Increased Mechanoreceptor Stimulation Explains the
Exaggerated Exercise Pressor Reflex Seen in Heart Failure

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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, 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 (1, 11). 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,” 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 “post-exercise 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 minutes 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 ((18);
Figure). 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 utilized 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, while 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 utilized, specifically exercise type, site, duration and degree. Unlikely, since 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: lowlevel rhythmic exercise also engages central command and perhaps even metaboreceptors, involuntary contraction can be painful and recruitment patterns are not physiologic, 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 utilized. For example, metabolically sensitive group IV neurons can be selectively activated by capsaicin infusions into the arterial supply of the hindlimb muscle. In the infarct-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 alpha, beta-methylene ATP enhanced the BP response to muscle stretch to a greater degree in HF rats compared to controls. Similar results were reported from an independent laboratory using a similar, but not identical, protocol (17). Moreover, in the infarct-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 was observed in healthy rats, but was significantly blunted in HF rats (17). Furthermore, when muscle mechanoreceptors were blocked using gadolinium, this exaggerated EPR in HF rats during muscle contraction was eliminated. In summary, studies using the rat infarct 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


**FIGURE LEGEND**

*Figure.* The graph shows the comparison of percent change in MSNA in HF subjects compared to control subjects during 2 min of static handgrip exercise,
and during post-handgrip regional circulatory arrest (PHG-RCA). MSNA levels returned to baseline levels in the HF patients, but not the controls, consistent with blunted muscle metaboreceptor control of MSNA in HF.

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Increased metaboreceptor stimulation explains the exaggerated exercise pressor reflex seen in heart failure.

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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 oedema 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 indices of central hemodynamic status or pulmonary function and exercise tolerance (27). What was missing was the realization that in treated euvolaemic CHF, symptoms arose from the periphery and not the heart or lungs (3). During exercise patients demonstrate exaggerated ventilation, tachycardia, and without reaching a maximal cardiac output but rather because of intolerable symptoms, and the inability of skeletal muscle to receive and utilise 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, neurohumoral 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” (Figure). Damage to the heart and disturbance of central hemodynamics trigger compensatory mechanisms including neurohumoral and sympathetic activation, with initially peripheral vasoconstrictor and tachycardic effects, but in the longer term harmful changes in multiple organ systems, including importantly skeletal muscle structure, function, metabolism, peripheral vascular and endothelial responses including apoptosis, necrosis and inflammatory activation. These are responsible for substantial tissue loss, altered fibre type patterns, decreased oxidative enzyme number and function, mitochondrial destruction, metabolic disturbance, 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 focussed 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 while 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 dyspnoea) and harmful persistent neurohormonal hyper-activation. 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 sympahto-excitatory (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 post-infarct 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 renin-angiotensin system and the related renal responses. Selective abolition of exaggerated mechanoreflex is associated with improved physiological hemodynamic and chronotropic responses to exercise (26). Activation of the muscle reflex is reversible: in dog model, recovery from pacing-induced heart failure was associated with a fast return to normal cardiac function but a slow reduction of the muscle reflex activation, consistent with a different rate of recovery of the controlling system. (2)

Human studies. Overactivation of muscle metaboreflexes in human CHF has been shown to cause exaggerated ventilatory, hemodynamic and vasoconstrictor responses (16). Unlike central hemodynamics, these muscle reflex responses powerfully predict exercise intolerance and symptom generation (5,14). Deterioration of the syndrome is characterised by further increased metaboreflex activation (19) with a consequent further impairment of exercise tolerance, ventilatory abnormalities, higher risk of arrhythmias, and increased mortality (20).

CHF patients have an exaggerated metaboreflex response to both forearm (21,22) and lower limb muscular exercise (23): the strong correlation between metaboreflex activation assessed in different limbs has suggested that a unique mechanism is responsible for overactivation of the metaboreflex system.

Biochemical studies. Exaggerated metaboreceptor firing in human heart failure is dependent on systemic acidosis, prostaglandin and bradykinin release within the muscle. Modulation of these metabolite concentrations acutely reduces the muscle reflex activity, which suggests a causative role in triggering and/or mediating the ergoreflex response. The increased prostaglandin and bradykinin productions both at rest and during exercise in CHF were attenuated after ketoprofen infusion, associated with ergoreflex reduction(24). A reversal of hyperactive metaboreflex during exercise obtained by buffering the increased acidotic response has further supported the contribution of muscle catabolism in symptom generation for both fatigue and dyspnoea(25).

Body composition studies. Clinical deterioration is accompanied by peripheral muscle wasting and altered autonomic reflex control. A strong relationship between more advanced cardiac cachexia and heightened muscle reflex overactivity supports the crucial role played by maladaptive changes in the muscles. (18).

Intervention studies to reverse muscle reflex activation. The evidence of the beneficial effect of exercise training in CHF, in terms of symptoms, survival and hospitalisation reduction, further supports the muscle hypothesis (17). Training improves skeletal muscle alterations, demonstrating that peripheral abnormalities are not irreversible (1): it enhances mitochondrial density and oxidative enzyme activity, increases capillary density and shift towards aerobic metabolism (6,10) and reduces metaboreflex overactivation (16). All of these effects are seen despite little if any central hemodynamic change and even at sub-hemodynamically effective training workloads.
Conclusion

The muscle hypothesis adds another vicious cycle of deterioration that affects CHF sufferers: damaged muscle, causes exaggerated reflex responses, which limit exercise, cause symptoms and further augment harmful neurohormonal over-activity. Like other vicious cycles in heart failure initially useful physiological responses turn maladaptive over time. The importance of this should not be lost on us: it tells us the muscles and fitness might determine how symptomatic a patient is, it opens opportunities for prevention (metabolically targeted therapies) treatment (muscle therapies including training) and novel targets for therapeutic intervention over the whole exercise process, from metabolism, ventilatory and circuitry control, muscle growth and death and reflex modulation. Yes, the muscles are important and they talk to the brain through the metaboreflexes.
Figure. Skeletal muscle hypothesis

LV dysfunction

- Vasoconstriction
- Slow / reduced peripheral blood flow
- Sympathoexcitation
- Baroreflex impairment
- Reduced exercise tolerance
- Increased ventilation

Catabolic state

- Augmented ergoreflex
- Skeletal and respiratory myopathy

Reduced exercise tolerance

Increased ventilation
References


Rebuttal
Middlekauff and Sinoway

In the portion of the debate, Piepoli and Coats did an outstanding job reviewing the large body of work compiled by their group over the last decade or so. This body of work suggests that reflexes emanating from skeletal muscle play an important role in evoking increases in ventilation as well as sympatho-constrictor signals during exercise in congestive heart failure (HF). The author’s work suggests that peripheral limitations play an important role in determining exercise limitation seen in HF.

However, it would have been informative for the readers of JAP if the authors had dealt directly with the issue at hand namely “whether heightened mechanoreceptor or metaboreceptor responses explain the exaggerated reflex responses seen with exercise in HF”. In limiting their review to a discussion of their impressive body of work they presented no discussion as to why the controversy exists and why Piepoli and Coats and Middlekauff and Sinoway should be afforded the opportunity to debate this issue in the first place. For our part (Middlekauff and Sinoway) we think that the debate is real and is important. We should note that we as well as the protagonists in this debate believe that peripheral issues are crucial determinants of symptomatology during exercise in HF.

Speaking for our side, we were turned on to the issue of the role in the “periphery” in HF by the classic work of Zelis et al. (2) and later by LeJemtel and colleagues (1). The work cited in our review as well as that by Piepoli and Coats differed from that of Zelis et al. and LeJemtel et al. in that we assign a greater importance to the sympathetic constrictor influences seen than to the impaired vasodilatory capacity described by Zelis et al. and LeJemtel et al. Where we and our protagonists in this debate differ is that we believe that the heightened reflex responses seen in HF are due to the stimulation of afferents that are mechanically sensitive and not metabo-sensitive. In fact, the work we describe in our original review suggests that metabo responses are in fact attenuated. We describe a series of experiments over a 15-year period from a number of different laboratories that are consistent with this hypothesis. These studies span the continuum of hypothesis driven clinical investigation to studies using a decerebrate rat model of HF. We believe the experiments presented and the line of debate presented by us is systematic and compelling. We congratulate our adversaries on their important contributions to this body or work and only wish they had presented a compelling series of hypotheses upon which we could further the discussion and enhance the rate at which we learn about this important reflex system.

REFERENCES
Drs. Middlekauff and Sinoway did not to our surprise defend the classical hemodynamic explanation for abnormal exercise reflex responses in heart failure (HF), but rather acknowledged our “skeletal muscle hypothesis”. They then elegantly argued for mechanoreflex (type III afferents) rather than metaboreflex (type IV afferents), being of greater importance. We are almost disarmed by so much of our contention being accepted without argument in the opening parry.

Physiologically, considerable overlap exists between these two type of afferents; during exercise both are almost inevitably activated in a seamless transition. Ischemia (being the trigger of the metaboreflex) increased the muscle contraction responses of some group III fibers but not all group IV afferents (1). To get a clear picture we need to look at both animal and clinical studies. In a canine HF model during moderate exercise the metaboreflex was tonically active, stimulated at a lower threshold, and increased blood pressure primarily by reflex vasoconstriction (3). In HF patients we may quote the outstanding study of our opponents (6), where rhythmic forearm exercise lead to premature fatigue and accumulation of muscle metabolites and metaboreflex overactivation. Resting muscle levels of triggers of the metaboreflex, eg. $H^+$ and $H_2PO_4^-$, were similar between HF and controls, whereas peak exercise levels were greater in HF, demonstrating not only activation but the mechanism triggering the reflex responses. In an earlier study the muscle metaboreceptor responses to static exercise were seen to be attenuated (8). Our antagonist himself provides a possible explanation, based on the different responses to static versus rhythmic exercise: in the latter the hemodynamic abnormalities may be more exaggerated because of intermittent blood flow washing out metabolites (7).

The only human study using a similar protocol to ours but in disagreement, was performed in middle-aged CHF men with relatively preserved exercise tolerance (mean peak VO$_2$ 22ml/kg/min) exercising at a submaximal load (77% capacity), a situation in which different mechanisms may predominate (ie mechanoreflex, blood-borne factors) (2).

The main argument proposed for our opponents’ hypothesis is based on animal experiments where the response to vanilloid type 1 (VR1) receptor stimulation by capsaicin was attenuated. Since this receptor colocalizes with acid-sensing ion channels (ASIC) receptors, our opponents speculate that attenuated VR1 is a marker for impaired metaboreflex (4). However this is only part of the story since different triggers such as $H^+$ stimulate ASIC but not VR1. Moreover, animal models do not simulate human HF, for the animals are not treated nor live long enough to develop the syndrome.

Our opponents provide no explanation for the origin and aetiology of the described mechanoreflex hyperactivation, which remains an interesting acute exercise reflex of debatable clinical importance, in contrast to the major role of metaboreceptors in cachectic human HF.
References


