

Editorial Comment

Skeletal Muscle Failure in Heart Failure

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It is now well established that in patients with chronic heart failure, exercise capacity and clinical symptoms such as fatigue or dyspnea correlate poorly with the extent of left ventricular dysfunction. Several studies have demonstrated that peripheral alterations, e.g., reduced perfusion of skeletal muscle during exercise, contribute substantially to the functional state and exercise capacity of patients with chronic heart failure. Impaired oxygen transport is accompanied by muscle hypoxia and increased muscle lactate output at inappropriately low work rates. The increase in cardiac output caused by vasodilators, even if associated with increased oxygen transport to the exercising working muscle, cannot be translated immediately into increased exercise capacity and peak oxygen consumption in patients with chronic heart failure. Even when oxygen delivery to type I and IIA muscle fibers that depend heavily on oxidative metabolism can be enhanced by pharmacological intervention, oxygen utilization is not augmented acutely. These observations have prompted the hypothesis that in chronic heart failure, intrinsic abnormalities of skeletal muscle emerge that prevent acute improvement in peak VO₂ and blood lactate accumulation. Indeed, previous studies using ³¹P-NMR (nuclear magnetic resonance) spectroscopy clearly demonstrated abnormal skeletal muscle metabolism during exercise in patients with chronic heart failure even in the absence of reduced flow or under ischemic conditions. Recently, we and others have addressed this issue more directly by taking skeletal muscle biopsies from a heterogenous group of patients with heart failure who demonstrated a variety of different and, in part, conflicting abnormalities. Histological examination of skeletal muscle revealed a variable extent of atrophy, increased interstitial cellularity, and increase in type IIB fibers in these patients compared with normal patients. Ultrastructural analysis indicated that patients with chronic heart failure develop significant abnormalities skeletal muscle ultrastructural abnormalities indicative of depressed oxidative capacity. Biochemical analysis of skeletal muscle biopsies demonstrated that the activity of enzymes involved in aerobic metabolism are reduced in patients with chronic heart failure. These data clearly demonstrate morphological, biochemical, and metabolic alterations of skeletal muscle that should contribute significantly to the reduced muscle strength and rapid fatigue in patients with chronic heart failure.

Skeletal Muscle Atrophy in Heart Failure

In this issue of Circulation, Mancini et al report the prevalence of skeletal muscle atrophy and its relation to exercise capacity and abnormal muscle metabolism in a large cohort of patients with chronic heart failure. Although earlier studies have alluded to atrophy of skeletal muscle in this setting, this is the first study with a multidisciplinary approach that addresses the contribution of skeletal muscle to fatigue in chronic heart failure. Obviously, the a priori hypothesis of the authors was that muscle atrophy would be an important cause of fatigue in this setting. However, although atrophy could be identified in patients with moderate heart failure, the contribution of skeletal muscle atrophy to exercise intolerance was only modest. Instead, the present study demonstrated significant intrinsic alterations in skeletal muscle metabolism. Importantly, analysis of the time constant of recovery for phosphocreatine and determination of the maximal rate of resynthesis of phosphocreatine provides information on skeletal muscle metabolic function that is independent of work load, muscle mass, and muscle recruitment. Thus, this novel NMR spectroscopy analysis in the recovery period after exercise has advantages compared with previous NMR spectroscopy studies that focused on metabolic changes during exercise. As pointed out by Mancini et al, the precise work load, recruitment of skeletal muscle, and impact of different muscle mass is difficult to assess during exercise in the individual patient and thereby limits the latter approach.

The time constant of recovery correlated significantly better with work slope than did muscle volume, emphasizing that intrinsic alterations of muscle fibers rather than atrophy is the more dominant mechanism for reduced exercise intolerance in heart failure. These observations would certainly fit previous findings in patients with chronic heart failure, i.e., that the extent of ultrastructural alterations of skeletal muscle alterations is related to exercise capacity.

Potential Underlying Mechanisms

Numerous experimental and human studies have shown that exercise training induces major adaptations in skeletal muscle. These include increases in capillary supply, muscle mass, mitochondrial content including increased activity of oxidative enzymes, and a shift in the fiber type distribution, that is, a higher percentage

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of type I and IIA muscle fibers, which possess a higher oxidative capacity than type IIB fibers. This adaptation of skeletal muscle to training results in an increased respiratory capacity of the muscle fibers accompanied by metabolic consequences such as slower utilization of muscle glycogen, greater reliance on fat oxidation, and lower lactate production during exercise of a given intensity.\textsuperscript{16} In contrast, during prolonged immobilization, oxidative enzymes of skeletal muscle, muscle mass, and capillary density all decrease below baseline values.\textsuperscript{17-19} Because patients with chronic heart failure usually restrict their physical activity, in part based on the advice of their physicians, the hypothesis has been put forward that a deconditioning effect occurs in their skeletal muscle.\textsuperscript{20} Consistent with this concept, bicycle training in patients with chronic heart failure has been shown to improve exercise tolerance by peripheral mechanisms, e.g., by delaying the onset of anaerobic metabolism.\textsuperscript{21} Training-induced improvement of peripheral muscle metabolism appears to be independent of systemic adaptations. Both in normal individuals and patients with heart failure, an exercise program restricted to small muscle groups (such as forearm muscles) improves the metabolic state of skeletal muscle without altering cardiac performance.\textsuperscript{22}

Although these observations suggest that the alterations of skeletal muscle of chronic heart failure are a result of deconditioning, other potential factors should not be dismissed. Mancini et al\textsuperscript{14} suggest that decreased caloric and protein intake may be a major contributor to skeletal muscle atrophy. It would be interesting to see whether there is a relation between indexes of muscle atrophy and caloric intake — information not provided by the present study. Depressed caloric intake may be a significant factor in certain subsets of patients, particularly patients with alcoholic cardiomyopathy (19% of patients in the present study). However, given the frequent lack of signs of malnutrition, other factors are likely to be involved in the development of muscle abnormalities. These factors may include increased free radical activity,\textsuperscript{23} increased sympathetic tone, or myocyte activation associated with increased plasma levels of tumor necrosis factor.\textsuperscript{24,25} The latter activation, possibly linked to a stimulated renin–angiotensin system in severe heart failure,\textsuperscript{25} may cause endothelial dysfunction\textsuperscript{26} and adversely affect muscle metabolism and function.\textsuperscript{27} Indeed, there is evidence that in patients with cardiac cachexia, the net negative protein balance across leg tissue is associated with an increased rate of myofibrillar protein breakdown.\textsuperscript{28} Endothelial dysfunction, which has been shown in patients with heart failure,\textsuperscript{29} may further compromise skeletal muscle function by affecting skeletal muscle blood flow. Long-term angiotensin converting enzyme (ACE) inhibition improves skeletal muscle blood flow and oxygen extraction during exercise.\textsuperscript{30} In addition, preliminary data indicate that ACE inhibitors partially reverse ultrastructural abnormalities of skeletal muscle in this setting.\textsuperscript{31} Experimental evidence suggests that long-term ACE inhibitor therapy reduces vascular infiltration by monocytes and macrophages and restores endothelial function,\textsuperscript{32,33} possibly because of enhanced endothelium-autocoid formation inhibiting breakdown of endothelium-derived bradykinin.\textsuperscript{34} We are only beginning to realize the complexity of the peripheral alterations in congestive heart failure. Future studies taking advantage of cell physiology and molecular biology techniques should provide important information regarding the relation of skeletal muscle abnormalities to the renin–angiotensin system, cytokines, and endothelial function. It is entirely possible that chronic, absolute reductions in skeletal muscle blood flow during exercise are involved in the development of intrinsic alterations of large muscles. The fact that limitation in isometric force production and fatigue is more prominent in the large quadriceps muscle compared with a small hand muscle\textsuperscript{13} is consistent with the idea that absolute reduction in blood flow during exercise and reduced muscle use may be involved in the development of large locomotive muscle alterations.

**Primary Versus Secondary Defect**

The observations discussed so far support the view that alterations of skeletal muscle in heart failure are, after all, the consequence of impaired cardiac function. However, it has been speculated that a generalized myopathy may occur in a subset of patients with dilated cardiomyopathy.\textsuperscript{11,12} Dunnigan et al\textsuperscript{11} observed that young patients with cardiomyopathy who developed ventricular tachycardia or heart failure have histological abnormalities of skeletal and cardiac muscle, in particular, a type II skeletal muscle fiber atrophy. Caforio et al\textsuperscript{12} reported histological alterations characterized by selective type I atrophy that are similar to those observed in congenital and idiopathic myopathies and unrelated to cardiac functional New York Heart Association classes. These findings may support the notion that common underlying factors such as genetic or autoimmune disorders, which affect both cardiac and skeletal muscle, may be operating in a subset of patients with dilated or hypertrophic cardiomyopathy. However, these divergent morphological findings are based on qualitative histological and ultrastructural analysis of upper arm skeletal muscle in a limited number of young patients without clinically overt myopathy.\textsuperscript{11,12} In contrast, in most reports evaluating weight-bearing calf muscle, the abnormalities were similar in patients with heart failure whether due to coronary artery disease or to dilated cardiomyopathy, suggesting that, in the majority of cases, the reduced oxidative capacity of skeletal muscle is related to the state of heart failure and its severity.

**Clinical Implications**

Prolonged immobilization of patients with severe chronic heart failure has been advocated, although it is less practiced now. Restriction of physical activity is still recommended as a first step in treating patients with chronic heart failure.\textsuperscript{35} However, considering the effects of training versus immobilization on skeletal muscle, the strategy of restricting physical activity in patients with heart failure may be associated with the development of alterations of skeletal muscle and the peripheral vasculature. Physical training in chronic heart failure has been shown to improve skeletal muscle function, exercise capacity, and clinical symptoms in small controlled trials.\textsuperscript{36} Given the accumulating observations concerning skeletal muscle alterations in heart failure and the beneficial effects of training, isn't it time to reassess our approach of restricting daily physical activity in patients with chronic heart failure?
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References


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