A hallmark of congestive heart failure (CHF) is exercise intolerance. In this context, CHF can cause exercise-limiting changes in every key step in the oxygen transport system. For example:

- The lungs can be congested and the pulmonary capillary membranes thickened, limiting O₂ diffusion from lung to blood.
- The control of breathing is sometimes altered.
- The normal rise in cardiac output is both blunted and delayed.
- Blood flow to the active muscle is limited, and a CHF-associated muscle wasting can occur.
- Alterations take place in the capillary/skeletal muscle interface that limit O₂ diffusion from blood to muscle.
- Muscle metabolism can be dysfunctional and oxidative capacity can be limited, which leads to acidosis.

A key question, then, is are these maladaptations related or are they merely a summation of physiological “bad luck” associated with poor cardiac function and the resultant physical inactivity? Over the past 20 years one revolutionary idea has been that “overactivation” of the sympathetic nervous system in CHF makes a bad situation worse and broadly contributes to a downward spiral in many elements of the oxygen transport system. In addition, during exercise, an inappropriately robust sympathetic response further limits exercise tolerance by evoking larger (and faster) than normal increases in peripheral sympathetic activation from an already increased baseline. This excessive sympathetic response may have many unfortunate consequences, but one especially negative consequence may be the further sympathetic restraint of blood flow to the active skeletal muscles and even more skeletal muscle hypoperfusion. Together with the structural and biochemical changes in the muscle noted above, this further restraint of blood flow will, of course, make exercise intolerance even more “intolerable.”

In this issue of Circulation, Li and colleagues from Larry Sinoway’s laboratory at the Penn State Milton S. Hershey Medical Center provide key insight into how changes in muscle sensory nerve function contribute to the excessive sympathetic activation that is observed during exercise in CHF. Their findings also provide important clues about how dysfunctional muscle blood flow and metabolism are linked to the early and excessive peripheral sympathetic activation during exercise in CHF.

Normally, autonomic outflow and sympathoexcitation during exercise are governed by the interplay between so-called central command and afferent information from the exercising muscles. Central command is a feed-forward mechanism that can evoke changes in autonomic outflow that are proportional to the muscular effort associated with the exercise. It plays a key role in the heart rate and perhaps the renal sympathetic nerve responses to exercise, and it probably resets the arterial baroreflexes to facilitate the increases in heart rate and arterial pressure that are observed during exercise.

The brain stem also receives information from mechanically sensitive and chemically sensitive fine afferents in the contracting muscles. In general, the finely myelinated group III afferents respond to mechanical stimuli and the unmyelinated group IV afferents are sensitive to metabolites, especially acidosis. Together, these sensory nerves play a key role in the autonomic response to exercise and are especially important in governing sympathetic outflow to skeletal muscle. Although it is clear that the fine afferents contribute importantly to the regulation of muscle sympathetic nerve activity, the mechanosensitive afferents are probably also important regulators of renal sympathetic nerve activity during contractions.

The article by Li and colleagues reminds us again that typically the chemosensitive afferents predominate and that in most cases, skeletal muscle afferents do not play a major role in the pressor response to exercise until acidosis occurs in the active muscles. By contrast, in heart failure, the contribution of skeletal muscle afferents occurs almost instantaneously and is governed almost exclusively by a larger than normal contribution of the mechanosensitive afferents. It also appears that the group III afferents have been sensitized by ATP or some related compound. In addition, the chemosensitive afferents and their capsaicin-sensitive VR1 receptors are desensitized, perhaps as the result of repeated exposure to metabolites from poorly perfused skeletal muscle with limited oxidative capacity and dysfunctional metabolism.

Whatever the ultimate mechanisms, this desensitization means that in CHF, feedback from the active muscles makes a major contribution to the pressor response as soon as contractions start. This also means that sympathetic outflow
to muscle likely increases further and faster in CHF, a situation that can only make the already compromised skeletal muscle perfusion even worse. Even more important, the concept that the group III afferents are sensitized to fire early by ATP or related compounds suggests that metabolites that are associated with the chronic changes in muscle blood flow and metabolism in CHF in fact promote their early engagement.

This “bad news” from the sensitized muscle mechanoreceptor also may contribute to the augmented renal vasoconstrictions observed during exercise in patients with CHF. This would mean that even mild physical activity would lead to a state of almost constant activation of the renin–angiotensin system and the related renal responses.

In this context, a vicious circle of inappropriate regulatory responses is initiated that originates in the exercising muscles. Instead of mainly group IV afferents acting to raise arterial pressure and restore blood flow to the active muscles as they become acidotic, the sensitized mechanically sensitive group III muscle afferents act at the onset of contractions and probably further limit muscle blood flow, making a bad situation worse. The associated actions on the kidney would also escalate this vicious cycle to the systemic circulation as a whole.

In some ways, the downward spiral of dysregulation in exercising skeletal muscle suggested by Li and colleagues is similar to the larger picture in heart failure in which initially many of the physiological responses appear adaptive only to turn maladaptive over time. Li et al also remind us that in an era of aggressive interventions in clinical cardiology and an ongoing focus on the molecular basis of cardiovascular disease, the integrated function of the cardiovascular system is governed by complex regulatory mechanisms and coordinated in turn by the autonomic nervous system. When this coordination is lost, exercise tolerance is perhaps the earliest harbinger of the many problems that are sure to follow.

References


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