Metabolic Myopathy in Heart Failure

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Heart failure is a syndrome that also affects the periphery. Exercise intolerance and early fatigue seem to be linked in part to intrinsic alterations of skeletal muscle with decreases in both the production of ATP by mitochondria and the transfer of energy through the phosphotransfer kinases.

Heart failure is a syndrome resulting from the inability of the cardiac pump to meet the energy requirements of the body. Patients suffering from congestive heart failure (CHF) always complain of early muscular fatigue and exercise intolerance. Maximal exercise capacity is often reduced to 50% or less, and during exercise patients identify leg fatigue as their primary limiting factor. However, it is generally recognized that central hemodynamics or indices of cardiac function correlate poorly with exercise capacity in CHF. This has led to the conclusion that, in addition to hemodynamic alterations, peripheral factors are involved in the muscle weakness and increased fatigability of the patients. Attention has therefore been focused on factors such as alterations in skeletal muscle vascular function and intrinsic skeletal muscle abnormalities that may occur in this disease. Among the changes described have been an atrophy of the muscle fibers, a transformation of slow muscle to a faster phenotype, and a reduction in oxidative enzyme activity or mitochondrial volume or function. Evidence will be presented here that energy production and energy fluxes are altered in heart failure, and we will discuss how these alterations participate in the exercise intolerance of CHF patients.

Fatigue involves many factors that may be psychological, central, hemodynamic, or local. The functional defects of skeletal muscles that contribute to this syndrome are characterized by a decreased ability to maintain normal intensity and kinetics of contractile activity over time. The mechanism initially involves an imbalance between energy production and utilization, leading to the accumulation of metabolites and alterations in intracellular calcium homeostasis and contractility. 31P-NMR spectroscopy has revealed accelerated rates of utilization of phosphocreatine (PCr), accumulation of inorganic phosphate, and intracellular acidification during exercise in skeletal muscles of CHF patients.

Skeletal muscle energy metabolism and function

Skeletal muscle is a heterogeneous tissue composed of different fiber types that are characterized by velocity of contraction and type of energy metabolism. The assembly of different fibers generates the large diversity of muscle functions encountered in the animal kingdom. They provide for the different patterns of activity needed within a given body, and they underlie the extreme diversity of behavior from the very slow movement of turtles to the high-frequency flight of the hummingbird. To achieve such a large range of functions, skeletal muscle fibers exhibit a highly organized and compartmentalized cytoarchitecture in which the subcellular organelles have well-adapted structurofunctional organization.

Skeletal muscles have the ability to adapt in response to changes in functional requirements or hormonal stimulation. The large diversity of fiber types and the great plasticity of skeletal muscle fibers is due to the fiber type-specific expression of large isoform families of muscular proteins (for reviews, see Refs. 1 and 14). Determination of the myosin isoform profile is the most widely used method to delineate muscle fiber phenotype. In mammals, slow fibers (or type I fibers) mainly contain the slow isoform of myosin heavy chain (MHCII), whereas fast fibers can be separated into type Ila (expressing mainly MHCIla), IIX/d (MHCIIX/d), and the fastest, type IIB (MHCIIb). The fiber type-specific pattern of gene expression also includes other thick-filament proteins, such as myosin light chains, regulatory components of the thin filament (actin, troponin, tropomyosin), and proteins involved in calcium transport (the Ca2+-ATPase, calcium channels, etc.).

The type of energy metabolism is another important feature of skeletal muscle fibers. Indeed, their patterns and velocities of contraction also rely on energy production, transfer, and utilization. Briefly, a rapidly contracting muscle needs a large amount of energy within a short period of time. Large energy stores like PCr, together with a high creatine kinase (CK) activity, can phosphorylate ATP at a rate fast enough to cope with the high myosin ATPase activity of these fibers. Once energy reserves are exhausted, the amplitude and speed of contraction drop rapidly. Energy reserves are subsequently replenished by oxidative metabolism and glycolysis. This mode of contraction is described as “twitch now, pay later” and is found mainly in locomotion muscles (Fig. 1A). Conversely, because postural muscles (or heart muscle) have to work for prolonged periods of time (or continuously), they must permanently adjust their energy production to utilization. Because this can be only achieved through mitochondrial respiration, these muscles have high oxidative capacities. Moreover, they need efficient energy and signal transfers to fine tune mitochondrial energy production on a “pay as you go” basis.

The “servo control” of mitochondria by energy utilization is not fully understood. One possible mechanism is through the direct activation of mitochondrial dehydrogenases by calcium...
The creatine kinase (CK) system in muscle cells. A: in oxidative muscle, phosphocreatine (PCr) is synthesized in mitochondria owing to the localization of mitochondrial (mi-) CK close to the translocase. PCr is transferred to bound cytosolic (MM-) CK in myofilaments through near-equilibrium reaction in the cytosol. In myofilaments, bound MM-CK rephosphorylates the ADP produced by myosin ATPase. B: in glycolytic muscles, the large pool of PCr serves as a spatiotemporal buffer for ATP and bound MM-CK rephosphorylates the ADP produced by the ATPase. Mitochondria and glycolytic complexes participate in the replenishment of the PCr pool.

FIGURE 1. The cellular pathophysiology of the peripheral symptoms of CHF is far from being understood. Measurement of oxygen uptake in a patient during maximal exercise (VO2max) is a reliable index of functional capacity involving both central and peripheral factors. However, in CHF patients the peripheral factors are more important in limiting exercise capacity and oxygen uptake during exercise than they are in control subjects. Oxygen delivery is certainly limited in heart failure during exercise involving a large muscle mass such as cycling or running, but exercise limitation can also occur when only a small muscle mass is engaged in exercise. This finding suggests that defects in either oxygen delivery to the muscle and/or oxygen utilization inside the muscle play an important role in this disease. Thus, there may be a muscle myopathy in heart failure (2) in which specific metabolic abnormalities play a significant role in determining exercise capacity (7).

Decreased O2 utilization at the periphery can originate from a decreased peripheral blood flow and capillary density, a diminished muscle mass, alterations in the vasodilatory response to exercise, or decreased O2 utilization due to defective or missing mitochondria. Intrinsic modifications of skeletal muscle structure are also among the factors responsible for altered contractile function and exercise limitation. Muscle abnormalities observed in CHF patients have been extensively reviewed (6, 10, 15). The intrinsic abnormalities of skeletal muscle include fiber atrophy, cytoarchitectural remodeling, altered metabolism, and change in the fiber type composition. The main observation is a decreased proportion of type I (fatigue resistant) fibers, compensated for by an increased proportion of fast type II (fatigable) fibers. Moreover, the decrease in the proportion of slow MHC correlates with the decrease in VO2max in CHF patients, suggesting a participation of contractile protein profile remodeling in the exercise intolerance.

Studies of skeletal muscle function in heart failure are relatively sparse. Changes in contractile proteins toward a faster phenotype should have effects on mechanical properties. However, no major effects on the intrinsic contractile properties and calcium sensitivity of contractile proteins were observed in a rat model of heart failure, most probably because it affected only a few percent of the muscle fibers (4). Impaired calcium homeostasis, reduced force, and slowed kinetics were observed, findings that are in contradiction to the MHC profile changes (9). Data concerning the expression of SR proteins vary between studies and cannot explain the changes in calcium homeostasis. Thus it is highly probable that alterations in the contractile protein profile may not be the main determinant of exercise intolerance in CHF.
On the other hand, calcium homeostasis and contractile performance also depend on adequate energy supply. As a matter of fact, large metabolic defects are a main feature of skeletal muscles from CHF patients and animals. There is rapid PCr depletion and increased lactate production during exercise, and PCr recovery is delayed at the end of exercise. Skeletal muscles of CHF animals or patients usually contain an increased amount of glycolytic enzymes, a decreased mitochondrial volume, and depressed activity of marker enzymes of oxidative metabolism. The decreased mitochondrial volume correlates with the aerobic capacities of the patients, suggesting a major contribution of the altered oxidative muscle metabolism to the exercise intolerance in CHF (7). Functional evidence for a marked fall in maximal oxygen consumption per gram of muscle tissue, affecting oxidative (slow), glycolytic (fast), and even diaphragm muscles, was described recently in an animal model of heart failure (3, 4). Although in heart failure the contractile phenotype of the diaphragm muscle adapts toward a slower, more economical contraction as a result of increased and sustained workload, this adaptation is limited by the failure to increase mitochondrial capacity. In addition to decreased oxidative capacity, CHF results in perturbations of the control of the respiration by ADP and/or mitochondrial kinases (adenylate kinase and CK) in the oxidative muscles of CHF rats. However, alterations in skeletal muscle oxidative capacity are not so clear in patients. Comparing a group of CHF patients at the time of transplantation with age-matched sedentary or active controls, Mettauer et al. (11) recently showed that the oxidative capacity of vastus lateralis muscle biopsies from CHF patients was identical to that of sedentary individuals, suggesting that the mitochondrial oxidative phosphorylation pathway was preserved in these patients. Moreover, mitochondrial regulation by the phosphate acceptor ADP or by the mi-CK was also identical between sedentary individuals and CHF patients, both groups differing greatly from the more active individuals. This occurred despite lower CK and citrate synthase activities in the muscle of CHF patients. Thus, in humans, the physical activity level seems to have more impact on the muscle aerobic capacity than CHF per se, but the impact of new treatments of heart failure should also be considered.

It has long been recognized that there is a generalized alteration of the CK system in the myocardium of CHF patients consisting of a decrease in total enzyme activity and content and an alteration in the isoenzyme pattern (13). Perturbations of CK compartmentation in the cardiomyocyte contribute to the pathogenesis of heart failure by altering energy fluxes and calcium homeostasis (5). Although the focus of fewer studies, the CK system is also clearly altered in skeletal muscle, with the MM (Fig. 2, bottom) and/or the mi (Fig. 2, middle) isoforms of CK being affected (4, 8, 11). As in the myocardium, the CK isoenzyme alterations could alter the functioning of mitochondria and SR, producing a mismatch between energy production and utilization in the muscle and altered calcium homeostasis. Affecting the rate of calcium pumping by the SR, MM-CK deficiency would contribute to the slowing of the calcium transient and contractile kinetics in the CHF skeletal muscles.

The general conclusion is that heart failure markedly affects the mitochondrial capacity and regulation, rather than intrinsic contractile machinery of skeletal muscles. The fact that heart, fast, and slow muscles are all affected argues the case for a generalized metabolic myopathy in heart failure. The decreased oxidative capacity and altered mitochondrial regulation and energy transfer could be one mechanistic basis for the decreased oxygen utilization and exercise capacity seen in CHF. Indeed, in slow postural muscles, a reduced number of mitochondria leads to decreased endurance capacity and early fatigue. In fast skeletal muscle, decreased CK activity and faster utilization of PCr will impair contraction and accelerate the occurrence of fatigue while the lower oxidative capacity will severely delay the recovery of energy stores and contractile capacity. This provides an explanation for the paradoxical slowing of contraction and relaxation of skeletal muscle.
The mechanisms leading to such alterations during heart failure are at present unknown. Moreover, whether decreased mitochondrial function results from mitochondrial lesions or decreased mitochondrial biogenesis has not been investigated so far.

Nevertheless, several factors likely to affect the skeletal muscles can be identified (Fig. 3). In the course of the disease, muscles are subjected to inactivity or malnutrition, to altered neurohumoral status, and most probably to repeated episodes of oxygen limitation. Many of these factors are also characteristic of heart muscle. Actually, decreased oxidative capacity and altered mitochondrial regulation can be encountered in heart, slow-oxidative muscle, and fast-glycolytic muscle, as well as in diaphragm muscle.

**Muscle underperfusion**

Whereas in healthy subjects the upper limit for skeletal muscle perfusion can exceed the pumping capacity of the heart, in heart failure patients peripheral factors limit oxygen utilization during exercise. Two main factors contribute to decreased perfusion of skeletal muscles, namely altered capillarization and/or abnormal vasodilatory response. A decreased capillary-to-fiber ratio has often been reported in the lower limbs of patients or animal models of heart failure, but, due to the fiber atrophy, the capillary density is generally maintained so that decreased capillarization may not be a major factor in decreased oxygen delivery (18).

Increased vasoconstriction at rest is a hallmark of CHF and is related to adrenergic and renin-angiotensin system overdrive, increased endothelin levels, and decreased response to vasodilators. CHF induces a marked reduction in the endothelium-dependent vasodilation of the peripheral arteries and in the production and/or release of nitric oxide. Impairment of endothelial nitric oxide synthase (eNOS) expression in the vascular bed in heart failure may also contribute to limitations in exercise capacity through inadequate coronary or peripheral blood delivery. However, possible consequences of decreased blood flow or nitric oxide production on muscle mitochondrial content are not known at present.

**Muscle deconditioning**

The shift from a slow to fast phenotype can be interpreted as a response to the lower physical activity of the patients, leading to muscle deconditioning. Exercise training can partially prevent or even reverse alterations in hemodynamics, endothelium-dependent coronary and peripheral resistance, and peak oxygen uptake in heart failure patients or animal models. In the myocardium, it can also attenuate adverse remodeling of the myocardium and abnormal gene expression. At the periphery, exercise training can improve muscle blood flow and oxidative enzymes, and restore fiber type profile in those muscles activated during exercise. Because CHF patients have a reduced physical activity, muscle defects may originate from muscle deconditioning. As discussed above, oxidative capacity of skeletal muscle in severe CHF patients appears similar to that of sedentary control, arguing for a role.

**Factors responsible for altered skeletal muscles**

The pathophysiological mechanisms responsible for the skeletal muscle defects in CHF are still not understood (Fig. 3). Alterations in the cardiac pump function induce an activation of vasoconstrictor systems to maintain blood pressure as close as possible to normal. This hormonal overdrive has direct consequences with respect to cardiac, vascular, and skeletal muscle remodeling. On the other hand, heart failure patients have a reduced daily activity that can lead to muscle deconditioning and remodeling.

The muscle phenotype is under the control of neuronal, hormonal, and load- or activity-related factors (for review, see Ref. 17). Although many studies have been devoted to elucidating the regulation and modulation of the expression of contractile proteins, less is known concerning the factors and signaling pathways involved in the expression of the proteins implicated in energy production and transfer in muscle cells.
of deconditioning in the decreased oxidative capacity of CHF patients. However, other lines of evidence argue against a predominant role of this factor. First, specific metabolic enzyme alterations are present in these patients. Second, patients receive effective pharmacological treatments that may interfere with the progression and intensity of the disease and muscle remodeling. Third, in rats, skeletal muscle abnormalities correlate with the degree of heart failure but not with the degree of locomotor activity. Finally, studies of hindlimb suspension in animal models indicate a dissociation of metabolic and mechanical properties, with preserved mitochondrial function despite marked myosin isoenzyme and fiber type shifts. Moreover, the effects of muscle deconditioning are restricted to postural muscles like soleus, while all muscle types seem affected in heart failure.

**Neurohumoral status**

A general neurohumoral overdrive (renin-angiotensin system, sympathetic activation) accompanies heart failure, and it is conceivable that circulating factor(s) may be responsible for alterations at the periphery. In that case, muscles with different phenotypes or with different loads or activity patterns might be altered in a similar way. It is possible that prolonged exposure of the skeletal muscle to these circulating factors may eventually lead to muscle remodeling. Treatment of patients with an inhibitor of the angiotensin-converting enzyme (ACE) reverses the changes in fiber type and MHC isoform expression in CHF, although a positive impact of the treatment on energy metabolism has not been clearly established. The angiotensin pathway is involved in muscle growth, and interesting relationships between specific gene polymorphisms in the adrenergic or angiotensin system pathways and exercise capacity have been highlighted recently (12). Chronic treatment of CHF patients with ACE inhibitors or angiotensin II receptor blockers improves skeletal muscle blood flow and peak oxygen consumption during exercise and prevents or reverses apoptosis-dependent atrophy and changes in MH Cs. Moreover, such treatment decreases vascular peripheral resistance and improves the expression of eNOS. However, whether it acts directly on muscle remodeling or indirectly through improved vasodilation and decreased peripheral resistance remains to be established.

The use of β-blockers has proven to be successful in the treatment of heart failure. β-Blocking agents efficiently reduce cardiac and vascular remodeling in heart failure. Chronic treatment with β-blockers has been shown to improve cardiac CK and lactate dehydrogenase and to reduce free radical activity. Effects on skeletal muscle contractile and metabolic properties have not been extensively studied so far. Interestingly, administration of clenbuterol, a β2-agonist, to rats increases the proportion of fast fibers and decreases oxidative enzyme activity. Thus increased sympathetic tone can be involved in skeletal muscle remodeling, potentially leading to reduced resistance to fatigue.

On the other hand, a positive impact of heart failure treatment on the intrinsic properties of skeletal muscle may help to explain the differences observed in the peripheral muscle response to heart failure between patients and animal models. An interesting possibility, still to be verified, is that the beneficial effects of ACE inhibitors or β-blocking drugs result in part from an improvement in energy metabolism.

**Oxidative stress**

Recent data suggest that oxidative stress could also be related to exercise intolerance in CHF patients. In heart failure, reactive oxygen species (ROS) generation is enhanced in hindlimb and heart and is associated with a concomitant increase in the peroxidation of lipids. Mitochondria are the principal place of ROS production, as well as the main target of their deleterious action in the cell, so that an excessive ROS production may lead to mitochondrial damage and decreased oxidative capacity. Various neurohumoral factors, including catecholamines, angiotensin II, and cytokines, all known to increase in heart failure, can activate the generation of ROS. For example, a high level of TNF-α, a major cytokine in heart failure, is associated with exercise intolerance and neurohumoral activation in CHF patients. Because mitochondria and CK are also prone to deteriorate due to oxidative stress, the possibility that increased oxidative stress is involved in the generalized metabolic alterations should also be envisaged. Oxidative stress can also participate in the accelerated apoptosis and atrophy of skeletal muscle fibers that have been described in humans and in animal models with CHF.

**Conclusions**

Intolerance to exercise is one of the main symptoms of CHF. This decreased exercise capacity seems at least in part to be caused by abnormalities lying in the skeletal muscle itself. Their occurrence and severity depends on the degree and duration of the heart failure. Alterations in energy production, transfer, and utilization are a hallmark of skeletal muscle abnormalities. This has led to the proposal of a metabolic myopathy in heart failure. Though several mechanisms have been suggested, the pathogenesis of this “failing energetics” is far from being understood and will be the subject of exciting future research.

**References**


