When Hearts Fail So Does Skeletal Muscle
Breaking a Vicious Cycle

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In heart failure, keeping up with the oxygen demands of working skeletal muscles becomes compromised during exercise. As if this situation is not bad enough, as with many aspects of the heart failure syndrome, there are more vicious mechanisms at work. It has been known for some time that skeletal muscle function is also depressed in patients and animals in heart failure. The depression has been attributed to disuse atrophy, changes in fiber types, and abnormal metabolism. Thus the impaired cardiac function in patients not only limits exercise, but depressed skeletal muscle function itself inhibits the ability to exercise causing further depression of cardiac function.

In the current issue of Circulation Research, Lunde et al report evidence which supports the concept that heart failure leads to a primary depression in the force generating capacity of skeletal muscle, and which provides new insights into the mechanism. Their approach involved investigation of single living fibers isolated from the soleus muscle of rats whose hearts had been stressed by ligation of the coronary arteries (MI mice) 6 weeks before the experiments. In technically demanding experiments, Lunde et al simultaneously determined the force and intracellular \( \text{Ca}^{2+} \) ([Ca\(^{2+}\)]i) in single soleus cells under nonfatiguing and fatiguing conditions. Under nonfatiguing conditions contraction and \( \text{Ca}^{2+} \) transients of sham and MI-fibers were not significantly different, but there was a depression in the levels of \([\text{Ca}^{2+}]_i\) during the tetani. Compared with controls, MI-fibers had no major changes in expression of membrane proteins involved in \( \text{Ca}^{2+} \) regulation. After fatigue, the tetanic force developed in MI-fibers was significantly decreased in the absence of a further change in the level of \([\text{Ca}^{2+}]_i\). In fibers from shams the tetanic force was less affected and associated with a decrease in tetanic \([\text{Ca}^{2+}]_i\). These data provide the first evidence that, when bathed in identical solutions, intact single slow skeletal fibers from MI-stressed animals fatigue more severely than controls in the absence of major \([\text{Ca}^{2+}]_i\), alterations. Earlier determinations of force and intracellular \( \text{Ca}^{2+} \), as measured using the aequorin technique, indicated a defect in excitation contraction coupling. What’s new in the work reported by Lunde et al is the explicit identification of a mechanism at the level of the single cell involving a defect in skeletal muscle function during fatigue related to an alteration in the response of the sarcomeres to \( \text{Ca}^{2+} \) rather than a depression of \( \text{Ca}^{2+} \) delivery to the sarcomeres.

A depression in sarcomeric response to \( \text{Ca}^{2+} \) also appears to be an important mechanism in failure of the heart. Evidence supporting this hypothesis has been reviewed elsewhere and indicates that the mechanisms involve posttranslational modifications involving phosphorylation, proteolysis, and generation of reactive oxygen species (ROS). Familial cardiomyopathies genetically linked to mutations in sarcomeric proteins also involve altered sarcomeric response to \( \text{Ca}^{2+} \). In this case there is no dispute that the primary defect resides in the sarcomeric proteins.

ROS-Induced Alterations in Sarcomere Response of Skeletal Muscle to \( \text{Ca}^{2+} \) in Heart Failure

An altered contraction of skeletal muscle that occurs without a change in \([\text{Ca}^{2+}]_i\), implies a cardiac dysfunction-induced modification of the skeletal sarcomeric proteins. The mechanism may involve an increase in skeletal muscle ROS resulting from mitochondrial dysfunction. Hearts of MI rats exhibit increased mitochondrial ROS production, increased protein oxidation, and a decrease in the force–frequency relationship, which can be reversed by treatment with a ROS scavenger. This heart failure induced increase in ROS may be central to the development of skeletal muscle dysfunction at the sarcomeric level.

Increased generation of ROS in muscle has been implicated in protein modification, increased fibrosis, and an increase in the rate of extracellular matrix turnover, and may cause the modification or degradation of sarcomeric proteins. The degradation of both troponin I and troponin T have been demonstrated to occur in cardiac muscle resulting from ischemia-reperfusion and in skeletal muscle resulting from hypoxia/fatigue. The degradation products of troponin I and troponin T directly affect muscle contraction to alter maximal force production and \( \text{Ca}^{2+} \) sensitivity. Furthermore, fatiguing stimulation is presumably exacerbated in skeletal fibers of heart failure patients leading to increased hypoxia. Yet in the report by Lind et al there was a full restoration of maximal tetanic force with application of caffeine after 30 minutes of recovery from fatigue. This observation suggests, but does not rule out, the initial increase in \( \text{Ca}^{2+} \) sensitivity and the
decrease in developed force after fatigue of MI skeletal muscles was the result of a readily reversible sarcomeric protein modification and not a degradation event.

As pointed out by Lunde et al., it is likely that their findings are related to ROS generation. Among the sarcomeric proteins that may be altered by ROS, we think that actin and tropomyosin may be particularly important. Direct evidence linking the ROS modification of tropomyosin and actin to the alteration of skeletal muscle function is lacking, however the central role of these proteins in the Ca\(^{2+}\) regulation of muscle activation strongly suggests their modification could affect muscle function. ROS-induced modification of cardiac tropomyosin in heart failure, as well as in skeletal muscles after recovery from MI, has been reported. Although the functional significance of the ROS-induced tropomyosin modifications has not been directly investigated, the significant effects of point mutations and phosphorylation of Tm indicate that oxidative modification of troponins could alter muscle contraction. Muscle actin is also modified in both cardiac and skeletal muscles by oxidative stress. After ischemia–reperfusion both cardiac and skeletal muscle actin exhibit ROS modification. In a rat model of MI, Chen and Ogut demonstrated a reduction in maximally developed force of skeletal cardiac trabeculae containing the ROS modified actin, as well as a depressed in vitro polymerization and cooperativity of binding to tropomyosin compared with unmodified actin.

**Abnormal Skeletal Muscle Function in Heart Failure Most Likely Represents the Integrated Effects of Multiple Factors**

Factors in addition to ROS-induced modifications are likely to be important in the altered response of skeletal muscle to intracellular Ca\(^{2+}\) in heart failure. There is substantial evidence that alterations in intracellular milieu associated with fatigue depress force through direct effects on the myofilaments. The alterations most prominent in this effect are acidosis and an increase in inorganic phosphate (Pi) arising from the breakdown of creatine phosphate. An important and yet poorly understood question is whether skeletal sarcomeric proteins modified by ROS or proteolysis respond differently than controls to a rise in Pi and H\(^+\) in the intracellular milieu. There is evidence that this might occur from studies of skinned fiber preparations containing troponin T with a point mutation linked to familial hypertrophic cardiomyopathy. Whether ROS-induced modification or proteolysis of skeletal sarcomeric proteins in heart failure exacerbates or ameliorates the effects of acidosis or increased Pi on the force-Ca\(^{2+}\) relation has not yet been investigated to our knowledge.

**Perspectives**

The findings of Lunde et al and others beg the question as to whether there is anything that can help break the viscous cycle of altered function in both heart and skeletal muscle. Several studies indicate that there is hope. One of these studies reports that carvedilol, a beta-1 and beta-2 adrenergic receptor blocker commonly used to treat heart failure, also has a remarkable ability to block production of ROS. Treatment of rats in heart failure with carvedilol prevented the ROS modification of skeletal sarcomeric proteins and restored the depressed force generation that occurred in untreated rats. Bisoprolol, a selective beta-1 blocker, could only weakly prevent ROS modification and had no effect on function. Reversal of oxidative damage to sarcomeric proteins can also occur with exercise. Thus restoration of exercise capacity in heart failure by carvedilol has an added advantage. Whatever the case, the results reported by Lunde et al emphasize the importance of developing and evaluating therapies with consideration of effects on striated muscle fibers in both cardiac and skeletal muscles.

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**References**


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