Exercise training in heart failure: reduction in angiotensin II, sympathetic nerve activity, and baroreflex control

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NEUROHUMORAL EXCITATION has been considered the hallmark of heart failure. At the humoral level, cardiac dysfunction has been shown to be associated with increased angiotensin II, aldosterone, and vasopressin levels. The clinical implication for such humoral dysregulation is the increase in salt and water retention, which contributes to clinical heart failure. It has also been shown that patients with cardiac dysfunction have augmented peripheral norepinephrine levels and cardiac norepinephrine spillover. In addition, elevations in muscle sympathetic nerve activity levels directly measured in the peroneal nerve by microneurography correlate with the severity of heart failure.

Accumulating evidence shows that sympathetic hyperactivity plays an important role in the vasoconstrictor state of heart failure. Patients with chronic heart failure have greater renal cortical vascular resistance and muscle vascular resistance than healthy individuals (5). Phentolamine, an α1-adrenoceptor antagonist, infused into the brachial artery significantly increases forearm blood flow in patients with severe cardiac dysfunction. Moreover, in contrast to acetylcholine alone, acetylcholine associated with phentolamine increases forearm vascular conductance responses during mental stress toward normal levels (9). Unknown are the causes of sympathoexcitation in heart failure. Alterations in arterial and cardiopulmonary baroreceptors, central and peripheral chemoreceptors, cardiac chemoreceptors, and central nervous system abnormalities have all been proposed to contribute to the increased sympathetic activity in heart failure.

Persistent morbidity and mortality in patients with heart failure, despite advances in pharmacological treatment, have led many investigators to search for new strategies in the treatment of heart failure. Exercise training has emerged as a new and efficient nonpharmacological treatment for patients with heart failure. Dr. Zucker’s group has provided many contributions to our understanding of the mechanisms underlying the beneficial effects of exercise in heart failure. Using a pacing-induced model of heart failure in rabbits, these investigators (4) have previously reported that exercise training for 1 mo significantly reduced renal sympathetic nerve activity. These findings were recently confirmed in a rat model of ischemia-induced heart failure (7). Similar findings have been reported in humans. Four months of exercise training significantly reduced muscle sympathetic nerve activity levels in patients with chronic heart failure and ejection fraction <45% and categorized as functional class II and III under New York Heart Association guidelines (8). This decrease in muscle sympathetic nerve activity was so dramatic that muscle sympathetic nerve activity levels after exercise training were not different from those observed in healthy controls.

The mechanisms underlying the powerful effect of exercise training on sympathetic hyperactivity in heart failure remain under investigation. Liu et al. (4) have reported that exercise training restored arterial baroreflex control of renal sympathetic nerve activity and heart rate, which was associated with an improvement in the aortic depressor sensitivity (7). At the central nervous system level, exercise training reduces angiotensin II type I receptors in the paraventricular nucleus, rostral ventrolateral medulla, and nucleus tractus solitarius (11). In a recent study, Gao et al. (1) demonstrated that the normalization in renal sympathetic nerve activity and arterial baroreflex control in rabbits with pacing-induced heart failure was associated with an upregulation of superoxide dismutase and a downregulation of the NADPH oxidase subunit gp91 expression in the rostral ventrolateral medulla.

In the recent article in the Journal of Applied Physiology by Mousa et al. (6), the group demonstrates that exercise training reduces renal sympathetic nerve activity and improves arterial baroreflex sensitivity in rabbits with pacing-induced heart failure. In addition, these investigators show that exercise training prevents the increase in angiotensin II and downregulated mRNA and protein expression of angiotensin type I receptors in the rostral ventrolateral medulla in this animal model of heart failure. Interestingly, when angiotensin II levels were maintained experimentally near levels of untrained rabbits with heart failure, the amelioration in arterial baroreflex sensitivity was prevented. These findings are consistent with the notion that the improvement in the arterial baroreflex control and central nervous system integration depends on the reduction in angiotensin II and angiotensin type I receptors in the rostral ventrolateral medulla.

As with all good scientific studies, the Mousa et al. (6) study leaves us with more questions than it answers. 1) How does exercise training decrease angiotensin II levels? 2) Is there a threshold effect for the amount and type of exercise necessary to decrease angiotensin II levels, or is it a continuum? Wisløff et al. (10) have recently reported that patients with postinfarction heart failure submitted to aerobic interval training had a more effective reversion of the left ventricular remodeling and improved aerobic capacity, endothelial function, and quality of life than when submitted to moderate continuous exercise training. 3) Is there a threshold effect at which circulating angiotensin II will trigger increases in sympathetic nerve activity, or is this a graded effect? 4) Finally, is exercise training an acceptable alternative to pharmacological interruption of the renin-angiotensin-aldosterone system, especially in patients in
whom low blood pressure or intolerable side effects prohibit adequate pharmacological dosing?

What are the implications of the inhibitory sympathetic changes caused by exercise training in heart failure? The obvious consequence of the sympathetic inhibition is the increase in peripheral blood flow and oxygen supply. These responses reduce the expression of inflammatory cytokines and the production of reactive oxygen species. These antioxidative effects of exercise training are further demonstrated by the normalization of lipid peroxidation and nitrotyrosine formation in skeletal muscle of patients with heart failure (3). Moreover, the anti-inflammatory effect of exercise training restores oxidative capacity in heart failure, since there is an inverse correlation between the decrease in inducible nitric oxide synthase and the mitochondrial isoform of creatine kinase (2). Finally, the reduction in inflammatory cytokines may decrease protein degradation via the ubiquitin/proteasome system and muscle atrophy. All of these changes associated with exercise training seem to act in concert to increase exercise tolerance and quality of life in patients with heart failure.

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