_2 rebreathing integrated with a standard exercise test. This modification was important because it is difficult to imagine that the complex procedure of invasive measurements could be implemented during the standard clinical exercise test. Two hundred and nineteen patients with mild HF (mean peak VO_2 23 mL/min/kg) were studied. Peak CPO was a stronger predictor than peak VO_2. CPO incorporates blood pressure into the exercise hemodynamic assessment. The CPO takes into account both the flow and pressure generating ability of the heart, and Tan (189) has argued that it could be viewed as a comprehensive indicator of cardiac function. The equipment for the rebreathing CO_2 method of measuring CO is not widely available and there are methodological problems. CO is measured during a separate run at a work rate corresponding to the peak work rate in the preceding incremental test, and so CPO, as measured, reflects a high work load, but not the true peak CPO. Cohen-Solal (36) proposed another index, the “peak circulatory power” which is the product of the peak VO_2 and the last systolic arterial pressure measurement. He argued that the information for its calculation is available from any cardiopulmonary exercise test without the need for special equipment. The value of the “circulatory power” was assessed in a study involving 175 HF patients. During a 25 ± 10 month follow-up, 16% died and 18% underwent cardiac

transplantation. Multivariable analysis demonstrated that the peak "circulatory power" (chi-square = 19.9, $P < 0.001$) was the only variable predictive of death or need for transplant. When this was analyzed in terms of quartiles of peak VO_2 or circulatory power, it appeared that prognosis was worse as peak VO_2 declined, but that circulatory power aids in selecting subgroups with particularly poor prognosis—those with both reduced peak VO_2 and reduced blood pressure.

Over the last 5 years, there have been advances in technology which now permit easily obtainable noninvasive measurement of cardiac output at rest and during exercise. Inert gas rebreathing is a novel, noninvasive method to measure cardiac output during exercise and is reliable, safe, and easily performed in patients with CHF (97, 99). The Innocor rebreathing system uses an oxygen enriched mixture of an inert soluble gas (0.5% nitrous oxide [N_2O]) and an inert insoluble gas (0.1% sulfur hexafluoride, [SF_6]) N_2O concentration decreases during the rebreathing maneuver, with a rate proportional to pulmonary blood flow. Recently we applied this technology in 171 consecutive CHF patients during symptom limited bicycle exercise (96). An accurate measure of peak CO was obtained in 148 patients (85% of patients). Endpoints consisted of death, urgent heart transplant or left ventricular assist device implantation (LVAD). Duration of follow-up averaged 1 year. Univariable and multivariable analyses were performed using cardiopulmonary exercise variables (i.e., peak VO_2, peak CO, peak cardiac power, VE/VCO_2 slope, and VO_2 at anaerobic threshold). Event-free survival for the entire cohort was 83% with 5 deaths, 4 LVAD implants, and 16 urgent transplants. In this cohort, peak VO_2 was 12.9 ± 4.5 mL/kg/min and peak cardiac power was 1.7 ± 0.9 watts. Univariable predictors of adverse outcome were peak VO_2, peak CO, peak cardiac power, VE/VCO_2 slope, and VO_2 at anaerobic threshold. By multivariable analysis, peak cardiac power and peak CO were predictive of outcome with peak cardiac power being the most powerful independent predictor of outcome ($P = 0.01$).

Safety of exercise testing

Exercise intolerance is one of the primary characteristics of chronic HF. Though widely utilized now to categorize the severity of HF, exercise testing was not routinely used in the diagnosis and management of patients with HF due to safety concerns. In one study cohort, low-level exercise testing has been used in 607 patients with moderately advanced HF (mean peak VO_2 14.5 ± 3.9 mL/kg/min). These patients underwent two graded symptom-limited bicycle exercise tests. The initial stress test was terminated in only 10 (1.6%) of patients for arrhythmias, and in only one patient for hypotension, but no major complications occurred during testing (196). The low incidence of adverse events with exercise stress testing in HF patients demonstrates that stable patients with HF can safely exercise in a well-supervised setting.

Limitations

Like much HF research, studies of cardiopulmonary exercise have focused largely on systolic HF and have enrolled mainly middle-aged men (reflecting the central role of these studies in the evaluation of heart transplant candidates). However, recent studies have begun to investigate the prognostic value of peak VO_2 in women, the elderly, and in those with

diastolic HF. In a study by Elmariah (50), peak VO_2 identified those women with the worse prognosis, though the overall survival of women was significantly better than of their male counterparts. These findings were confirmed by Green (65). Furthermore, exercise testing has been used rarely in the geriatric populations, but several recent studies have also demonstrated the predictive value of peak VO_2 in this population (93,160). Recently, Parikh demonstrated the prognostic value of peak VO_2 in 396 patients with HF over 65 years of age (160).

Benefits of exercise for the treatment of chronic HF

Exercise is a physiologic intervention with a broad variety of positive cardiovascular effects that include changes in lipid metabolism, insulin resistance, weight, arterial hypertension, inflammation, endogenous anabolism, and mood (93). It seems, in fact, justified to hypothesize that metabolic abnormalities associated with the primarily sedentary lifestyle in modern western civilizations are not only counteracted but normalized by physical activity. Therefore, regular exercise would be a physiologic correction rather than a medical treatment intervention.

Exercise programs distinguish between primarily aerobic dynamic (e.g., running and cycling) and resistance (e.g., strength training) exercises. Dynamic exercise with alternating muscle contraction and relaxation results in a steady rise of systolic blood pressure when intensity increases, while the diastolic pressure varies minimally. In contrast, resistance exercise is characterized by prolonged isometric muscle contraction before relaxation with high interstitial pressure that causes collapse of arterioles and capillaries. Blood pressure increases in relation to intensity and duration of the contraction. Although of minimal benefit with respect to cardiac adaptions (73,182), strength training has been shown to also be safe and effective at correcting muscle atrophy and weakness (182), two parameters that are generally less affected by aerobic-type training.

Effects of aerobic exercise on the myocardium have been well established. Regular dynamic exercise increases stroke volume, cardiac output and reduces beta-adrenergic stimulation (22). Exercise training increases myocardial mass, left ventricular dimensions, and stroke volume in healthy subjects (22, 93). In chronic HF, exercise has been shown to improve exercise tolerance and symptoms which is attributed to peripheral adaptations such as improved endothelial function and skeletal muscle strengthening (163). Moreover, exercise training has been associated with reversal of molecular and structural changes in the myocardium of hypertensive animals (93).

Exercise training has long been advocated as a means to delay aging, and decrease cardiovascular mortality in normal subjects. The evidence to support either one of these outcomes in normal or disease states is lacking. However, aerobic training can confer a multitude of significant hemodynamic, morphologic, and metabolic changes in man. We now will address the potentially beneficial effects of exercise in cardiac disease states with primary focus on aerobic exercise training.

Many of the central and peripheral changes induced by aerobic training may have a marked therapeutic effect in patients with HF. Potential advantages of training in HF (Table 2) include central hemodynamic changes such as an increase in stroke volume, and a potential increase in contractility, alteration of autonomic tone with a decrease in sympathetic stimulation, an improvement in endothelial and vascular function with a decrease in peripheral vascular resistance, muscle enzymatic changes with an increased oxidative capacity, and decrease in lactate production.

Central cardiac effects of exercise training in HF

Animal models have been used to investigate the effects of exercise training on the failing heart. Using an ischemic rat model of HF, Musch et al. (148) studied the effects of endurance training. The training protocol consisted of 60-min sessions of treadmill exercise 5 days a week for 10 to 12 weeks. Following the training program in the rats with HF, VO_2 was higher, succinate dehydrogenase activity increased and lactate levels were lower during submaximal exercise. No differences were observed in regional perfusion or in hemodynamic measurements. In this rat model of HF, all derived benefits of training were from peripheral mechanisms. Central cardiac function was not altered.

Todaka et al. (195) using a pacing-induced model of HF in dogs demonstrated both central and peripheral effects of exercise training. One group received daily treadmill exercise (4.4 km/h, 2 h/day) while the other dogs remained sedentary. At 4 weeks, *in vivo* hemodynamic measurements revealed relative preservation of maximum rate of pressure rise and left ventricular end-diastolic pressure in the exercised compared with the sedentary dogs. Subsequent *in vitro* analysis of cardiac function revealed similarly depressed systolic functions in both groups. However, whereas the diastolic myocardial stiffness constant was elevated in the sedentary group, it was normal in the exercise training group (32 ± 3 in sedentary dogs, 21 ± 3 in exercised dogs, and 20 ± 4 in otherwise normal dogs). Thus, daily exercise training preserved *in vivo* hemodynamics and *in vitro* measures of diastolic stiffness. The authors concluded that changes in heart function may contribute to the overall beneficial hemodynamic effects of exercise training in this canine model of CHF by a significant effect on diastolic properties.

In patients with CHF, a wide range of hemodynamic changes have been observed in response to exercise training also impacting on reverse remodeling (35,73,185). However, one study reported an increase in peak cardiac output (34). The same work load is achieved at a lower heart rate and rate-pressure product (34), indicating a more efficient utilization of myocardial work and oxygen consumption. Similarly, Demopoulus et al. demonstrated the diastolic wall stress significantly reduced at the lower than at the conventional training rates in patients with severe HF (41). In contrast, echocardiographic studies in patients early postmyocardial infarction involved in a 12-week exercise training program demonstrate deleterious effects of training. In this study, Jugdutt (84) showed further distortion of left ventricular shape, increased infarct size, reduced scar thickness, and ejection fraction.

Peripheral effects of exercise training in HF

Several studies have attempted to characterize the physiologic mechanisms for the clinical improvement in patients with HF. Sullivan studied 12 patients with HF with a mean VO_2 of 16.3 mL/kg/min and an ejection fraction 21% (185). Aerobic training was performed 3 to 5 h a week for 6 months. With exercise training, peak VO_2 rose 23% from 16.8 to 20.6 mL/kg/min. Peak cardiac output, peak A-VO2 difference and peak leg blood flow also significantly increased but ejection fraction was unchanged. Training decreased leg lactate production. Leg blood flow during submaximal exercise did not increase suggesting that the major benefit derived from training was via increased oxygen extraction by the skeletal muscles and the largest proportion of the increase in VO_2 was derived from peripheral adaptation with a possible small central contribution.

Other studies using selective arm training (56,58) and aerobic exercise (209) have demonstrated an improvement but not normalization in the metabolic abnormalities observed with exercise in patients with HF. Percutaneous muscle biopsies of the vastus lateralis showed that aerobic training increased the volume density of mitochondria. Oxidative enzyme activity in skeletal muscle also increased with exercise training indicating improved oxidative function (71).

Belardinelli investigated the value of low intensity exercise training in patients with HF randomized to training versus control groups (17). The exercise prescription in this study called for three weekly training sessions of bicycle exercise at 40% of peak VO_2 for 8 weeks. Peak VO_2, serum catecholamines, lactate and vastus lateralis skeletal muscle biopsies were performed before and after training. Peak VO_2 increased, serum lactate and catecholamine levels declined during submaximal exercise, and the volume density of mitochondria were enhanced at the conclusion of the study only in the trained group. Similarly, Demopoulus et al. demonstrated the value of low intensity training in patients with severe HF (41). Using a semirecumbent stationary bicycle, patients trained below 50% of peak VO_2, 1 h/day, 4×/week, for 3 months. Peak VO_2 rose from 11.5 to 15 mL/kg/min. Peak reactive hyperemia of the calf but not the forearm muscle increased with training. In this study, left ventricular diastolic wall stress was measured during bicycle exercise at low (<50%) and more conventional training workloads (70%−80% peak VO_2). Diastolic wall stress was significantly reduced at the lower than at the conventional training rates in these patients.

Several recent studies have analyzed the impact of exercise training in patients with HF with preserved ejection fraction (HFpEF). Kitzman et al. showed that exercise training improved peak oxygen uptake compared to the control group and increased peak power output, exercise time, 6-min-walk distance and the ventilatory anaerobic threshold (90). These findings have been confirmed by Edelmann et al. who showed that exercise training improves exercise capacity and physical dimensions of quality of life in HFpEF. This benefit was associated with atrial reverse remodeling and improved left ventricular diastolic function (49).

Skeletal muscle mass is also reduced in chronic HF and could lead to early skeletal muscle fatigue and decreased exercise capacity (131). Physical deconditioning may contribute to

wasting, especially of the leg muscles. The specific role of physical training on increasing leg muscle bulk versus function has yet to be determined but may well contribute to the increased exercise tolerance seen after training.

The effect of aerobic training on endothelial function has also been studied. Isolated forearm training using handgrip exercise resulted in improved flow-dependent dilatation (75). L-NMMA attenuated this improvement implying that the normalization of flow-dependent dilatation with training resulted from enhanced endothelial release of NO. This is an important finding in that it may indicate that with training there is an improvement in skeletal muscle perfusion. Also improvement in the endothelial function of large conduit vessels may decrease impedance to the failing left ventricle and thus improve left ventricular ejection fraction. At this point, other investigators have demonstrated increases in skeletal muscle leg perfusion and cardiac output at maximal but not during submaximal activity.

Modulation of “sympathetic overdrive” is another beneficial effect of exercise training. Training increases the parasympathetically mediated component of heart rate variability as well as prolonged exercise duration and increased peak VO_2 (88). Similarly, the effect of training on autonomic tone assessed by heart rate variability and radiolabeled norepinephrine spillover demonstrated a shift from sympathetic to enhanced vagal activity (35). Other investigators have demonstrated a decrease in serum catecholamine levels both at rest and during submaximal exercise in these patients following aerobic training (71,84).

In summary, exercise capacity in patients with HF is limited not only by changes which affect the ability to increase cardiac output but also by changes which occur in the blood vessels, the muscles, and the lungs as a consequence of their disease.

Impact of exercise training on respiratory function in HF

Modification of respiratory muscle function with an appropriate shift in perceived dyspnea could demonstrate the importance of respiratory muscle function in the development of dyspnea. If respiratory muscles were a key modulator of the sensation of dyspnea than selective respiratory muscle training should attenuate exertional dyspnea and may also improve exercise performance particularly in patients limited by dyspnea. Accordingly, the effect of selective respiratory muscle training on exertional dyspnea and exercise capacity has been examined in HF. In one study, we examined the effect of respiratory muscle training in HF. Supervised respiratory muscle training was performed for 3 months. Maximal sustainable ventilatory capacity, maximal mouth pressures, pulmonary function tests and submaximal and maximal exercise capacity were measured before and after training. The training protocol included a variety of elements including isocapnic hyperpnea at a predetermined maximal sustainable ventilatory level, strength training with repetitive maximal inspiratory and expiratory mouth pressures, pulmonary rehabilitation exercises, and resistive breathing using a commercial available device. Thus, the impact of both strength and endurance training of the respiratory muscles in HF patients was investigated. Respiratory muscle endurance was significantly improved with training as evidenced by increases in maximal sustainable ventilatory capacity by 57%. Respiratory muscle strength, submaximal and maximal exercise capacity (6-min walk, peak VO_2) were significantly improved with selective respiratory muscle training. Dyspnea was subjectively improved in

the majority of trained patients. In contrast, no significant improvements were observed in the controls (127).

Other investigators (38,100,102,205) have studied respiratory muscle training in these patients using predominantly resistive pressure threshold load devices or computer controlled biofeedback trainers. Training has been performed at a wide range of inspiratory pressure loads (15%−60% of Pimax). Even though the training regimens have varied, the overall results consistently demonstrated an improvement of respiratory muscle strength, peak VO_2 and 6-min-walk tests. The consistency of the improvement in overall peak VO_2 has lead to studies to identify the mechanism for the enhanced exercise capacity (Table 3).

Chiappa et al. hypothesized that the improvement in peak VO_2 may result from a redistribution of blood from the lungs to the locomotor muscles (30). Inspiratory muscle loading results in a reduction of blood flow to resting and exercising muscle which following respiratory muscle training is alleviated in patients with HF and respiratory muscle weakness. Borghi Silva et al. (23) also have demonstrated that unloaded ventilation improves submaximal exercise and skeletal muscle perfusion in HF.

Conversely, if skeletal muscle metaboreceptors modulate the sensation of dyspnea then selectively improving leg muscles may similarly alleviate dyspnea. As aerobic training results in training of both the leg and respiratory muscles, selective low-level leg training was performed in 17 HF patients. Low-level bicycle and treadmill exercise where minute ventilation was below 25 L/min was performed along with leg exercises. Perceived dyspnea during submaximal exercise was reduced in the patients with low-level training suggesting that skeletal muscle function impacts this sensation (19).

The HF-ACTION trial

The HF-ACTION trial was a large multicenter, randomized study examining the effects of exercise training on patients with HF (2331 patients with an ejections fraction <35% enrolled over 4 years). Its primary hypothesis was based on the multiple studies demonstrating beneficial effects of aerobic exercise training in patients with HF. The primary endpoint of the study was overall mortality. The study did not meet its primary endpoint. The substudy analysis, which adjusted for mortality predictors, did show an exercise dose-dependent benefit in QOL, oxygen uptake, and functional capacity. All patients were treated under recent pharmacotherapeutic standards. The observed exercise effect was very modest with an increase of peak VO_2 or only 0.3 mL/min/kg. The study showed that exercise training was safe in patients with HF over an extended period of time in a closely supervised setting with frequent follow-up. Unlike previous studies suggesting that women and older patients may not respond well to exercise training, the HF-ACTION substudy demonstrated that exercise-related benefits are consistent across sex, race, age, and other subgroups (153).

The modest effect of exercise training on peak functional capacity in the HF-ACTION trial also argues against disuse playing an important role in the pathogenesis of muscle alterations in HF. However whether these findings simply reflect the difficulty with adherence to exercise training in a large study population is unclear. The findings of the HF-ACTION trial

do not invalidate the previously well documented beneficial effects of exercise training on functional capacity and muscle mass in smaller populations of HF patients.

Potential limitations of exercise training in HF

Many questions remain regarding the value of exercise training in patients with HF. Currently, it is unclear which mode of training is optimal for these patients and whether training has effects on long term morbidity and mortality.

Initial studies by Letac (109), Lee (107), Williams (207), and Conn (37) established the safety of training in this population. They also demonstrated that patients with reduced left ventricular function can demonstrate the hallmarks of training, that is, improvement in work capacity with a concomitant decline in heart rate. In contrast, a study by Jugdutt (84) suggests that a 12-week-exercise training program in patients after extensive anterior infarctions can further distort left ventricular shape, increase infarct expansion, reduce scar thickness, and reduce ejection fraction. Endurance training in rats after large myocardial infarctions resulted in reduced survival and left ventricular dilation (56). However, in the exercise in anterior myocardial infarction trial on patients with EF <40% postmyocardial infarction, exercise training did not produce greater ventricular dilatation or reduction in ejection fraction compared to the control group. In a subgroup analysis on patients with ejection fractions below 40%, no echocardiographic evidence of deterioration of LV function was observed. However in this group mean LVEF was still quite high averaging 35% and only a small percent of patients were maintained on ACE inhibitors.

To circumvent the potential deleterious effect on high-intensity aerobic training, a few studies have focused on either low-intensity or specific-muscle training. Studies which focus on small muscle mass training which does not stress the cardiovascular system may have the added advantage of inducing peripheral skeletal muscle changes without adverse cardiac effects.

Aerobic training does not invariably result in improved exercise capacity. Compliance with the training regimen is the most frequently cited marker to predict success. However, some studies suggest that the initial cardiac output response to maximal exercise may determine the response to exercise training. In a study on patients with HF with hemodynamic measurements during treadmill exercise prior to enrolling in a rehabilitation program, patients were divided the patients into normal and reduced cardiac output response to exercise using the formula $CO = 0.5\ VO_2 + 3$ (209). Patients with a “normal” cardiac output response to exercise tolerated training and achieved therapeutic benefit with training defined as > 10% increase in both peak VO_2 and anaerobic threshold. In contrast, the patients with a reduced cardiac output response had a high drop-out rate during training due to exhaustion.

Conclusion

Exercise training appears to have therapeutic benefits for individuals with CHF. Improvements in regional blood flow, skeletal muscle histology, and biochemistry, and improvements in the autonomic imbalance likely account for the increase in exercise capacity and delay in fatigue that the trained group experiences. The beneficial effects

therefore appear to be primarily related to peripheral rather than cardiac mechanisms. Improved peripheral extraction or use of oxygen during exercise leads to the increased maximal oxygen consumption seen in trained patients. However, the survival implications of enhanced maximal oxygen consumption due to training are unknown. Future studies investigating the clinical benefit of low intensity exercise training and/or regional muscle group training in patients with HF appear warranted. These studies will elucidate the optimal regimen and the long-term effects of exercise training in patients with HF.

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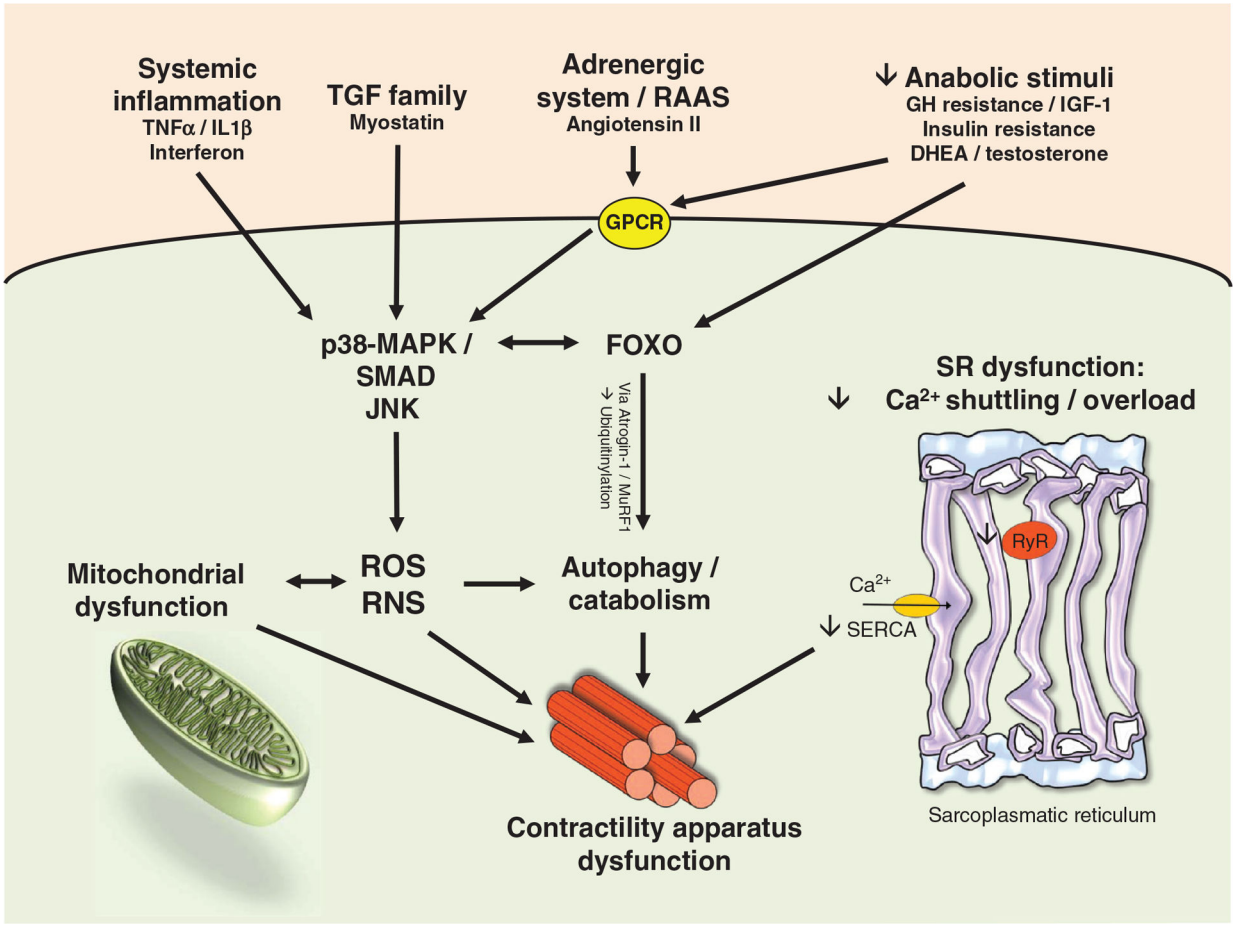

Figure 1.
Pathophysiological mechanisms impairing skeletal muscle function in heart failure.

Table 1

Skeletal Muscle Fiber Types

Fiber type	Type I	Type IIa	Type IIX
Color	Red	Red	White
Contraction time	Slow	Moderate	Fast
Oxidative capacity	High	High	Medium
Mitochondrial density	High	High	Medium
Glycolytic capacity	Low	High	High
Resistance to fatigue	High	Intermediate	Lower
Major storage fuel	TAG	CP/glycogen	CP/glycogen
Capillary density	High	Intermediate	Low

Abbreviation: CP, creatine phosphate, TAG, triglyceride.

Table 2

Effects of Exercise in Patients with Chronic Heart Failure

Investigator	*n*	LVEF%	Duration (months)	Training effects
LETAC	8 (CAD)	<45	2	↑WC, ↓HR, ↓BP
LEE	18 (CAD)	35	12–42	↑WC, ↓HR, ↔HD, ↔EF
COBB	6 (CAD)	<35	6	↔EF, ↓HR
CONN	10 (CAD)	<27	12	↑VO_2
JETTE	39 (CAD)	<50	1	↔HD, ↑WC
SULLIVAN	12 (CAD/IDC)	24	4–6	↑VO_2, ↓A-VO2, ↓HR, ↓lactate, ↑peak muscle flow
COATS	11 (CAD)	19	2	↑VO_2, ↓HR
HF-ACTION	2331	<35	12	↑VO_2, ↓HR, no difference in survival reduced hospitalization

Abbreviations: CAD, coronary artery disease; IDC, idiopathic dilated cardiomyopathy; WC, work capacity; HR, heart rate; BP, blood pressure; HD, hemodynamics; EF, ejection fraction; VO_{2max}, maximal VO_2; A-VO_2, arterial-venous oxygen difference.

Table 3

Clinical Trials of Respiratory Muscle Training in Heart Failure

Investigator	*n*	NYHA	LVEF%	Protocol	Outcome
MANCINI	14	I-IV	22 ± 9	Isocapnic hyperpnea Resistive breathing at 30% Pi_{max} Strength training	Increase Pi_{max} Increase MVV Increase 6 min walk Increase VO_{2max}
WEINER	20	II-III	<30	Resistive breathing at 15%–60% Pi_{max}	Increase Pi_{max} Increase resp muscle endurance Increase 12 min walk test No change peak VO_2
LAOUTARIS	37	II-III	24 ± 1	60% Pi_{max}	Increase Pi_{max} Increase VO_{2max} Increase 6 min walk
DALL'AGO	32		<45	30% Pi_{max}	Increase Pi_{max} Increase VO_{2max} Increase 6 min walk
LAOUTARIS	38	II-III	28 ± 1	60%Pi_{max}vs. 15% Pi_{max} (control)	Increase Pi_{max} Increase peak VO_2 Increase 6 min walk
LAOUTARIS	23	II-III	29 ± 1	60% Pi_{max} 15% Pi	Increase Pi_{max} Increase peak VO_2 Increase 6 min walk

Abbreviations: Pi_{max}, max. inspiratory pressure; VO_{2max}, max. aerobic capacity; MVV, max. voluntary ventilation.