Exercise Training in Heart Failure Patients
Does Reversing the Peripheral Abnormalities Protect the Heart?

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Exercise and activity intolerance are the most frequent and debilitating symptoms in patients with mild and moderate congestive heart failure (CHF). Paradoxically, the severity of these symptoms correlates poorly with indexes of cardiac function such as the ejection fraction and hemodynamic measurements. This discordance has focused attention on pathophysiological changes in the periphery to explain the mechanism of impaired exercise capacity. However, the heart and the periphery are inextricably linked, both in normal physiology and in CHF. The article by Coats and coworkers in this issue of Circulation illustrates this linkage and its potentially profound clinical implications.

Peripheral Mechanisms of Exercise Intolerance in CHF

It has long been recognized that in CHF, exercising muscle exhibits impaired O2 utilization and an early onset of anaerobic metabolism. This was assumed to reflect impaired muscle blood flow caused by abnormal cardiac reserve. However, in a series of elegant studies, Zelis and colleagues showed that patients with CHF have impaired peripheral vasodilator capacity during forearm exercise and posts ischemic reactive hyperemia. Potential mechanisms for these changes include impaired arteriolar compliance caused by sodium and fluid retention, increased neurohormonally mediated vasoconstriction, and endothelial dysfunction.

Other data indicate that the primary peripheral abnormality may be in the muscle itself rather than in its blood supply. Indexes of muscle performance are frequently impaired, even when CHF is mild. The most consistent and striking change is increased muscle fatigability defined by the decline in maximal voluntary force during sustained contraction and diminished endurance during repetitive exercise. This change is present even when blood flow to the exercising limb is occluded, suggesting that it does not reflect impaired blood flow alone, although hypoperfusion may play an important role in the genesis of muscle dysfunction. In CHF patients, muscle endurance correlates closely with systemic exercise capacity, indicating that muscle function may be an important determinant of exercise performance; in contrast, in normal subjects, exercise capacity is largely determined by maximal cardiac output. A reduction in muscle strength has also been observed in CHF patients, but in our experience, this is inconsistent when comparisons are made to age-matched, sedentary controls.

Muscle metabolism, assessed by 31P magnetic resonance spectroscopy, is also altered in CHF. Intracellular pH declines more rapidly during exercise in CHF patients, which together with the more rapid rise in venous lactate at submaximal exercise is indicative of an earlier onset of anaerobic glycolysis. The more rapid decline in phosphocreatine and rise in inorganic phosphate during exercise also indicate impaired oxidative metabolism. Significantly, both H+ and inorganic phosphate have been implicated in the genesis of muscle fatigue, and the metabolic responses to exercise correlate better with clinical status than cardiac function. As with indexes of muscle function, these differences between patients and controls persists under ischemic conditions.

Muscle atrophy is common in CHF patients, especially when the syndrome is advanced. By using magnetic resonance imaging measurements, we found that muscle size is smaller in CHF patients and that muscle strength but not muscle endurance is proportional to muscle size. This observation suggests that in CHF patients, the decline in endurance may reflect a qualitative change in muscle rather than nonspecific muscle atrophy. This conclusion is supported by findings in several studies that analyzed muscle biopsies from CHF patients. Although the findings have been variable, most studies demonstrate a decline in histochemical, biochemical, and ultrastructural indicators of oxidative capacity, including the proportion of type 1 (oxidative) fibers, the activity of oxidative enzymes, mitochondrial density and structure, and decreased capillarization.

Relation of Muscle Changes to Deconditioning

The biochemical and metabolic changes observed in CHF patients are directionally opposite to those seen with exercise training and similar to those accompany-
ing detraining.\textsuperscript{21,22} This raises an important but as yet unanswered question: Are the abnormalities in the periphery in CHF patients the result of inactivity or do they represent a more specific change associated with the CHF syndrome? Unfortunately, there are few data available that characterize the periphery in subjects with chronic activity limitation (in contrast to either detraining or complete immobilization). Despite the similarities, however, there are significant differences. Unlike the pattern in CHF patients, detraining is not usually associated with an alteration in fiber type distribution or some of the mitochondrial abnormalities. One could postulate that in addition to inactivity, factors such as chronically increased sympathetic stimulation,\textsuperscript{23,24} cytokine-mediated muscle atrophy,\textsuperscript{25} chronic muscle underperfusion, or lack of intermittent activity-related hyperperfusion could cause many of these muscle abnormalities.

To investigate whether a localized training regimen that does not affect systemic hemodynamics could mitigate the peripheral abnormalities, we subjected CHF patients to wrist flexor training of the nondominant forearm 15 minutes per day for 4 weeks.\textsuperscript{26} This training regimen improved both the endurance and metabolism of the trained muscle but had no effect on the untrained forearm. Although this result indicates that training improves the muscle abnormalities characteristic of CHF patients, it does not prove whether the initial changes are due to deconditioning or determine to what extent systemic training can improve overall exercise capacity.

**Exercise Training in CHF Patients**

A number of groups have now shown that patients with severe left ventricular dysfunction can be safely entered into exercise training programs and that by the usual indexes of exercise heart rate, ventilatory, and peak VO\textsubscript{2} responses achieve a favorable training response.\textsuperscript{27} Sullivan et al\textsuperscript{28} demonstrated that 4–6 months of aerobic training increased exercise capacity and both blood flow and O\textsubscript{2} extraction in the exercising limb. The most interesting observations were made at submaximal exercise after training; there was a rise in O\textsubscript{2} uptake, decrease in lactate production, and a marked increase in endurance.\textsuperscript{29}

The study by Coats et al\textsuperscript{3} confirms the benefits of exercise training in CHF patients by using a randomized, controlled design and, for the first time, a home exercise regimen. At the end of the training phase, the patients experienced a significant reduction in symptoms and increased exercise capacity. However, the major importance of this study lies in the observations related to measures of autonomic nervous system activity. Resting norepinephrine spillover and the low-frequency component of the ECG power spectral analyses, which are both indexes of sympathetic nervous system activity, declined, whereas the high-frequency component and RR variability (measures of parasympathetic activity) increased. Thus, exercise training appears to reverse the neurohormonal activation, which may be a major determinant of the rate of progression and of mortality in CHF patients. These findings assume added importance in light of previous reports that exercise capacity may be the most powerful predictor of survival in CHF patients.\textsuperscript{2}

What is the mechanism of these autonomic changes? Decreased resting sympathetic tone and increased parasympathetic activity are part of the training response in normal subjects, although the underlying physiology is poorly understood.\textsuperscript{22,30} It is possible that additional factors are operative in CHF patients. Muscle underperfusion, tissue acidosis, and baroreceptor dysfunction, which accompanies deconditioning, may increase sympathetic activation. Training, by virtue of its effects on muscle and the peripheral circulation, may reverse these abnormalities.

**Exercise Training in CHF: Implications**

The article by Coats et al\textsuperscript{3} and the growing literature on exercise and muscle physiology in CHF lead to a number of important conclusions, speculations, and questions. Earlier prohibitions and concerns not withstanding,\textsuperscript{31,32} appropriately selected CHF patients can be safely entered into exercise training programs and even be counseled to pursue home exercise regimens. Significant improvements in exercise tolerance and symptoms can be anticipated, and further psychological benefits are likely to accrue from encouraging patients to participate actively in their own treatment. Indeed, the clinical benefits reported by Coats et al and others are quantitatively similar to those achieved with most effective drug treatments. Whether the peripheral abnormalities that are now recognized as important determinants of exercise capacity are initiated by deconditioning remains unresolved, but it is clear that many of these can be reversed by exercise training and that activity restriction should be avoided in most patients with stable CHF.

The alterations in autonomic function associated with exercise training naturally lead to speculation as to whether the natural history of CHF may be favorably altered by this approach. It will be difficult to answer this question because of the large magnitude and great complexity of an adequate clinical trial. However, it is possible that the enhanced survival with vasodilator therapy may be partially mediated by the increase in activity facilitated by these drugs. Additional studies will also be required to examine the multifold potential interactions between various pharmacological therapies and exercise training in the management of CHF patients.

Nearly three decades ago, the hemodynamic interrelation between the heart and the peripheral circulation was recognized and provided the rationale for vasodilator therapy. It is now becoming clear that neurohormonal interactions between the periphery and the heart are important determinants of the symptoms and prognosis of patients with CHF. Interventions that alter these interactions are now accepted therapeutic approaches. Exercise should be considered one of these.

**References**


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