Increased mechanoreceptor/metaboreceptor stimulation explains the exaggerated exercise pressor reflex seen in heart failure
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The following letters are in response to the Point:Counterpoint series “Increased mechanoreceptor/metaboreceptor stimulation explains the exaggerated exercise pressor reflex seen in heart failure” that appears in this issue.

To the Editor: The Point:Counterpoint concerning the issue of mechanoreceptor vs. metaboreceptor control of sympathetic nerve activity (SNA) in chronic heart failure (CHF; Refs. 1, 2) relates exclusively to input from exercising skeletal muscle. Although both sides make cogent points on the basis of published data, in our opinion the debate has not been conclusively settled and will not be using the types of experiments carried out in human subjects. First, it is certainly not clear if passive exercise simulates true dynamic exercise and, second, if capsaicin injections simulate the ischemic stimulus observed during exercise in the CHF state. We offer an alternative hypothesis as to the mechanism for exaggerated SNA during exercise in the CHF state. Clearly exercise evokes a stimulus from muscle but also may increase neural signaling from cardiac and chemoreflexes in the heart and in the arterial system. Cardiac sympathetic afferents respond to ischemic metabolites, which are likely to be elevated in CHF patients during exercise. These largely c-fiber afferents are sensitized in animals with CHF (5). The cardiac sympathetic afferent reflex is clearly augmented in CHF (6). In addition to this particular sympathoexcitatory reflex, the arterial chemoreflex is sensitized in CHF (3). It is not inconceivable that carotid hypoxia during exercise (perhaps as a result of pulmonary interstitial edema) evoking an increase in carotid body activity acts as another sympathoexcitatory reflex. Because both of these afferent pathways appear to be enhanced even under normoxic resting conditions and because our recent data indicate that these inputs to the nucleus of the solitary tract augment sympathoexcitatory stimuli (4), they can not be excluded as potential contributors to the exaggerated SNA responses to exercise.

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To the Editor: Because endothelium modulates exercise neurogenic vasoconstriction and upregulates muscle perfusion (1), diseases causing endothelial dysfunction (ED) are conceivably associated with exercising muscle hyperperfusion and local overproduction of metabolic by-products that trigger the exercise pressor reflex. Hence, ED in CHF (4) might be a reason for muscle oversignalling, and CHF might not be the only condition eliciting overstimulation of skeletal muscle neural afferents. Atrial fibrillation (AF) is a model suitable to verify these possibilities, because it is associated with endothelial oxidative injury and endothelial function recovers with cardiovascular (CV) or antioxidant vitamin C (2, 3). In lone atrial fibrillation we found that after vitamin C and following CV, the endothelial brachial artery flow-mediated dilatation (FMD) increased and the ergoreflex component of the ventilatory response to handgrip (EVR) and the slope of ventilation to V˙CO₂ production (V˙E/V˙CO₂) significantly reduced. In AF associated with diabetes (additive endothelial impairment), no changes in EVR and V˙E/V˙CO₂ slope occurred after CV and FMD was refractory to either intervention (3). Ventilatory inefficiency (steep V˙E/V˙CO₂ slope) and a low arterial CO₂ pressure to incremental exercise occur in AF and both are brought back to normal by CV (2). Since arterial O₂ saturation was normal and unaffected by CV, a reasonable explanation for a less-efficient ventilation is an intervention of extrapulmonary peripheral factors (2, 3). These results altogether are consistent with the thesis of an increased mechanoreceptor activity (5) and strengthen the thesis of an increased metaboreceptor activity (6). The same may be true of CHF.

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failure (HF) than the role of metaboreceptor activity. Their main argument is based on animal experiments, which do not simulate human heart failure. De Meersman and colleagues (1) presented some interesting data on passive limb movement showing an increase in VO2 of almost 90% the size of the increase produced by active unloaded exercise. This study supports several other group findings that indicate more elaborate and sensitive testing is required to further examine this reflex. We are aware that the mechanoreflex has a role in stimulating the EPR, but the extent of its role is less than the metaboreflex (3).

Piepoli and Coats (4) provide a thorough background into the established “skeletal muscle hypothesis.” Their defense, or offence, of the metaboreceptor and its role with the EPR is supported by complete studies with reproducible results. The metaboreflex is very well supported; the degree of receptor dominance does need to be investigated with testing protocols that are consistent and on HF patients that indeed are significantly classified as human HF. Piepoli and Coats provide an in-depth assessment of the issue at hand, including the pathological (“skeletal muscle hypothesis”) and therapeutic (exercise training beneficial effect) implication. Instead, Middlekauff and Sinoway provide no background for why the mechanoreflex is dominant in their eyes: it is difficult to defend their position without clear evidence of the physiological inference.

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To the Editor: We read the debate between Drs. Middlekauff and Sinoway and Drs. Piepoli and Coats on the exercise pressure response (EPR) in heart failure (HF) with great interest. We want to thank these investigators for providing us with such an outstanding discussion regarding sensory muscle fibers, which are responsible for the reflex abnormalities during exercise in HF patients. Both sides have relevant arguments for the role of the muscle mechanoreceptors and metaboreceptors in the exaggerated EPR in HF (1, 2, 4). However, we are convinced that the increased mechanoreceptor activity explains the augmented EPR in HF patients. The significant increase in muscle sympathetic nerve activity (MSNA) during passive exercise (2) and low-intensity exercise (10% MVC; Ref. 3) and the augmented renal vascular resistance during mechanoreceptor stimulation (1) strongly favor the increased mechanoreceptor activity in HF patients. On the other hand, it is unlikely that the increased muscle metaboreceptor activity is responsible for exaggerated EPR in HF. Different studies have shown that, during post-exercise muscle circulatory arrest, when the metaboreceptors are isolated from central command and mechanoreceptors, MSNA remains elevated in healthy individuals, whereas in HF patients it returns to baseline (3, 6). These findings demonstrate that the muscle metaboreceptor sensitivity is reduced in HF patients. In addition, the argument that muscle circulatory arrest also stimulates nociceptive neurons is unfounded. A recent study showed that 2 min of this maneuver after 3 min in a quiet resting position caused no changes in MSNA and mean BP levels when compared with baseline in normotensive individuals and hypertensive patients (5).

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To the Editor: The conclusion by Middlekauff and Sinoway (3) that “the metaboreflex is blunted in heart failure” is unjustified because the contribution of this reflex to elevations in baseline muscle sympathetic nerve activity (MSNA) in heart failure has not been evaluated. Because MSNA is elevated at rest in low cardiac output heart failure, it is possible that (as suggested in Ref. 1) at least in severe heart failure, the metaboreflex is nearly saturatingly recruited at rest, and this may be why their additional contribution to the exercise pressor response (EPR) is attenuated. In contrast, an increase in MSNA (2-tailed P = 0.07, based on data in Table 1, Ref. 5) occurred only during the second minute of static forearm exercise in control subjects, suggesting that the metaboreflex was recruited only then.

Second, endothelial function defective in its vasodilator capacity likely explains why the vasoconstricting effect (especially in exercising skeletal muscle) of an elevation in MSNA during exercise is exaggerated in heart failure (also noted by Guazzi in response to this call for comments). Endothelium-dependent and endothelium-independent vasodilation is impaired in patients with even mild heart failure (2).

Finally, in references 12–16 and 18 of Middlekauff and Sinoway’s article (3), the authors of the cited studies did not specifically distinguish muscle mechanoreceptor and metaboreceptor contributions to the EPR but have collectively used
the term metaboreceptors (or ergoreceptors) to refer to both of them. Thus Middlekauff and Sinoway (3) are mistaken in inferring these results as contradicting with theirs.

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To the Editor: I much enjoyed reading both sides of the debate between Piepoli and Coats (4) on the one hand and Middlekauff and Sinoway (2) on the other. It is encouraging to see ever-widening acceptance of the “muscle hypothesis” for the explanation of symptoms in chronic heart failure (1). The present debate between the protagonists is akin to that between Big-Endians and Little-Endians in Gulliver’s Travels (6); there is little profound difference between the two sides, and both take for granted that the muscle hypothesis is correct.

Neither side of the debate, however, convincingly deals with the other’s key points. There is no convincing explanation for the apparent blunting of the metaboreflex in heart failure seen in sympathetic nerve activity recordings from Piepoli and Coats (4) and, equally, no convincing explanation for the enhanced metaboreflex demonstrated when considering ventilatory responses to exercise from Middlekauff and Sinoway (2) despite the fact that both sets of experiments used a similar design of exercise with postexercise regional circulatory occlusion.

Although it might be uncomfortable for both sides to accept, a possible resolution to the debate is to accept that although the periphery does indeed drive exercise responses, the exercise response (like many other systems in the body) is marked by duplication and redundancy. It is surely possible—indeed, as the present debate makes clear, probable—that different aspects of the exercise response are predominantly driven by different aspects of the peripheral response; the sympathetic response might be driven predominantly by mechanoreflexes and the ventilatory response by metaboreceptors.

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To the Editor: In this Point:Counterpoint, two opposite theses have been exposed to explain the exaggerated exercise pressor reflex in heart failure (HF): metaboreceptor vs. mechanoreceptors overactivation (4, 6). Both theories agree that a sympathetic overdrive originating from muscular receptors occurs during effort, and the only real difference between the two opponents is the muscular receptor being activated. However, both theories do not take into account the effect of the activation of these receptors on central hemodynamics. We demonstrated that the metaboreflex engagement obtained by postexercise muscle ischemia (PEMI) can elicit substantial enhancement in cardiac performance in healthy individuals (1, 2). The PEMI maneuver clearly rules out any contribution of mechanoreceptors to this contractility response because mechanoreceptors are not operating in this setting. Moreover, circulatory occlusion without previous exercise (i.e., without metabolic end-products accumulation within muscle) did not cause any relevant hemodynamic consequence (1, 2). Thus, in normal subjects, a myocardial contractility modulation is possible via metaboreflex recruitment. However, the possibility that metaboreflex can still evoke a contractility response in HF patients has never been investigated, although recent studies conducted on animal models of HF suggest that the limited capacity to enhance ventricular performance is responsible for a functional shift from cardiac output to systemic vascular resistance increase in the mechanism by which the cardiovascular system responds to metaboreflex (3, 5). Thus it appears that the hemodynamic disarrangement shown by HF patients may also derive from the incapacity of the failing circulation to increase contractility in response to metaboreflex.

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To the Editor: In this Point:Counterpoint discussion on the relative role of the mechanoreceptor and metaboreceptor reflexes in the enhanced skeletal pressor responses found in heart failure (HF; Refs. 3, 4), both discussants accept the importance of skeletal muscle afferents. While Middlekauff and Sinoway use animal models to argue that pharmacological inhibition of mechanoreceptor stimulation results in elimination of the pressor response seen in HF, this does not completely mimic human physiology. They cite human data from their own laboratory showing that the pressor response during low-level rhythmic exercise in HF patients was measurable earlier than in normal subjects (2), which they argue may signify an enhanced mechanoreceptor response. However, this may simply reflect a lower threshold for activation of the metaboreflex in HF subjects than normals (1), and they also concede that this activity will also stimulate metaboreceptors.

Piepoli and Coats and colleagues (4, 5) present the case for enhanced metaboreceptor sensitivity having attempted to clinically separate the two types of receptor in humans. Although they found it impossible to entirely eliminate the mechanoreceptor response despite using only passive exercise, they clearly demonstrated the significantly greater contribution from the metaboreceptor than the mechanoreceptor.

What is clear from the clinical experiments cited by both authors is that complete separation of the two types of muscle stimulus is difficult in normal subjects, and using current methodology this question seems set to remain unresolved. One wonders whether studying patients with reduced muscular tone (either secondary to neurological disease or muscle relaxants given during general anesthesia) may add useful information to this debate.

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