Point:Counterpoint: Increased mechanoreceptor/metaboreceptor stimulation explains the exaggerated exercise pressor reflex seen in heart failure

PURPOSE AND SCOPE OF THE POINT:COUNTERPOINT DEBATES

This series of debates was initiated for the *Journal of Applied Physiology* because we believe an important means of searching for truth is through debate where contradictory viewpoints are put forward. This dialectic process whereby a thesis is advanced, then opposed by an antithesis, with a synthesis subsequently arrived at, is a powerful and often entertaining method for gaining knowledge and for understanding the source of a controversy.

Before reading these Point:Counterpoint manuscripts or preparing a brief commentary on the content, the reader should understand that authors on each side of the debate are expected to advance a polarized viewpoint and to select the most convincing data to support their position. This approach differs markedly from the review article where the reader expects the author to present balanced coverage of the topic. Each of the authors has been strictly limited in the lengths of both the manuscript (1,200 words) and the rebuttal (400). The number of references to publications is also limited to 30, and citation of unpublished findings is prohibited.

POINT: INCREASED MECHANORECEPTOR STIMULATION EXPLAINS THE EXaggerated EXERCISE PRESSOR REFLEX SEEN IN HEART FAILURE

The concept that exercise limitation in patients with chronic heart failure (HF) is due to elevated filling pressures or inadequate cardiac output has been largely abandoned and replaced by a new paradigm. “The Muscle Hypothesis of HF,” originated by Drs. Coats and Piepoli (1, 11), hypothesizes that abnormalities of skeletal muscle, including the sensory nerve fibers that mediate reflex changes in the circulation during exercise underlie the exercise limitations in HF. The question debated today is which sensory fibers are responsible for the reflex abnormalities during exercise?

Located within skeletal muscle, the sensory nerves mediating the reflex changes during exercise, termed the “exercise pressor reflex” (EPR), consist of type III mechanoreceptor fibers that are principally sensitive to mechanical stimuli and type IV metaboreceptor fibers that are principally sensitive to ischemic metabolites generated during exercise (3). In healthy humans, it is generally agreed that the muscle metaboreceptors, in conjunction with a contribution from the central nervous system (“central command”), mediate the increase in EPR. The notion that muscle mechanoreceptor sensitivity is augmented in HF was launched following the report that the muscle metaboreceptor contribution to EPR is blunted in HF (18). In humans, the muscle metaboreceptor contribution to reflex responses during exercise is isolated by “postexercise circulatory arrest” (PECA), in which a blood pressure (BP) cuff proximal to the exercising muscle is inflated to suprasystolic levels at the termination of exercise. This traps ischemic metabolites within muscle and selectively engages metaboreceptors without stimulating mechanoreceptors or central command. During 2 min of moderate handgrip exercise in NYHA Class II-IV HF patients, muscle sympathetic nerve activity (MSNA) increased, but then during PECA, which isolated the muscle metaboreceptors, plummeted to baseline levels (Fig. 1). Thus the metaboreflex is blunted in HF and replaced by another system, such as muscle mechanoreflex or central command. If the muscle mechanoreflex were the mediator of the EPR in patients with HF, we would anticipate an immediate increase in MSNA at the onset of exercise, which would return to baseline during PECA. Low-level rhythmic exercise preferentially stimulates muscle mechanoreceptors over metaboreceptors. During low-level rhythmic handgrip (5), MSNA increased within the first minute of exercise in HF patients, but only in the third minute of exercise in healthy humans, consistent with heightened muscle mechanoreceptor sensitivity in HF. To further isolate the muscle mechanoreceptors from central command, passive exercise was employed and MSNA was recorded (5). MSNA increased significantly during passive exercise in HF patients, but not in healthy humans. This sensitization of muscle mechanoreceptor control in HF has been reported to be proportional to HF severity (8). Furthermore, muscle mechanoreceptor control of renal vascular resistance during exercise is also augmented in humans with HF (6, 7).

The evidence presented thus far is compelling and convincing that in advanced HF, increased mechanoreceptor stimulation explains the exaggerated EPR. However, Notarius and colleagues (9) found that muscle metaboreceptor control of BP and MSNA was augmented in patients with HF, and this augmented muscle metaboreceptor control was inversely proportional to severity of HF. Additionally, a body of outstanding work published almost exclusively by our adversaries in this debate, suggests that the muscle metaboreceptors are not only intact, but are sensitized, underlying the role of the exaggerated EPR in HF (10, 12–16). These investigators have focused on a component of the EPR not measured in the studies mentioned.
above, the heightened reflex ventilatory response to exercise that characterizes HF. Piepoli and colleagues (11–13) reported increased metaboreceptor control of ventilation and BP with increasing severity of HF; unfortunately, the muscle metaboreceptor effect on BP was not always reported (12, 13). Surprisingly and inexplicably, a different group of investigators, using similar subjects and methods as used above, did not confirm the findings of heightened muscle metaboreceptor control of ventilation in HF (2).

How do we reconcile these conflicting results of heightened muscle metaboreceptor versus mechanoreceptor sensitivity in HF? Let’s consider the possible explanations.

1) The increased metaboreceptor sensitivity position largely depends on measurement of the ventilation, whereas the increased mechanoreceptor sensitivity position largely depends on neurovascular measurements; is it possible that augmented mechanoreceptor control of BP and MSNA coexists with augmented metaboreceptor control of ventilation? Possible, but unlikely. At present we know of no other neural circuitry in humans or animals that behaves in this fashion.

2) Variability in the exercise protocols used, specifically exercise type, site, duration, and degree. Unlike, inasmuch as our adversaries have reported the satisfactory reproducibility and significant correlation of muscle metaboreceptor contribution to ventilation during the EPR during both handgrip exercise and cycling in HF patients (12, 13).

3) These human experiments rely on specific maneuvers to preferentially isolate one neural control system over another, but there may be overlap. For example, PECA isolates the metaboreceptor contribution to the EPR and some patients will complain of pain during PECA. However, subjects do not normally complain of pain during the EPR; thus, in some individuals, PECA may actually stimulate nociceptive neurons not engaged during the EPR. These changes seen by PECA may be mediated by muscle metaboreceptors and to an unknown extent by nociceptors. Each of the techniques have been used to isolate the muscle mechanoreceptor contribution to the EPR is imperfect: low-level rhythmic exercise also engages central command and perhaps even metaboreceptors, involuntary contraction can be painful and recruitment patterns are not physiological, and passive exercise may evoke an arousal response. Thus one explanation for discrepant results is that the techniques to isolate one muscle receptor type may inadvertently stimulate another.

Finally, 4) each small group of HF patients studied by different investigators, or even by the same investigators, is likely heterogeneous in many respects, including degree of cachexia and muscle atrophy, daily activity level, nutritional status, confounding diseases including diabetes and renal insufficiency, HF etiology, gender, HF duration, duration on treatment, and types of treatment. In summary, heterogeneous patient populations studied with imperfect techniques likely underlie the controversy explored in this debate.

Let us now look to animal models of HF, in which we can be more secure regarding the homogeneity of the study group and the selectivity of the afferents being engaged by the various maneuvers used. For example, metabolically sensitive group IV neurons can be selectively activated by capsaicin infusions into the arterial supply of the hindlimb muscle. In the infract model of HF in rats, intra-arterial capsaicin led to a blunted BP response in HF rats compared with controls (4).

Muscle mechanoreceptor stimulation with α, β-methylene ATP enhanced the BP response to muscle stretch to a greater degree in HF rats compared with controls. Similar results were reported from an independent laboratory using a similar, but not identical, protocol (17). Moreover, in the infract model of HF in rats, the EPR, including BP and heart rate, were significantly exaggerated in HF rats compared with controls during static muscle contraction. A dose-dependent increase in BP in response to intra-arterial capsaicin was observed in healthy rats, but was significantly blunted in HF rats (17). Furthermore, when muscle mechanoreceptors were blocked using capsaicin, this exaggerated EPR in HF rats during muscle contraction was eliminated. In summary, studies using the rat infract model of HF provides convincing data that increased mechanoreceptor stimulation explains the exaggerated EPR seen in HF. These data strongly support our premise that metaboreceptor activity is reduced and mechanoreceptor activity is increased in HF.

Although we are indebted to Drs. Coates and Piepoli for their work examining the role muscle afferents play in mediating symptoms in HF, we think that they have erred in the details. We hope that we have now set the record straight.

REFERENCES


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COUNTERPOINT: INCREASED METABORECEPTOR STIMULATION EXPLAINS THE EXAGGERATED EXERCISE PRESSOR REFLEX SEEN IN HEART FAILURE

The diagnosis of chronic heart failure (CHF) depends on both cardiac dysfunction and symptoms. Traditionally, these symptoms were attributed solely to the effects of altered central hemodynamics, dyspnea being due to pressure and volume overload causing pulmonary congestion and reduced cardiac output causing muscular fatigue. The trouble was that as simple and as popular as this explanation was, it just did not fit the facts. The majority of heart failure patients we see in the 21st Century are treated, not congested, do not develop pulmonary edema on exercise, and their cardiac output is rarely the limiting factor when they exercise. Nevertheless, they are very symptomatic (28).

Investigator after investigator has found little or no correlation between indexes of central hemodynamic status or pulmonary function and exercise tolerance (27). What was missing was the realization that in treated euvolemic CHF, symptoms arose from the periphery and not the heart or lungs (3). During exercise, patients demonstrate exaggerated ventilation and tachycardia and stop without reaching a maximal cardiac output because of intolerable symptoms and the inability of skeletal muscle to receive and use oxygen and nutrients (4,8).

Skeletal Muscle Hypothesis. Heart failure affects every step in the oxygen transport system, from the center (heart, lung, central neural control) to the periphery (circulation, neurohormonal status, reflexes, muscle metabolism). The peripheral changes become the weakest link in the exercise chain and become the cause of exercise-limiting symptoms (9).

The past 20 years have witnessed the development of an initially controversial but now widely accepted and elegantly simple idea: the “muscle hypothesis” (Fig. 2). Damage to the heart and disturbance of central hemodynamics trigger compensatory mechanisms, including neurohumoral and sympathetic activation, with initially peripheral vasoconstrictor and tachycardic effects. However, in the longer term, these compensatory mechanisms also trigger harmful changes in multiple organ systems, including skeletal muscle structure, function, metabolism, peripheral vascular and endothelial responses, including apoptosis, necrosis, and inflammatory activation. These are responsible for substantial tissue loss, altered fiber type patterns, decreased oxidative enzyme number and function, mitochondrial destruction, metabolic disturbance, and hormonal resistance syndromes, including both insulin and growth hormone resistance (6).

It is easy to see how this structurally and functionally damaged muscle could cause fatigue, but could it explain dyspnea (19)? To investigate this, studies have been focused on the compensatory reflex mechanisms such as skeletal muscle ergoreceptors, which communicate to the brain stem information about the level of muscle work (13). They are grossly differentiated into two types: metaboreceptors and mechanoreceptors. The mechanoreceptors, finely myelinated group III afferents mainly respond to mechanical stimuli, whereas the metaboreceptor, unmyelinated group IV afferents, are sensitive to metabolites, especially acidosis (25), but also prostaglandins and bradykinins (24). Once activated, they directly stimulate sympathetic drive, ventilation, and vasoconstriction in the nonexercising limbs, the combined effect of which is to divert more well-oxygenated blood to the working skeletal muscles (12). In CHF patients with their damaged and wasted skeletal muscle, their signal is grossly overactive and contributes to exaggerated ventilatory and circulatory responses, symptoms (including both fatigue and dyspnea) and harmful persistent neurohormonal hyperactivation. This “muscle hypothesis” explains how in CHF a vicious cycle ensues in which cardiac failure is responsible for an acquired skeletal myopathy that in turn aggravates cardiac dysfunction by activation of sympathoexcitatory (and symptom generating) muscle reflexes.

Muscle Reflexes in Heart Failure. The Evidence

Experimental studies. In animal models of heart failure, abnormal responses to both mechanoreflex and metaboreflex stimulations have been documented. The heightened metaboreflex activation, when confronted with an inability to increase myocardial contractility causes an exaggerated vasoconstriction during exercise (7, 15). In response to mechanical stimuli, an overactivity of finely myelinated group III afferents (mechanoreflex) was evident in a postinfarct rat heart failure model starting at the beginning of the contraction and contributing to the pressure response (11). Therefore even mild physical activity would lead a state of almost constant activation of the