Effects of exercise training on neurovascular control and skeletal myopathy in systolic heart failure

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Negrao CE, Middlekauff HR, Gomes-Santos IL, Antunes-Correa LM. Effects of exercise training on neurovascular control and skeletal myopathy in systolic heart failure. Am J Physiol Heart Circ Physiol 308: H792–H802, 2015. First published February 11, 2015; doi:10.1152/ajpheart.00830.2014.—Neurohormonal excitation and dyspnea are the hallmarks of heart failure (HF) and have long been associated with poor prognosis in HF patients. Sympathetic nerve activity (SNA) and ventilatory equivalent of carbon dioxide (VE/VO2) are elevated in moderate HF patients and increased even further in severe HF patients. The increase in SNA in HF patients is present regardless of age, sex, and etiology of systolic dysfunction. Neurohormonal activation is the major mediator of the peripheral vasoconstriction characteristic of HF patients. In addition, reduction in peripheral blood flow increases muscle inflammation, oxidative stress, and protein degradation, which is the essence of the skeletal myopathy and exercise intolerance in HF. Here we discuss the beneficial effects of exercise training on resting SNA in patients with systolic HF and its central and peripheral mechanisms of control. Furthermore, we discuss the exercise-mediated improvement in peripheral vasoconstriction in patients with HF. We will also focus on the effects of exercise training on ventilatory responses. Finally, we review the effects of exercise training on features of the skeletal myopathy in HF. In summary, exercise training plays an important role in HF, working synergistically with pharmacological therapies to ameliorate these abnormalities in clinical practice.

heart failure; exercise training; sympathetic nerve activity; vasoconstriction; skeletal myopathy

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Chronic heart failure (HF) affects almost 6 million of Americans, is responsible for more than 1 million primary hospitalizations yearly, and is directly associated with 1 in 9 deaths in the United States. Nearly half of these HF patients suffer from systolic dysfunction, and the progression of their HF is attributable to neurohormonal excitation leading to adverse cardiac remodeling and multi-organ dysfunction (38). Pharmacological therapies that target and counteract this neurohormonal activation lead to decreased morbidity and improved survival in HF patients. Exercise training also targets neurohormonal excitation and is now recommended as part of the standard therapeutic armamentarium for stable HF patients (111). Exercise training leads to improved neurovascular control and also has been shown to reverse features of the skeletal myopathy and abnormal ventilatory responses in HF, leading to improved functional status (66).

Neurohormonal excitation, specifically, increased resting sympathetic nerve activity (SNA), first measured by plasma norepinephrine levels, has long been recognized as a marker of poor prognosis in untrained HF patients (23, 32). Muscle SNA (MSNA) can be measured directly and quantitatively with microneurography, and increased MSNA is directly correlated with the clinical severity of HF. Resting MSNA is elevated in moderate HF patients and is increased even further in severe HF patients (55, 78). This increase in MSNA in untrained HF patients is present regardless of age, sex, and etiology of systolic dysfunction (4, 5, 79). The mechanisms involved in the sustained increase in SNA in HF remain poorly understood, but investigations in animals and humans have shown that abnormalities of peripheral reflex control and central neural integration play important roles (33, 77, 115).

Neurohormonal activation is the principle mediator of the peripheral vasoconstriction characteristic of untrained HF patients. Intra-arterial infusion of phenotamine (α-adreno-receptor antagonist) significantly reverses this vasoconstriction and increases muscle blood flow in resting HF patients (75). Moreover, phenotamine infusion significantly increases muscle vasodilatory responses during mental stress and exercise, and
reverses the paradoxical muscle vasoconstriction during hypoxia in HF patients (2, 75, 92). Non-neuronal factors, including blunted nitric oxide-mediated endothelial reactivity, also contribute to the vasoconstriction in untrained HF patients (76). In addition to muscle vasoconstriction, patients with systolic HF have diminished resting renal cortical blood flow when compared with age-matched healthy individuals (69). Reduced renal blood flow likely further exacerbates neurohormonal activation, resulting in activation of the renin angiotensin system, and contributing to the positive feedback of progressive HF (18).

In addition to neurohormonal activation, HF causes dyspnea and alterations in the respiratory pattern. Patients with HF have lower ventilatory efficiency when compared with healthy individuals, and periodic breathing is often observed. Ventilatory equivalent of carbon dioxide (VE/VCO2 ratio) is increased and associated with exercise intolerance in HF patients (63). Heightened arterial chemoreflex sensitivity likely underlies the altered pattern of ventilation characteristic of HF (26). Finally, HF causes skeletal myopathy, which is thought to be the major mediator of exercise intolerance in patients with HF (Table 1) [for review, Middlekauff (66)]. Peripheral vasoconstriction slows oxygen kinetics, which shifts the energy production from oxidative metabolism to glycolytic metabolism in skeletal muscle (84, 93, 94). Elevated ANG II increases oxidative stress and muscle protein degradation (discussed below), contributing to the reduced muscle mass (28, 96, 113). HF also is associated with a shift from oxidative muscle fibers to glycolytic muscle fibers (93, 94). These fiber changes result in increased glycolysis and premature acidosis independently of changes in blood flow (59). Mancini et al. (60) reported a significant relationship between fiber type and peak oxygen consumption (VO2), suggesting that the change in fiber type is one more factor contributing to the exercise intolerance in HF. A longstanding controversy is whether the myopathy of HF is attributable to disuse and deconditioning, or if it is an active process driven by the neurohormonal and inflammatory mediators characteristic of the HF milieu (85).

In this review, we will discuss the beneficial effects of exercise training on resting SNA in patients with systolic HF. Furthermore, we will review recent work on potential mechanisms underlying this sympathetic excitation, focusing particularly on the interstitial muscle afferent neurons and the central neural integration, and its implications in exercise capacity. We will also focus on the effects of exercise training on ventilatory responses and the underlying augmented arterial chemoreflex sensitivity. Finally, we will review the effects of exercise training on sympathetically mediated skeletal muscle vasoconstriction and on features of the skeletal myopathy of HF. We argue that exercise training should assume a major role in the treatment of HF, working synergistically with pharmacological therapies, to ameliorate these abnormalities in clinical practice.

Effects of Exercise Training on SNA

According to the American Heart Association/American College of Cardiology guideline for the management of HF, exercise training is now a Class I recommendation for stable HF patients (111). One of the most remarkable effects of exercise training in HF patients is the reduction in resting sympathetic activation. First reported as a reduction in plasma norepinephrine levels in HF patients following training (21), the decrease in SNA has been precisely and repeatedly demonstrated with direct microneurographic recordings of MSNA (Fig. 1). Our group has consistently shown that 4 months of supervised moderate exercise training significantly decreases MSNA in patients with chronic systolic HF (4, 5, 31, 88). Before β-blocker therapy became standard in the treatment of HF patients, we compared the impact of exercise training in the MSNA levels in HF patients and found that training significantly decreased resting MSNA compared with that of untrained HF patients, and in fact MSNA was no longer elevated above normal (31). In a follow-up study, we found that the training benefits were similarly observed in HF patients on β-blocker therapy (31) (Fig. 2). Furthermore, middle-aged and older HF patients derived similar sympatholytic benefits from exercise training (4). Likewise, the reduction in MSNA with exercise training was not different between women and men with HF (5). Finally, Ueno and colleagues (106) demonstrated

![Muscle Sympathetic Nerve Activity](image-url)
that exercise training decreased the severity of obstructive sleep apnea and decreased resting MSNA in HF patients with sleep apnea. In fact, the neurohormonal benefits were even more pronounced in this cohort.

The mechanisms underlying the reduction in the sympathetic modulation in exercise-trained HF patients remain uncertain, but several likely contributors will be discussed. In patients with chronic myocardial infarction but without HF, training-related reduction in MSNA is associated with improvement in baroreflex control (62). In the rat infarct model of HF, exercise training increases the inhibitory aortic afferent nerve discharge during fluctuations in blood pressure, consistent with improved baroreflex function localized to the afferent limb (87). Because baroreflex dysfunction has long been posited as an important mechanism underlying the sympatho-excitation in chronic HF (61), it is plausible that improved baroreflex function with exercise training contributes to its normalization. Exercise training has also been shown to improve arterial chemoreflex control of SNA in the rabbit pacing model of HF. Following exercise training in the HF rabbit, the exaggerated increase in renal sympathetic nerve activity (RSNA) in response to oxygen arterial partial pressure variation is attenuated (56). Moreover, these changes seem to be due to an improvement in carotid body nitric oxide production (102, 103). In summary, exercise training has beneficial effects on both arterial baroreflex and arterial chemoreflex control of sympathetic nerve activity, which likely contribute to the observed reductions in resting SNA in trained HF patients.

Most recently, our laboratory has focused on skeletal muscle afferent nerve fibers, including muscle metaboreceptors, which are unmyelinated group IV fibers sensitive to ischemic metabolites, and muscle mechanoreceptors, thinly myelinated group III fibers sensitive to mechanical stimuli. Data from animal HF models, as well as from untrained HF patients, support the concept that muscle metaboreflex control of MSNA is blunted and muscle mechanoreflex sensitivity is augmented (35, 67, 68, 100). The molecular mechanisms underlying these altered skeletal muscle reflexes in HF are not completely understood. Transient receptor potential vanilloid type-1 (TRPV1) and cannabinoid receptor type-1 (CB1) receptors are colocalized on muscle metaboreceptors. In animal models of HF, these receptors are downregulated on muscle metaboreceptors (98, 107, 109). Wang et al. (108) observed that exercise training initiated soon after myocardial infarction before the onset of HF in the rat infarct model of HF increased expression of TRPV1 receptors in dorsal root ganglia and prevented blunted metaboreflex sensitivity. Nerve growth factor (NGF) is a trophic factor for TRPV1 expression, and NGF is downregulated in HF models, suggestive of a possible mechanism to explain the decreased TRPV1 expression in HF. The impact of exercise training in HF rats on NGF has not been studied. Switching our focus to the mechanoreflex, cyclooxygenase-2 (COX) metabolites and purinergic 2X (P2X) receptors have been shown to modulate the sensitivity of muscle mechanoreceptors in animals models of HF (107). Exercise training reduces the expression of P2X receptors in skeletal muscle afferents in animals with HF (108).

We hypothesized that the reduction in resting SNA following exercise training in humans with HF would be mediated by changes in muscle mechanoreflex and metaboreflex sensitivity. To isolate the muscle metaboreceptor, we used the technique of post-exercise circulatory arrest, in which a sphygmonanometer cuff placed on the limb proximal to exercising muscle is inflated to supra-systolic levels at the conclusion of exercise, trapping ischemic metabolites in the vicinity of the muscle metaboreceptors. Moderate exercise training for 4 months significantly increased MSNA responses during metaboreceptors stimulation (6). Furthermore, this increase in muscle metaboreflex sensitivity was associated with an increase in expression of TRPV1 and CB1. Moderate exercise training also significantly decreased MSNA responses during muscle mechanoreceptor stimulation (6). The changes in mechanoreceptor sensitivity were accompanied by reduction in COX-2...
Central command, a signal generated in the cerebral cortex proportionate to perceived effort during exercise, also increases SNA and heart rate responses during exercise. In animals with HF, Koba et al. (54) found that exercise training normalized the central command control of RSNA during electrical stimulation of the mesencephalic locomotor region, which was attributed to antioxidative effects in the medulla. In humans with end-stage renal failure in whom reflex control of the circulation is altered, central command control of HR is augmented (82); central command control of SNA has not been studied. Similarly, central command control of SNA has not been studied in humans with HF. It remains unknown, but possible, if the changes in SNA due to exercise training are mediated in part by changes in central command, and further studies are needed.

Exercise training also ameliorates abnormal central neuronal signaling, which may contribute to the observed decrease in resting SNA following exercise training [for review, Haack and Zucker (43)]. To date, data exist only in animal models to illuminate the role for the central nervous system signaling in HF. Central ANG II levels and expression of angiotensin II type 1 (AT1) receptors are increased in the rostral ventrolateral medulla (RVLM) in HF models and may contribute to the exaggerated sympathetic outflow in HF models. Exercise training reduces gene expression of ANG II receptors in the rostroventrolateral medulla in HF animals (33). Because ANG II modulates central sympathetic outflow, it is plausible that the reduction in efferent SNA following exercise training in HF is due to attenuation in ANG II activity in the sites of central neural integration. In fact, an association between the changes in central AT1 receptor type 1 (AT1) gene expression and the reduction in RSNA has been reported in the rabbit pacing model of HF (73). More recently, Kar et al. (50) showed that exercise training normalizes the balance between angiotensin converting enzyme (ACE) and ACE2 in the central nervous systems of animals with HF. This finding suggests an important role of ANG II/ANG 1–7 interaction in the exaggerated central sympathetic outflow in HF (50). Exercise training also increases the bioavailability of nitric oxide (NO) in the central nervous system due to an increased expression of neuronal NO synthase (nNOS) in paraventricular nucleus (114). Finally, exercise training reduces oxidative stress by reduced protein expression of NAPH oxidase subunit gp91(phox) and increased expression of CuZn superoxide dismutase in rostral ventral lateral medulla in HF rabbits (34).

In summary, exercise training decreases the elevated MSNA levels in HF toward normal and ameliorates the abnormal reflex control of MSNA during acute exercise. The finding that these beneficial effects of exercise training on sympathetic activation are accompanied by a decrease in muscle inflammation suggests an association, although it is impossible to know which factor - inflammation or SNA - is the driver. Evidence supports a role for both. To summarize (see Fig. 3): acute sympathetic excitation (likely baroreflex mediated) following a myocardial infarction or similar injury leads to an acute increase in efferent MSNA and reduced muscle and renal blood flow. This chronic muscle hypoperfusion may then generate skeletal muscle inflammation, diminished NGF levels, and altered afferent muscle neuronal receptor expression (e.g., TRPV1). Renal hypoperfusion leads to activation of the renin angiotensin system, specifically ANG II. Consequently, central reflex control of MSNA during exercise is altered, further contributing to increase in MSNA and RSNA, poor exercise tolerance, and skeletal myopathy (6). Although pharmacological therapies partially interrupt the neurohormonal excitation and improve muscle and kidney blood flow, these pharmacological strategies are insufficient. Only exercise training has been shown to restore the neurohormonal balance and reverse many key features of the skeletal myopathy in patients with HF from systolic dysfunction.

Effects of Exercise Training on Ventilatory Response

Dyspnea is a common symptom in patients with HF. Several mechanisms have been suggested to explain the abnormal ventilatory pattern and increased arterial chemoreflex sensitivity in HF patients. This complex issue has been attributed to pulmonary congestion, peripheral hypoxemia, and hypoperfusion in consequence of a low cardiac output [for review, Dempsey (26)]. In addition, animal data support the notion that carotid body alterations play a role in the altered respiratory pattern in HF. HF patients have enhanced chemoreflex sensitivity mediated by augmented afferent input from carotid body. These alterations are associated with upregulation of ANG II system and decreased nNOS expression in carotid body, which contribute to the enhanced carotid body sensitivity in HF (Fig. 3) (95). More recently, respiratory disturbances have been associated with abnormal afferent skeletal muscle reflex control. Olson et al. (81) demonstrated that inhibition of afferent feedback from skeletal muscle, via lumbar intrathecal injection of fentanyl, significantly decreased the ventilator responses during submaximal exercise in HF patients. Because exercise training improves muscle mechanoreflex and metaboreflex control of MSNA in patients with HF as previously reported (Antunes-Correa), it is reasonable to raise the question whether the improvement in muscle afferent reflexes following exercise training also contributes to the amelioration of the respiratory pattern in HF. This potential benefit of exercise training has not yet been investigated. Furthermore, it is likely that exercise-induced improvement in chemoreflex control also plays a role in the amelioration of respiratory pattern in HF patients. Exercise training normalizes afferent carotid body chemoreflex activity by reversing alterations in ANG II systems and nNOS expression in carotid body in animals with HF (56). The improvement in the VE/VCO2 ratio during exercise has been consistently demonstrated in exercise-trained HF patients (5, 31). This is an important response because reduc-
tion in work of breathing during exercise may increase blood flow to the skeletal muscle, thereby improving exercise capacity.

Effects of Exercise Training on Skeletal Myopathy

The skeletal myopathy of HF is recognized as an important contributor to exercise intolerance in chronic systolic HF (20, 22, 66). Exercise training has been shown to significantly improve many of the key features of the skeletal myopathy in HF patients (Table 1), including increased muscle capillarization, muscle blood flow, and flow mediated dilation (4, 11, 30, 31, 93, 99, 106). Importantly, significantly augmented circulating bone marrow-derived progenitor cells, which restore the diseased endothelium, have been detected in exercise-trained HF patients (29). All these changes in vascular architecture and function favor oxygen diffusion capacity into skeletal muscle and energy production [for review, Poole et al. (84)]. Exercise training restores aerobic metabolism in HF by improving oxidative pathways. Exercise training increases maximal citrate synthase activity in HF (11, 72). Exercise training also increases mitochondrial volume and enzyme content, improving the metabolic capacity in HF (11, 30, 52, 91). These metabolic changes contribute, at least in part, to the improvement in functional capacity and reduction in exercise intolerance in patients with HF.

At the skeletal myocyte level, exercise training results in key changes in protein expression. Exercise training reduces skeletal muscle TNF-α gene and protein expression in patients with HF, presumably leading to a decrease in reactive oxygen species (ROS) production (28, 36). Among the many damaging effects of oxidative stress, ROS mediate the translocation of NF-κB to the nucleus, which activates catabolic genes (“an atrophy program”), leading to skeletal muscle wasting (42, 57, 90). In a mouse model of sympathetic hyperactivity-induced
HF, exercise training reduces lipid hydroperoxidation and carbonylated proteins, markers of sustained ROS (24).

In humans with HF, muscle atrophy is present in some, but not all, skeletal muscle biopsies and in its most profound state is known clinically as cardiac cachexia. Exercise training ameliorates protein degradation pathways in animal models, including the mouse model of sympathetic hyperactivity-induced HF. Ubiquitin-proteasome system (UPS), the final common pathway of protein degradation, is known clinically as cardiac cachexia. Exercise training reduces lipid hydroperoxidation and carbonylated proteins, markers of sustained ROS (24).

Exercise training significantly reduces the components of E3 ligases; Atrogin-1, MuRF-1 and E3α gene expression are all decreased by exercise training (24, 40).

Insulin-like growth factor-1 (IGF-1) signaling pathway is a key pathway involved in skeletal muscle anabolic/catabolic balance (90). Godard et al. (39) found that IGF-1 is downregulated in skeletal muscle of HF patients, even before anatomical alterations are present. Only 4 weeks of exercise training significantly reverses the downregulation of the IGF-1 signaling pathway in humans with chronic systolic HF (37). Importantly, these changes in muscle protein degradation pathways are associated with increased quadriceps muscle cross-sectional area and mass (24). Similar findings have been reported in ischemic models of HF and in HF patients following exercise training (24, 37, 47, 72).

Pharmacological interruption of the renin angiotensin system is a mainstay of HF therapy; elevated ANG II levels despite angiotensin converting enzyme inhibitor therapy is associated with increased mortality (86). Following myocardial infarction or similar cardiac injury, elevated RSNA and decreased renal perfusion increase ANG II (97). ANG II remains elevated in the plasma, organs, and tissues contributing to the progression of HF (see Table 2) (41, 51, 86, 97). We found an association between the improvement skeletal myopathy and the reduction in plasma ANG II concentrations (40). Exercise training emerges as an important strategy that works synergistically with pharmacological therapies for the comprehensive treatment of HF.

Clinical Implications

The translational studies reviewed substantially extend our understanding of the role of exercise training on clinical outcomes in patients with HF. The clinical benefits accompanying the physiologic benefits of reducing SNA and the improved in respiratory pattern following exercise training in HF patients are important. SNA exacerbation precipitates cardiac arrhythmias, increases afterload, and decreases ventricular function. Increased MSNA is an independent predictor of mortality in HF patients (12). Similarly, VE/VCO2 predicts a poor prognosis in HF patients (8, 10). Reversal of the elevated MSNA increases endothelial-mediated vasodilation in skeletal muscle (92). The increase in peripheral blood flow may improve the skeletal myopathy of HF. Finally, these exercise-induced physiological changes contribute to the improvement in exercise tolerance and quality of life in patients with HF.

Exercise Training Paradigm

What is the ideal prescription for exercise for patients with HF? During the last decades, several studies demonstrated that both supervised and nonsupervised exercise training substantially benefit patients with left systolic dysfunction, although compliance with supervised exercise is certainly better (83). In the HF-ACTION Study a large proportion of HF patients did not complete the unsupervised exercise program. Moderate aerobic exercise training has been the preferred modality of exercise training, and patients likely benefit from moderate strength training as well (4–6, 25, 31, 88, 106). Recent studies have suggested that intense exercise alternates moderate exercise during a session is safe and well tolerate in HF patients,

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and the benefits produced by more intense exercise seem to be superior to those achieved by moderate exercise (7, 9, 49, 110). Selection criteria for intense exercise training in HF patients are uncertain. Much work needs to be done on tailoring the exercise training program to the individual HF patient. When should exercise training start? Because inactivity accelerates the progression of exercise intolerance and worsening of the quality of life, it is legitimate to suggest that exercise training for HF patients starts as soon as possible. An ongoing multicenter, randomized, prospective, open, controlled trial will provide more information regarding this subject in the near future (65).

Final Remarks

Exercise training improves neurovascular control and ventilatory responses in HF patients with chronic systolic dysfunction, including patients optimized on medical therapy (Fig. 4). Exercise training decreases resting MSNA in chronic HF patients, independent of age, sex, etiology of HF, and comorbidities. Exercise training reverses abnormal reflex control of MSNA and increases expression of the neuronal afferent receptors TRPV1 and CB1. Exercise training decreases muscle inflammation and ANG II levels, presumably through its sympatheolytic and vasodilatory effects. Reversal of muscle inflammation and increased ANG II restores the balance of the muscle catabolic-anabolic pathways, thereby reversing muscle atrophy. Exercise training is associated with improved quality of life in patients already on optimal, guideline directed medical therapy and is playing an increasingly important therapeutic role in the treatment of HF (111).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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Fig. 4. Effects of exercise training in systolic heart failure. Note that exercise training reduces plasma and tissue renin-angiotensin system, and angiotensin II activity in the central nervous system. In addition, exercise training improves arterial baroreflex, chemoreflex, and muscle pressor reflex controls. All together, these responses lead to remarkable reduction in sympathetic nerve activity (SNA) and renal vasoconstriction and ventilatory responses (see text for more details). TRPV1, transient receptor potential vanilloid type-1.
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