The best medicine: exercise training normalizes chemosensitivity and sympathoexcitation in heart failure

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CHRONIC HEART FAILURE (CHF) is well characterized by excessive sympathoexcitation at rest, as well as an exaggerated sympathoexcitatory response to exercise. While sympathetic activation is an initial beneficial compensatory mechanism in CHF to maintain cardiac output and blood pressure, chronic sympathoexcitation contributes to further cardiovascular deterioration and has been shown to be inversely associated with survival (1). Thus it is perhaps not surprising that therapeutic interventions, such as adrenergic receptor blockade and angiotensin-converting enzyme inhibition, dramatically improve survival in CHF.

Despite the rapid expansion of effective therapeutic interventions for patients with CHF, the fundamental mechanisms contributing to increased sympathetic nerve activity (SNA) in CHF are surprisingly poorly understood. Skeletal muscle chemoreflex, mechanoreflex, and baroreflex dysfunction have all been implicated as significant contributors to SNA in CHF. Interestingly, augmented carotid chemoreflex activity is well known to increase SNA, and enhanced carotid chemoreceptor sensitivity has been demonstrated in both clinical (9) and experimental CHF (13) and is predictive of patient mortality (9).

Previous work in Dr. Schultz’s laboratory has shown that the enhanced carotid chemoreceptor sensitivity at rest contributes, at least in part, to sympathoexcitation in CHF, as inhibition of chemoreceptor activity with 100% inspired O2 decreases renal SNA in CHF but not healthy animals (13). Through an insightful series of experiments, Dr. Schultz and colleagues have demonstrated that enhanced chemoreceptor sensitivity in CHF is due to a reduction in neuronal nitric oxide (NO) bioavailability (4, 13) and increased angiotensin II (ANG II) and ANG II type I receptors at the level of the carotid body (5), with cardiac sympathetic afferent activity also contributing to the amplification of the carotid chemoreceptor afferent signal in the nucleus tractus solitarii (2). These reductions in NO bioavailability appear to be due to increases in NAD(P)H oxidase-derived reactive oxygen species, as acute treatment with superoxide dismutase mimetics or inhibitors of the NAD(P)H oxidase can normalize carotid body function.

Although exercise has been hailed as the most effective “ounce of prevention” against cardiovascular disease, there are only limited studies examining the effects of exercise on morbidity and mortality in patients with CHF, and the first large, randomized trial examining the effects of exercise treatment on reducing adverse outcomes in CHF is now underway (HF-ACTION) (14). Despite relatively limited data, exercise training has become an integral part of Cardiac Rehabilitation Programs. Although patients typically demonstrate increases in exercise capacity, skeletal muscle aerobic capacity, and quality of life following exercise training, the neural and reflex adaptations to exercise remain poorly understood.

In the current article in the Journal of Applied Physiology by Li et al. (3), the group extends its previous work, providing major insight into chemoreflex plasticity by examining the effect of exercise training on carotid chemoreceptor activity and sympathoexcitation in CHF. In this study, exercise training reduced renal SNA in CHF compared with sedentary CHF animals, while exercise training normalized the chemoreflex in CHF. Exercise training in CHF increased neuronal NO, while reducing ANG II concentration at the carotid body. The exercise-induced normalization of the chemoreflex could be reversed in CHF by inhibiting neuronal NO or increasing ANG II at the carotid body, providing confirmation that the exercise adaptation is operating via increasing bioavailability of NO and reducing ANG II at the carotid body.

A particularly important observation in this study was that exercise did not protect against increases in chemoreceptor activity/sensitivity associated with the addition of exogenous ANG II in isolated carotid bodies and did not affect carotid body function in sham animals. Thus it appears that exercise exerts its protective effect on carotid chemoreceptor sensitivity in CHF primarily via reductions in circulating and tissue ANG II levels. Using a similar model of heart failure, colleagues of the group have shown that exercise training also enhances the baroreflex in CHF by an ANG II mechanism (8). It has been well demonstrated that there is an interactive effect between the baro/chemoreceptors, and thus it would be of interest to examine how exercise impacts the integration of these signals at the level of the brain stem.

There are numerous pathways via which exercise may modulate redox balance and NO bioavailability in a variety of tissue beds (see Fig. 1). First, it has been reported that antioxidant defense mechanisms are reduced and prooxidant mechanisms are increased in CHF. A growing body of literature suggests that exercise results in the coordinated upregulation of antioxidant defense mechanisms in CHF (6), as well as a downregulation of prooxidative enzymes. Second, there is an ever-growing list of isofoms, subcellular localization, and tissue-specific expression of antioxidant enzymes. Which subcellular compartments and reactive oxygen species are critical for exercise-induced adaptations remains largely unknown. Third, it is unknown whether shear stress and its dramatic effects on endothelial function provide a much needed paracrine signal
for initiating early changes in gene expression in the carotid body following exercise.

It is evident through a growing body of literature that exercise can also limit the deleterious effects of ANG II by reducing ANG II type I receptors. Several studies have shown that exercise reduces both circulating and tissue ANG II levels (10). The mechanisms by which exercise reduces circulating ANG II levels is not clear. Some putative targets that need to be examined in future studies include reductions in hepatic production of angiotensinogen, systemic or regional reductions in angiotensin-converting enzyme type I, or increases in angiotensin-converting enzyme type II. Understanding these interactions will not only shed insight into the basic biology of the effects of exercise on the renin-angiotensin system, but may also lend insights into the role of genetic variation on the responses to exercise training in humans (e.g., identifying “responders” and “non-responders” based on single nucleotide polymorphism screening, etc.).

The enhanced carotid chemosensitivity in CHF has an important functional consequence, as demonstrated by recent work showing inhibition of the carotid chemoreceptor causing vasodilation at rest and during exercise via reduced sympathetic vasoconstriction outflow (11). Likewise, inhibiting the carotid chemoreceptor also reduces muscle SNA during exercise in healthy humans (12). Enhanced carotid chemoreceptor sensitivity is also likely to play a key role in determining the magnitude of the hyperventilatory response to exercise in CHF (9), with the resultant increases in respiratory muscle work and dyspneic sensations being significant determinants of locomotor limb blood flow and exercise tolerance (7). Collectively, these data indicate that the carotid chemoreceptor can play a major role in cardiorespiratory control in CHF at rest, as well as during exercise in both health and CHF. It is unknown whether the current results reporting a training-induced normalization of the chemoreflex in CHF will directly influence the exaggerated sympathetic and/or ventilatory response to exercise in CHF.

Although most patients acknowledge that regular exercise positively impacts their quality of life, long-term exercise adherence is notoriously poor. Even patients with CHF that do adhere to an exercise program are likely to suffer from acute decompensatory events or hospitalizations, which would lead to at least short-term inactivity. Thus it would be of great interest to examine the chemoreceptor and sympathetic response to detraining in CHF, as rapid losses in exercise-induced adaptations in the carotid body would likely contribute to exacerbated sensations of dyspnea when an exercise program is restarted. Another question of perhaps equal importance would be to determine the minimum threshold of exercise frequency and intensity needed for adaptation at the carotid body.

The superb paper by Li et al. (3) published in this month’s Journal of Applied Physiology details how exercise training increased neuronal NO, while reducing ANG II concentration at the carotid body, thereby reducing the carotid chemoreflex and sympathoexcitation in CHF. NOS, NO synthase; eNOS, endothelial NOS; nNOS, neuronal NOS; SOD, superoxide dismutase; AT,R, angiotensin type I receptor; NTS, nucleus tractus solitarii.

**ACKNOWLEDGMENTS**

The authors thank Teresa Ruggle for preparation of the figure.

**GRANTS**

This work was supported by a Canadian Institute of Health Research New Investigator Award to M. K. Stickland and a Pathway to Independence Award from the National Heart, Lung, and Blood Institute to J. D. Miller.

**REFERENCES**


