**Exercise Training in Chronic Heart Failure**

How to Harmonize Oxidative Stress, Sympathetic Outflow, and Angiotensin II

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*Life is movement.*

—Aristotle (fourth century BCE)

Heart failure is a major clinical and public health problem in Western countries. It is estimated that nearly 23 million people have heart failure worldwide. In the United States, 550,000 new cases are reported each year, and the age at diagnosis shifted from 65±9 years in 1950 to 1969 to 80±10 in 1990 to 1999. Approximately 69% of men and 45% of women die within 5 years of the onset of symptoms. In the United States, half of inpatients >65 years of age with chronic heart failure (CHF) are readmitted within 6 months of hospital discharge, suggesting insufficient coordination of care among different operators and/or inefficient comprehensive discharge planning.

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The difficulty in determining ROS activity in vivo, the presence of confounding comorbidities, and the disappointing results of large clinical trials using antioxidant therapy are unresolved problems indicating that the relationship between ROS and heart failure is complex. Nonetheless, ROS, particularly the superoxide anion (O$_2^-$), have an important role as mediators of angiotensin II (AII) signaling. AII not only augments ROS formation and increases oxidase activity but also upregulates mRNA of most NAD(P)H oxidase subunits both in vitro and in vivo. Moreover, ROS are implicated in the regulation of sympathetic nerve activity. As a matter of fact, a decrease in central O$_2^-$ by tempol, a superoxide dismutase (SOD) mimetic, reduces sympathetic outflow in animal models of CHF, whereas an increase in central O$_2^-$ induced by the SOD inhibitor diethyldithiocarbamate has the opposite effect. All increases the activity of NAD(P)H oxidase, the major source of O$_2^-$ in the vasculature, and stimulates O$_2^-$ production in the central nervous system. Intracerebral infusion of NAD(P)H oxidase inhibitor antagonizes the increase in renal sympathetic nerve activity induced by AII centrally. Moreover, the overexpression of SOD in the brain abolishes the central pressor effect of AII. Promoter neurons that maintain tonic sympathetic vasomotor outflow are located in rostral ventrolateral medulla, where AII exerts its major effects through activation of AII type 1 (AT$_1$) receptors. There is evidence that NAD(P)H oxidase–derived O$_2^-$ activates p38 mitogen-activated protein kinase, which mediates the AII sympathoexcitatory effect through AT$_1$ receptors in rostral ventrolateral medulla. Losartan attenuates the sympathoexcitatory outflow by inhibiting O$_2^-$ production induced by AII.

In this issue of Circulation, Gao and colleagues present a study that aerobic exercise normalizes sympathetic outflow and arterial baroreflex function in rabbits with pacing-induced CHF. This beneficial effect has been associated with an upregulation of SOD expression and a downregulation of the NADPH oxidase subunit gp91phox expression in the rostral ventrolateral medulla. Because a decrease in baseline renal sympathetic nerve activity has been observed after central SOD overexpression via gene transfection with AdCuZn-SOD, it is possible to speculate a link with exercise-induced decrease in sympathetic outflow. In another study, exercise training reduced vascular expression of NADPH oxidase and AT$_1$, resulting in decreased local ROS generation, which was associated with improved acetylcholine-mediated coronary artery vasodilation and reduced AII-induced vasoconstriction. We may speculate that there is a link between sympathetic outflow and endothelium-dependent vasodila-
tion, and oxidative stress seems to play a major role. The restoration of autonomic function through central antioxidant mechanisms may provide a novel explanation for the beneficial effects of exercise training in CHF. Exercise increases arterial baroreflex sensitivity and lowers resting renal sympathetic nerve activity in rabbits with CHF. AT1 receptor blockade enhances baroreflex sensitivity in control CHF rabbits but has no effect in trained animals.11 A positive correlation has been found between sympathetic nerve activity and plasma AII. Moreover, exercise induces favorable gene expression in endothelial cells, ie, nitric oxide synthase and extracellular SOD, which improves nitric oxide biological activity.12 Treadmill exercise training increases endothelial NOS and extracellular SOD expression in wild-type mice but has no effect on extracellular SOD expression in mice lacking endothelial NOS, suggesting that this effect of exercise is mediated by endothelium-derived nitric oxide.

In this issue of Circulation, Wisloff and colleagues13 show that high-intensity interval training reduced left ventricular remodeling and improved aerobic capacity and quality of life in a group of postinfarction patients 75 ± 11 years of age in addition to standard medications. Aerobic interval training has been superior to endurance moderate training. Peak VO2 increased 46% versus 14%, respectively, and was correlated with both skeletal muscle peroxisome proliferative–activated receptor γ coactivator-1α, an indicator of mitochondrial biogenesis, and Ca2+ reuptake into sarcoplasmic reticulum (r = 0.71 and 0.56, respectively). The improved peak VO2 also was correlated with brachial artery flow-mediated dilation, which had a more marked improvement after interval training than endurance training. Interval training was associated with a 15% increase in total antioxidant status, which was correlated with enhanced flow-mediated dilation (r = 0.67).

An increased skeletal muscle oxidative capacity after exercise training confirms the results of previous studies in animal and human models of CHF.14,15 Exercise acts as a modulator of gene expression in different districts involved in its biological effects. It is of interest that high-intensity aerobic interval exercise determines more marked improvements than traditional moderate-intensity exercise in CHF. At present, we do not have definitive explanations. We know that in human ischemic cardiomyopathy the presence of viable myocardium is a prerequisite for improvements in peak VO2 and myocardial perfusion.16 On-off bursts of exercise may exert preconditioning of myocardial cells and may act as an amplifier of biological adaptations. The precise underlying mechanisms are not yet defined. A hypothesis may be that intermittent high-intensity exercise, by increasing the nitric oxide–redox–based signaling, may induce expression of genes implicated in the regulation of sympathetic outflow and endothelium-dependent relaxation.17 Increased ROS generation induced by exercise stimulates antioxidant defenses, which induces favorable biological adaptations in the central nervous system and the periphery. Gene expression is adjusted to oxygen availability by several mechanisms, including regulation of gene transcription by the hypoxia-inducible factor 1α, which regulates the transcription of several genes, including many involved in angiogenesis, vascular remodeling, control of ROS, vasomotor reactivity, and inflammation. The result is an improved aerobic capacity, which translates into a more active lifestyle and a better quality of life.

The 2 studies presented in this issue of Circulation are related to each other in their demonstration of decreased oxidative stress after exercise training in CHF. The study by Gao and colleagues8 provides a novel explanation for the therapeutic effect of exercise training in CHF. To the best of my knowledge, this is the first demonstration that exercise training restores autonomic function by acting on the central nervous system. The results of this study open a window on the interpretation of autonomic effects of exercise training in heart failure, suggesting that the reduced sympathetic activity is not due merely to peripheral adaptations. It must be clear that these demonstrations have been made in rabbits with pacing-induced heart failure and that they need to be confirmed in humans with CHF. The results of the study by Wisloff et al13 add a methodological explanation to the therapeutic effect of exercise training in CHF. Interval training at high intensity not only is safe in humans with CHF but also determines greater improvements in important measures of outcome such as functional capacity and quality of life than continuous moderate aerobic exercise. These improvements are related in part to changes in oxidative capacity of skeletal muscles and in part to enhanced endothelium-dependent relaxation, depending on a 15% increase in total antioxidant status in blood plasma. Thus, the link between the 2 studies is the demonstration that in CHF exercise conditioning improves the balance between pro-oxidants and antioxidants in favor of the latter. This improvement has been obtained with 2 different exercise training methodologies: interval aerobic and continuous aerobic exercise. Evidently, the type of exercise is not the limiting factor. However, interval exercise seems to be preferred over continuous exercise for its more marked effect on oxidative stress.

Future research is needed to confirm these interesting results. Most published reports on this topic have demonstrated improvements in peak VO2 ranging from 12% to 31% after moderate-intensity endurance aerobic exercise.18 High-intensity exercise is associated with greater plasma lactate levels, which increase symptoms of fatigue and dyspnea, as confirmed by higher Borg’s scale during training sessions. Because peak VO2 and ventilation patterns represent 2 of the most important prognostic indicators in CHF, the greater the improvement is after training, the better the outcome is. However, benefits after short-term training programs have to be maintained for years to be associated with a better quality of life and possibly a more favorable outcome.19 High-intensity exercise does not seem to satisfy this necessity because patients generally prefer to exercise at light to moderate workloads.

In conclusion, any problem requires a solution, and any disease needs a remedy. CHF is a complex clinical syndrome generating a series of maladaptive responses in different districts that creates a viscous cycle of self-deterioration. The improved pharmacological options have reduced the death rate in the hospital, but they also contributed to the chronicity of heart failure and to the increase in the number of ambulatory patients requiring medical care and assistance.
There is agreement that a multidisciplinary approach provides more significant benefits in patients with CHF, translating into decreased rates of hospital readmission and costs. Exercise is a nonpharmacological therapy that determines important adaptations and potentiates the effects of some medications. The choice of an exercise training program should be based on patient’s preferences with the objective that it be maintained as long as possible. We are still awaiting a definitive demonstration of a reduced mortality after exercise training in CHF.

Medicine is a compromise between choice and need, between hypotheses and facts. The results of the studies published in this issue of Circulation add important demonstrations of the effects of exercise training on the autonomic balance and the reduction in oxidative stress that seems to play a major role on the sympathetic activation at the level of central nervous system. However, we should not forget that what we have demonstrated in animals needs confirmation in humans and that what we have demonstrated in preliminary small studies in humans requires confirmation in larger prospective trials.

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None.

References
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