Sympathetic nervous system and muscle: A two way interaction in health and disease

ABSTRACT

This review deals with the several mechanisms that control the fine balance between muscle energy expenditure and neurally mediated vascular responses during exercise. During exercise the SNS is activated as an opposing mechanism to the endothelium - derived vasodilatation in order to preserve hemodynamic balance (and teleologically protect against inadequate perfusion of vital organs like the heart and the brain). The activation of SNS is finely modulated (functional sympatholysis) to maintain blood pressure and tissue oxygen delivery. Overall, the neural control of vascular tone during exercise has two components: central command and muscle reflex. The latter consists of a reflex, which arises from stimulation of mechanically sensitive (driven by mechanical forces) and metabolically sensitive (driven by changes in the biochemical milieu) afferent nerve endings within the exercising muscle. Together these systems are integrated and regulate SNS tone. In heart failure the abnormal muscle causes an enhanced muscle reflex to exercise, which further promotes an excessive ventilatory response subjectively perceived as breathlessness (the "muscle hypothesis"). It has been proposed that chronic overactivity of the muscle reflex may be responsible for the chronic sympathetic activation seen in HF state. In early hypertension the basal sympathetic tone is increased. It has been hypothesized that the rise in the sympathetic tone of the kidney contributes to a resetting of the renal BP-natriuresis relationship to higher levels of BP. This theory integrates the classic Guyton model (pressure-natriuresis relationship) with the central regulating role of the SNS. Some preliminary data show that muscle perfusion is abnormal in hypertension (due possibly to rarefaction), and this may be accompanied by alterations of the muscle reflex and sympathetic tone response during exercise. The mechanisms of this altered response are speculative.

A close relationship exists between intensity of exercise and several cardiopulmonary physiologic mechanisms. The sympathetic nervous system (SNS) plays an important role in regulating blood flow and oxygen supply to active skeletal muscles. This review will discuss the several mechanisms that control the fine balance between muscle energy expenditure and neurally mediated vascular responses during exercise. In the first part, the mechanisms of skeletal vascular responses to sympathetic nervous activation will be presented. In the second part, observations regarding the origin of neural stimulus elicited by muscle activity will be reported. In the third part, data regarding the derangement of these mechanisms in
disease states (mainly in heart failure and to a lesser extent in hypertension) will be presented.

**PART 1. THE EFFECT OF SNS ACTIVATION ON SKELETAL MUSCLE VASCULARITY**

In the exercising muscle there are three vasomotor tone regulating mechanisms. First, there is the modulating influence of the endothelium, producing vasodilation through release of NO secondary to luminal shear stress exerted by the flowing blood. Peripheral blood flow capacity has been documented to be greater than maximal cardiac output. For example it has been found that during dynamic exercise of the knee extensors, peak blood flow in the exercise muscle can increase up to 100-fold above resting values. In order to avoid hemodynamic collapse and to preserve cerebral and cardiac perfusion two other vasoconstricting mechanisms are being involved: first, myogenic contraction of smooth muscle cells in response to blood pressure and secondly, vasoconstriction through engagement of the SNS. The magnitude of the sympathetic response is dependent on the intensity of muscle work and the presence of fatigue.

A question arising is if the vasoconstriction promoted by SNS is accompanied by suppression of oxygen supply to the exercising muscle fibers. Several studies in the past have shown contradictory results. A previous study from this laboratory showed a fall in the forearm venous pH during exercise with simultaneous enhancement of the sympathetic constrictor tone after application of 60 mm Hg of negative pressure in lower body. The muscle vasculature consists of large “feed” arteries and of smaller first, second and third order arterioles. When SNS activation is sustained (2-3 min) distal arterioles tend to “escape” from sympathetic vasoconstriction. Recently in a hamster retractor muscle preparation, it was shown that sympathetic activation causes vasoconstriction in feed arteries and first order arterioles, whereas in second and third order arterioles the effect was opposite. It is possible that a number of substances may contribute to metabolic attenuation of the effect of the released norepinephrine. This elective vasoconstriction leading to redistribution of intramuscular flow could also be attributed to the differential distribution of $\alpha_1$ and $\alpha_2$ post junctional receptors on smooth muscle cells within different levels in the arterial tree. The smaller distal branches of the arterial tree are mainly control by $\alpha_2$ receptors (which are more susceptible to metabolic inhibition), whereas the larger proximal parts are controlled by both $\alpha_1$ and $\alpha_2$ receptors (less susceptible to inhibition). Given that: 1) there are several subtypes of both $\alpha_1$ receptors ($\alpha_{1A}$, $\alpha_{1B}$ and $\alpha_{1D}$) and $\alpha_2$ receptors ($\alpha_{2A/D}$, $\alpha_{2B}$ and $\alpha_{2C}$) with as yet undefined individual contribution to sympathetic responses and 2) many vessels express more than one receptor subtypes, it is difficult to ascertain specific physiologic role for each subtype. In conclusion, during exercise the effect of SNS activation seems to be diminished in the active muscles but preserved in the inactive muscles, leading to the classic theory of “functional sympatholysis”.

**PART 2. THE GENERATION OF SYMPATHETIC STIMULUS DURING EXERCISE**

The next question arising is how and where the stimuli for SNS activation are generated during exercise? Two basic theories (not mutually exclusive) have evolved. The first has been termed “cen-
tral command” and it suggests that motor cortical signals irradiate to cardiovascular and respiratory centers in the brainstem. In turn, sympathetic and parasympathetic activity are regulated. In other words, there is a parallel, simultaneous excitation of the locomotor and the cardiorespiratory systems in the brain, thus serving as a feedforward control mechanism.

The second mechanism suggests that exercise increases SNS activity via engaging a reflex, which arises from stimulation of mechanically sensitive (driven by mechanical forces) and metabolically sensitive (driven by changes in the biochemical milieu) afferent nerve endings within the exercising muscle, the “exercise pressor reflex.” The greater the muscle tension is, the greater the magnitude of the sympathetetic response. Skeletal muscle is innervated by five types of sensory nerves, which are labeled as I through IV, (the first group has two subtypes Ia and Ib). This classification scheme is based on the diameter and the degree of myelination, which are important determinants of axonal conduction velocity. The free nerve endings of both group III and IV afferent fibers have been identified in the interstitial spaces and appear to be in close proximity to lymphatics and blood vessels of muscle and tendon tissue. Some of these nerve endings represent the chemo-sensitive metabo-receptors. Other populations of group III and IV fibers have been identified within the interstitium proximal to collagen bundles. These locations are probably the sites of mechanically sensitive receptors (mechano-receptors). In a series of studies, it was shown that static muscle contraction (stimulation of the mechano-reflex) in cats stimulated group III fibers (thus predominantly mechanosensitive), whereas ischemia (and therefore increasing concentration of chemical byproducts of muscle contraction) increased the discharge from unmyelinated group IV fibers (thus predominantly metabo-sensitive). The concept of “strong morphologic/physiologic fiber differentiation” has been challenged by subsequent studies, including one from this laboratory, showing that both mechanical and metabolic stimuli produce a response in both groups III and IV of muscle fibers.

Overall, the neural control of vascular tone during exercise has two components: central command and muscle reflex. The latter is driven by mechanical and metabolic stimuli generated in the exercising muscle. Together these systems are integrated and regulate SNS tone.

An important question that arises is about the relative contribution of each mechanism in different phases of exercise. In order to elucidate this issue, a series of experiments were performed recently in this laboratory. In this report, renal vascular resistance (RVR) (assessed by Doppler measured renal flow velocity and by beat to beat measurement of blood pressure) was a measure of SNS activity. In the first protocol, static handgrip exercise to fatigue increased RVR by 76%. Just immediately before the handgrip exercise was ended, a previously placed arm cuff was inflated to 250 mm Hg producing a circulatory blockade in the arm (and thus trapping metabolic products of muscle activity locally). In this phase RVR remained above baseline, but was only 40% of the end-grip RVR value. In the second protocol, the subjects performed hand grip exercise of several intensity grades. It was found that RVR increased at intensity levels of 50% and above of maximal voluntary contraction and within 6 seconds from the initiation of the exercise. In the third and fourth protocol, voluntary and involuntary (through electrical stimulation) biceps contractions also raised RVR, and this effect was not associated with significant blood pressure rise. (Overall, these protocols collectively showed that muscle contraction evokes renal vasoconstriction (SNS activation). The theoretical mechanisms which could explain these findings could have been: a) myogenic reflex (ie. vasoconstriction in response to increase of blood pressure), (b) central command, c) mechanoreflex (mechanical stimulation of muscle), d) metaboreflex (metabolic stimulation of the muscle). The myogenic reflex did not seem to play a significant role in renal vasoconstriction, since there was no significant BP rise in the biceps contraction protocol. Also, the involuntary biceps contraction protocol suggested that central command was not necessary to evoke renal vasoconstriction with muscle contraction. Finally, since the circulatory blockade response represented only a small percentage of the whole handgrip exercise to fatigue response, it seems most likely that the stimulus arising from muscle contraction is not mainly chemical (metabolic) in nature. Furthermore, the vasoconstriction was observed early in all contraction protocols (and therefore could not be attributed to accumulation of metabolic products). The only mechanism that could satisfactory explain all
protocols was the mechanoreflex engagement. In conclusion, SNS activation and renal vasoconstriction during static exercise were closely associated with the muscle mechanoreflex.

Further research in the field showed that the muscle mechanoreflex induced vasoconstriction is augmented in advanced age and is not affected by muscle mass and was similar in men and women. Other studies shed light in the biochemistry of afferent nerve sensitization. It was found that ATP does sensitize mechanically sensitive afferents and that this sensitizing effect requires stimulation of purinergic receptor \(2X^{28}\). Another substance that has been found (in most but not all studies) to directly sensitize and stimulate muscle afferents is lactic acid. Its response is mediated through the acid-sensing ion channel (ASIC) receptor, which belongs to the amiloride-sensitive epithelial sodium channel (ENaC) family, and it is often found on sensory neurons.

**PART 3. THE MUSCLE REFLEX IN HEART FAILURE AND HYPERTENSION**

**Muscle reflex and heart failure**

Breathlessness and fatigue on exertion are the dominant symptoms seen in heart failure (HF). Traditionally, it has been hypothesized that the inadequate cardiac pump fails to perfuse muscles during exercise, which is perceived by the brain as fatigue; at the same time the cardiac output is maintained through an increase of the ventricular filling pressure that may cause pulmonary interstitial or alveolar edema leading to breathlessness. Several studies during the last decade have proposed the muscle and the SNS as central components in the pathophysiologic mechanism of HF. It is known that sympathoexitation plays a prominent role in the disease progression and prognosis. It is also known that skeletal muscle is abnormal in HF patients (reduced muscle bulk, reduced muscle strength and endurance). The question, which arises, is what is the role of the muscle (mechano and metabo-) reflex in the pathophysiology of HF.

In an earlier study performed in this laboratory, subjects with and without heart failure performed static handgrip exercise, as the SNS activity was assessed by using microneurography (a technique in which there is direct recording of the sympathetic bursts from small needle-probes inserted in the peroneal nerve) (Fig. 1). At the end of the 2-min handgrip the circulation to the forearm was arrested by inflation of a pre-placed cuff. This causes trapping of metabolic products of muscle activity locally. During handgrip the SNS activity was

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**Fig. 1.** Representations of Muscle Sympathetic Nervous Activity (MSNA) responses to a bout of static handgrip for 2 min. The increase in the MSNA at end grip was relatively similar in the two groups; however during Post Hand Grip Circulatory Arrest (PHG-CA), MSNA remained elevated in control subjects and fell toward baseline in the heart failure group.
increased equally in both groups. However, during circulatory arrest the SNS activity continued to rise in normal controls, whereas in HF patients fell towards baseline. The interpretation of the study was as follows: During exercise in both groups the muscle reflex (mechano- and/or metabo-receptors) provoked an increase in SNS activity. The decreased sympathetic response during the second phase (ie. the circulatory arrest) was due to attenuation of the metaboreceptor reflex (since they are mainly engaged in this phase of metabolites trapping). Since both groups had the same sympathetic response at the end of hand grip it seemed that there was an enhanced stimulation of mechanoreceptors to compensate for the diminished metabo-reflex. In a subsequent study it was suggested that the desensitization of the metaboreceptors was associated with the severity of HF. In a recent study from our laboratory it was shown that the renal vasoconstrictor effect of SNS activation caused by static handgrip was increased in HF subjects in comparison to healthy controls. This was also attributed mainly to mechanoreceptors engagement (Fig. 2 and 3).

Dynamic exercise evokes different autonomic responses. Studies performed by others, or in this laboratory using microneurography during rhythmic handgrip showed an increased muscle metabo-reflex in HF patients. In the latter study it was shown that HF subjects were fatigued prematurely and this was associated with marked muscle acidosis and accumulation of H2PO4 and intracellular P+. It is clear that accumulated by-products of muscle metabolism are greatly increased in HF. There are many reasons for this altered metabolism

![Fig. 2. Renal blood flow velocity in control and heart failure subjects. Values in HF patients were significantly higher at all levels (10%, 30%, 50%, 70%) of maximum voluntary contraction (MVC).](image1)

![Fig. 3. Representation of sympathetic control in normal subjects and in patients with heart failure (HF). Left: with exercise, muscle reflex is initiated leading to increase in muscle sympathetic nerve activity (MSNA) and renal vasoconstriction. These effects seem to be mediated by stimulation of VR1 and/or acid sensing ion channels (ASIC) and purinergic receptor subdivision 2X (P2X). Right: In HF, stimulation of VR1-sensing anion channels is attenuated, and this likely contributes to the attenuated metabo-receptor response. On the other hand, P2X-mediated stimulation of mechanoreceptors is augmented, and this leads to accentuated renal vasoconstriction.](image2)
in muscle. These include muscle atrophy\textsuperscript{41}, reduced diffusive O\textsubscript{2} delivery\textsuperscript{42}, abnormalities in mitochondrial structure (particularly the enzymes of oxidative chain)\textsuperscript{43} and a shift towards type II muscle fibres (which are more anaerobic)\textsuperscript{44}.

All these observations led to the formation of the “muscle hypothesis”: the structural abnormalities of skeletal muscle in HF lead to abnormal performance during exercise, objectively seen as reduced strength and and endurance and subjectively felt as the sensation of fatigue. The abnormal muscle causes an enhanced muscle reflex to exercise, which further promotes an excessive ventilatory response subjectively perceived as breathlessness\textsuperscript{31,70}. The metabolic derangements of HF are more likely to be manifested during rhythmic than dynamic exercise because isotonic exercise is more metabolically “costly” in comparison to isometric exercise\textsuperscript{29}. This explains the different responses of the metabo-receptor response between studies with static or dynamic exercise. Chronic overactivity of the muscle reflex may be responsible for the chronic sympathetic activation seen in HF state.

The next question arising is if the muscle alterations observed in HF can be solely attributed to the decreased peripheral perfusion (and limitation of muscle use (de-training) by HF patients). In normal subjects undergoing de-training there is little evidence of the fibre type shift seen in heart failure, and also since the HF muscle changes are seen in small muscles unlikely to be affected by disuse\textsuperscript{31}. Therefore, a systemic cause for the heart failure myopathy has been suggested. Heart failure has been proposed to be a multisystematic rather than a purely “hemodynamic” disease. Weight loss (affecting muscles, fat and bone) is lost early in the course of HF (cardiac cachexia) and is associated with worse prognosis\textsuperscript{45}. A shift in the anabolic – catabolic balance towards catabolism has been incriminated in this process. Several mechanisms can be involved in this shift: for example sympathetic stimulation is catabolic causing glycolysis and lipolysis\textsuperscript{46}. Also, in HF there is insulin resistance, growth hormone resistance\textsuperscript{47} and an increase of the ratio of cortisol/ dehydroepiandrosterone, which are all catabolic conditions. This shift in anabolic/catabolic balance may be due to continuous low grade haemodynamic stress. In summary, this theory views heart failure as a chronic, low grade catabolic process leading to skeletal muscle myopathy. As the stress endures, the increased muscle reflex stimulates sympathetic system, which in turn worsens left ventricular function in a vicious circle. The decreased muscle performance results in fatigue, whereas the increased sympathetic drive increases respiratory drive leading to breathlessness\textsuperscript{31}.

An interesting question with clinical implications is how exercise training can ameliorate the adverse symptoms of HF. Data from human and animal studies have shown that training causes an increase in the capillary density\textsuperscript{48}, the number of mitochondria\textsuperscript{49}, the concentration of oxidative enzymes\textsuperscript{49}, and an increased ability to extract oxygen\textsuperscript{50} and utilize glycogen\textsuperscript{51}. In a study performed in this laboratory, it was shown that the sympathetic activation (assessed by microneurography) during handgrip was far less in athletes (body builders) than in controls\textsuperscript{52}. This, together with the results of other studies show that physical conditioning has beneficial effects mediated by a reduction of the activity of muscle (metabo-) reflex\textsuperscript{53}. Other deranged autonomic mechanisms in HF like decreased heart rate variability can also be improved by physical training. It has been shown that exercise ameliorates the autonomic dysfunction by increasing the parasympathetic component of heart rate variability. Overall, physical training partially reverses the detrimental mechanisms in HF, and therefore, training packages in the routine care of HF patients should be encouraged.

**Muscle reflex and hypertension**

The SNS is clearly involved in the regulation of blood pressure (BP) and in the development of hypertension. However, the precise links between sympathetic tone and blood pressure regulation are not well understood. Sympathetic nerve activity recorded by electrodes placed in the peroneal nerve (microneurography technique) shows elevated frequency and intensity of bursts in hypertensive subjects compared to controls (i.e. increased sympathetic output)\textsuperscript{54} (Fig. 4). The direct rise in the sympathetic tone of the kidney and/or the production of hormones (like angiotensin II, which are partly controlled by the autonomous nervous system) produce a resetting of the renal BP-natriuresis relationship to higher levels of BP\textsuperscript{55}. This theory integrates the classic Guyton model (pressure-natriuresis relationship)\textsuperscript{30} with the central regulating role of the SNS.

The components of the neural network that regulate basal sympathetic tone include the rostral
ventrolateral medulla (RVLM), in the hypothalamus (the paraventricular nucleus) and the nucleus of the solitary tract (NST). This core sympathetic network is regulated by many classes of sensory afferent nerves. These afferents include: a) the baroreceptors and other mechanoreceptors from the cardiopulmonary region which project to the NST and b) afferents that detect several physical parameters like muscle stretch, tissue hypoxia and metabolites which project to the spinal cord and from there they integrate in the RVLM or the NST. Several substances (angiotensin II, IL-1) influence the central neural network directly or through release of endothelial factors (NO, prostaglandins) that cross the blood brain barrier. Moreover, virtually every component of the central network is influenced by the brain angiotensin system, by radical oxygen species and possibly other mechanisms.

Although there is extensive literature on the function of baroreceptors in hypertension, there is a relative paucity of data on the mechanisms of fine regulation of central SNS by the muscle mechano- and metabo-efferents in hypertension. There are data showing that during isometric weight lifting the BP can rise as high as 220-330/170-250 mm Hg. Therefore, isometric exercise is contraindicated in patients with proliferative retinopathy to avoid intraocular bleeding or retinal detachment. On the other hand aerobic exercise is usually associated with moderate rise in the systolic BP with no change or even reduction in diastolic BP. This coupled with a large increase in blood flow leads to a reduction in vascular resistance as well as to vasodilatation in the exercising muscle. The activation of the mechanism of muscle reflex in patients with hypertension under static or dynamic exercise is not known.

In hypertension, remodeling of the microvascular vessels occurs, leading to an early functional and afterwards anatomical reduction in the number of arterioles or capillaries in a given vascular bed (capillary rarefaction). Capillary rarefaction induces an increase in blood pressure and a relative decrease in tissue perfusion. Therefore, it has been hypothesized that hypertension is a tissue perfusion disorder. In a recent study, 61 hypertensive patients with three different patterns of capillary rarefaction (mild, moderate, severe) and 20 controls underwent an ergometer exercise test. The microcirculatory functioning before and after exercise was assessed by laser-Doppler flowmetry that measured the reflection beam from circulating blood cells in the capillaries of the skin. During exercise, the BP response was more exaggerated in the group with severe rarefaction. There was also a greater reduction in skin blood flow and a worsening of several hemorheological parameters (blood viscosity, soluble P-selectin etc) in patients with increased baseline capillary rarefaction. In conclusion, the authors stated that in hypertensives capillary rarefaction acted as a vascular amplifier that could increase the hypertensive stimulus of the exercise test leading to an ischemia-like condition. It is not improbable that derangements in the muscle metabolic milieu of exercising muscles of hypertensive patients could cause some alteration in the muscle reflex.

In the only study so far published on the muscle reflex in hypertensives, microneurography was used to record the sympathetic bursts (muscle sympathetic nervous activity - MSNA) during static handgrip and during postexercise circulatory arrest (by inflating an occlusion arm cuff (240 mm Hg) in 18 hypertensives and 22 controls. The main finding was a decrease in MSNA levels during circulatory arrest of the active muscle in the hypertensive patients. This finding shows an attenuation of the muscle metaboreflex, since this type of reflex is elicited by metabolites trapped in muscles during circulatory arrest. The mechanisms of this attenuated response are speculative. A previous study demonstrated that glucose uptake during sympathetic - mediated vasoconstriction was impaired in spontaneously hypertensive rats. This reduction in glucose metabolism can attenuate muscle acidosis during exercise and have as a consequence a decrease in metabo-receptor stimulation.

Apart from the acute changes during exercise, it is known that long-term training programs re-
duce both blood pressure are and sympathetic tone. Another interesting issue is the interaction of salt intake with SNS and blood pressure regulation. A line of evidence has shown that high dietary salt intake is followed by derangements in mechanisms of central sympathoinhibition and tubular sodium handling. It is not known how the sympathetic response driven by muscle reflexes will be modulated under different states of dietary salt intake (high versus low).

In conclusion, there are preliminary data showing that muscle perfusion is abnormal in hypertension, and this may be accompanied by alterations of the muscle reflex and sympathetic tone response during exercise. The paucity of the literature will make this field very appealing for the investigator who is interested in the physiology of exercise and hypertension.

REFERENCES


