Experimental Physiology – *Hot Topic Review*

Muscle afferent contributions to the cardiovascular response to isometric exercise

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The cardiovascular response to isometric exercise is governed by both central and peripheral mechanisms. Both metabolic and mechanical stresses on the exercising skeletal muscle produce cardiovascular change, yet it is often overlooked that the afferent signal arising from the muscle can be modified by factors other than exercise intensity. This review discusses research revealing that muscle fibre type, muscle mass and training status are important factors in modifying this peripheral feedback from the active muscles. Studies in both animals and humans have shown that the pressor response resulting from exercise of muscle with a faster contractile character and isomyosin content is greater than that from a muscle of slower contractile character. Athletic groups participating in training programmes that place a high anaerobic load on skeletal muscle groups show attenuated muscle afferent feedback. Similarly, longitudinal studies have shown that specific local muscle training also blunts the pressor response to isometric exercise. Thus it appears that training may decrease the metabolic stimulation of muscle afferents and in some instances chronic exposure to the products of anaerobic metabolism may blunt the sensitivity of the muscle metaboreflex. There may be surprising parallels between the local muscle conditions induced in athletes training for longer sprint events (e.g. 400 m) and by the low-flow conditions in, for example, the muscles of chronic heart failure patients. Whether their similar attenuations in muscle afferent feedback during exercise are due to decreased metabolite accumulation or to a desensitization of the muscle afferents is not yet known.

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During isometric exercise there is a well-established progressive increase in heart rate, blood pressure and muscle sympathetic nerve activity (Lind *et al.* 1964; Victor *et al.* 1988). This pressor response is controlled by both central and peripheral mechanisms. Central command arises from higher centres of the brain (e.g. the insular cortex) in parallel with motor signals directed to the exercising muscles and acts as a feedforward controller of the cardiovascular system (Goodwin *et al.* 1972; Thornton *et al.* 2002). In addition, type III and IV muscle afferent activity from the exercising muscles provides feedback regarding the mechanical and metabolic conditions within those muscles (Coote *et al.* 1971; McCloskey & Mitchell, 1972; Kaufman & Forster, 1996). Traditionally, type III afferents have been classified as predominantly mechanically sensitive and are therefore commonly known as 'mechanoreceptors'. Type IV muscle afferents are recognized as being more metabolically sensitive and are thus known as 'metaboreceptors' (Mense & Stahnke, 1983; Kaufman & Forster, 1996). However, both type III and IV afferents show a degree of polymodality and may readily respond to either mechanical or metabolic provocation (Adreani & Kaufman, 1998).

Muscle fibre type

For a given level of force production, the fast-twitch fibres produce a greater quantity of metabolites than slow-twitch fibres (Saltin & Gollnick, 1983). It is therefore reasonable to predict a greater pressor response arising from muscle with a higher proportion of fast-twitch fibres. Indeed, Petrofsky & Lind (1980) demonstrated in the cat that the pressor response arising from the predominantly fast-twitch gastrocnemius was greater than that from

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the slow-twitch soleus. Furthermore, selective activation of muscle fibre type using anodal and pharmacological blockade altered the pressor response (Petrofsky & Lind, 1980; Petrofsky *et al.* 1981). Contraction of slow-twitch fibres in the gastrocnemius produced an attenuated pressor response in comparison with that elicited by activation of a mixed fibre population or fast-twitch fibres alone in the same muscle. In confirmation of these findings, Wilson *et al.* (1995) used chronic low-frequency electrical stimulation of the tibial nerve in the rabbit to convert the predominantly fast-twitch gastrocnemius into a slow-twitch muscle. It was found that as the muscle slowed and its oxidative capacity increased there was an attenuation of the pressor response to isometric exercise. This again suggests that muscle fibre type has a profound effect on the magnitude of the afferent feedback during exercise.

Contrary to these clear findings in animals, the scientific literature concerning the relationship between muscle composition and the pressor response in man is more contradictory. This can largely be explained by three factors. Firstly, the use of voluntary exercise may allow central command to 'top up' attenuated muscle afferent feedback (e.g. Frisk-Holmberg *et al.* 1983; Leonard *et al.* 1985; Sadamoto *et al.* 1992). Secondly, in some studies biopsy samples were taken from muscles other than those exercised; for example, Frisk-Holmberg *et al.* (1983) exercised handgrip muscles and biopsied the vastus lateralis, arguing that the fibre type distribution in both muscle groups would be similar. Thirdly, the relative exercise intensity required to occlude circulation through a muscle depends upon the anatomical location of the muscle and in some locations the mass of active muscle (see Muscle mass section). White & Carrington (1993) ruled out the contribution of central command by using electrically evoked contractions. They compared the cardiovascular responses to exercise in groups of young and elderly subjects during 2 min of involuntary electrically evoked contractions of the ankle plantar flexors and elbow flexors. Ankle plantar flexors, shown to contract more slowly in the elderly subjects, elicited an attenuated diastolic blood pressure increase in elderly subjects compared with the younger subject group. However, the diastolic blood pressure response to electrically evoked contractions of the elbow flexors, in which there was no age-related difference in twitch contraction time, was the same in both groups. Therefore, the attenuated pressor responses produced by the plantar flexors might be explained by an altered peripheral input dependent upon the relative area of fast-twitch fibres. In further experiments, where blood flow was controlled by performing the exercise with local muscle ischaemia, muscle biopsies were taken from the exercised calf muscles (Carrington *et al.* 1995). A significant association between fast isomyosin composition and the magnitude of the cardiovascular changes to electrically evoked calf plantar flexion was shown.

In man, when central command and muscle blood flow are controlled, the influence of muscle fibre type on muscle afferent feedback is clearly revealed. It is also possible that there is a difference in the sensitivity and distribution of muscle afferents around fast and slow fibres (Mitchell *et al.* 1983). Though unlikely, since in mixed muscle fast-twitch and slow-twitch fibres are found next to each other, this possibility has not been fully investigated.

Muscle mass

The importance of muscle mass for the magnitude of the pressor response to isometric exercise is controversial. Lind *et al.* (1964) argued that the magnitude of the changes in blood pressure and heart rate was unrelated to the size of the active muscle but closely related to the relative intensity of contraction. This is now well accepted (e.g. Coote *et al.* 1971; Iwamoto & Botterman, 1985) and many researchers agree that muscle mass is unrelated to the magnitude of the pressor response (Freychuss, 1970; Davies & Starkie, 1985; Williams, 1991; White & Carrington, 1993; Grucza *et al.* 1994). Others, however, argue that muscle mass is an important contributor to the magnitude of the pressor response. McCloskey & Streatfield (1975) demonstrated that the pressor response elicited by electrical stimulation of both hindlimbs of anaesthetized cats was greater than that produced by stimulation of one hindlimb. Later, in humans, Mitchell *et al.* (1989) examined the pressor responses to isometric contractions performed at 40% maximal voluntary contraction (MVC) by the fingers (digits II and III), forearm (handgrip), knee extension and handgrip with simultaneous knee extension. A significant effect of muscle mass was found on the increase in heart rate and blood pressure. These findings were supported by Seals *et al.* (1983) and Seals (1989), who demonstrated that the increase in muscle sympathetic nerve activity (MSNA) produced during isometric handgrip exercise was greater (by 40–70%) during two-handed exercise at 30% MVC than with either arm exercising alone.

A possible limitation of the studies of Mitchell *et al.* (1983), Seals *et al.* (1983) and Seals (1989) may be that each exercise protocol involved a number of muscles. As shown by Barcroft & Millen (1939) and Humphreys & Lind (1963), the blood flow to different muscles is occluded at different percentages of maximum force. Therefore, especially during whole-body exercise, such as the dead lift, some muscles would be expected to be working ischaemically, so the magnitude of the metaboreflex would be greater. Under these conditions muscle blood flow, not muscle mass, would become the overriding factor governing the magnitude of the pressor response. Additionally, in exercise protocols that involve a number of active muscles it cannot be certain that each was activated at

the specified percentage of maximal force. Some muscles might have been contracting at higher relative tensions than reported, e.g. the forearms in a dead lift. This would mean that they would be producing more metabolites and subsequently eliciting a greater metaboreflex response than intended.

Freund *et al.* (1978) investigated the contribution of afferent feedback by occluding circulation to various muscle masses following exercise and found that the maintained elevation in mean arterial blood pressure (MAP) was muscle mass dependent. However, interpretation of this study is confounded by an inconsistent prescription of exercise intensity, possible continued metabolite efflux during postexercise circulatory occlusion (PECO) and progression from smaller to larger muscle masses in all experiments.

When the confounding affects of blood flow are controlled, it appears that muscle mass has little effect on the magnitude of the pressor response. In a study by Williams (1991), subjects performed forearm and quadriceps exercise at 70% MVC to fatigue. Importantly, at this intensity the blood flow to both muscle groups would be expected to be occluded. No significant difference was found between the blood pressures or heart rates at fatigue elicited by the forearm or quadriceps muscles. In studies where the confounding effects of central command are controlled, evidence also suggests that there is little effect of muscle mass on the cardiovascular responses to exercise. Davies & Starkie (1985) removed central command by using electrically evoked contractions at 30% MVC for 2 min and compared the cardiovascular responses of the biceps brachii and the triceps surae. No difference was found between the blood pressure responses between the two muscle groups despite the difference in mass. In summary, the effect of muscle mass on muscle afferent feedback, if present, is likely to be mediated through a combination of variance in intramuscular pressure and blood flow, and differences in central command and muscle fibre recruitment at the same relative exercise intensity in different muscles.

Elevated intramuscular pressure

It has been demonstrated that in animal studies mechanical deformation of the receptive fields of some afferents, by prodding (Kaufman & Forster, 1996) or venous distension (Haouzi *et al.* 1999), has increased their discharge and the resulting pressor response. In human subjects McClain *et al.* (1993) examined whether oedema, which increases interstitial volume and by extrapolation interstitial pressure, will augment the pressor response. Isometric handgrip exercise was performed with and without venous congestion (oedema) produced by inflation of a cuff, proximal to the forearm, inflated to 90 mmHg. MSNA was found to be significantly greater during exercise with venous congestion. During PECO, however, MSNA was not significantly different with venous congestion. In addition, ^{31}P-NMR showed that venous congestion did not alter pH or diprotonated inorganic phosphate but did increase subject's perception of effort. They concluded that venous congestion had sensitized the muscle mechanoreceptors, thus augmenting MSNA and the pressor response and concomitantly increasing the sensation of fatigue. These findings may have implications for chronic heart failure (CHF) patients, in whom chronic fatigue and exercise intolerance are common complaints, which are augmented by oedema.

In contrast to the findings of McClain *et al.* (1993), Baum *et al.* (1993) found that the pressor response to isometric calf exercise was attenuated by lower limb venous congestion, whilst it was augmented by local extracellular volume reduction. This may indicate that extracelluar volume changes can affect ischaemic exercise metabolite concentration without altering intramuscular pressure increase in the calf because its vascular bed is more distensible than the forearm. Alternatively, the assumption that increased limb extracellular volume is indicative of an increased intercellular volume may not be the case.

An alternative method of increasing intramuscular pressure is to employ external muscle compression. Williamson *et al.* (1994) demonstrated that compression of resting leg muscles, induced through antishock trouser inflation, could elicit increases in arterial and diastolic pressures but not heart rate. This response was eliminated by epidural anaesthesia; therefore, the authors concluded that the responses were reflexly mediated through stimulation of mechanoreceptors. Similarly, McClain *et al.* (1994) demonstrated that isometric handgrip with forearm compression at 110 mmHg augmented the increase in MSNA when compared to handgrip without compression. However, Williamson *et al.* (1994) did not consider the possibility of metabolite accumulation within the ischaemic muscle during the extended muscle occlusion and subsequent stimulation of muscle metaboreceptors. Indeed, blood pressure fell markedly when the circulatory occlusion to the thighs was removed, despite continued antishock trouser inflation. Furthermore, blood pressure did not increase when the thigh cuffs were re-inflated. Therefore, it is possible that the blood pressure increase was due to a metabolic stimulus. It is also a possibility that compression cuff inflation stimulates both skin mechanoreceptors and pain receptors. However, this is unlikely because Ubolsakka (2001) showed that local skin anaesthesia had little effect on the cardiovascular responses to muscle compression.

The influence of muscle mechanoreceptor activation on baroreflex sensitivity has been studied in man using external muscle compression during and after isometric exercise (Carrington *et al.* 2003) or during low-level involuntary exercise (which does not activate

the muscle chemoreflex; Iellamo *et al.* 1997). In these experiments baroreflex sensitivity is decreased during muscle mechanoreflex activation, which appears to be linked to an inhibition of cardiac vagal outflow (Gladwell & Coote, 2002). A 'purer' method of selective muscle mechanoreceptor activation, which more closely mimics the mechanical stresses placed on the muscle during exercise, is muscle stretch. Gladwell & Coote (2002) demonstrated that 1 min of passive stretch of the human triceps surae caused an increase in heart rate without a change in blood pressure. Respiratory-related heart rate variability, an index of cardiac vagal activity, was also reduced at this time. Murata & Matsukawa (2001) demonstrated that passive stretch of the cat triceps surae caused a sustained withdrawal of cardiac vagal activity, whilst cardiac sympathetic nerve activity was transiently increased. Taken together, both animal and human studies suggest that the main effect of muscle mechanoreflex activation is an inhibition of cardiac vagal tone. Thus it seems that the result of muscle mechanoreceptor activation on the cardiovascular system is similar to that of central command and indeed both act in parallel during exercise, particularly at the onset, to produce a rapid and sustained increase in heart rate.

Recent findings from our laboratory are that the cardiovascular response to stretch-induced muscle mechanoreflex activation is independent of the level of metaboreflex activation in that same muscle group (Fisher *et al.* 2004). This is in contrast to the findings of White & Bell (2003), who demonstrated that a standard level of external compression produced a progressively augmented blood pressure response when the muscle metaboreflex was progressively elevated. It appears that increasing metabolite accumulation may sensitize mechanically sensitive muscle afferents responsive to external compression, but not those sensitive to stretch (Fig. 1).

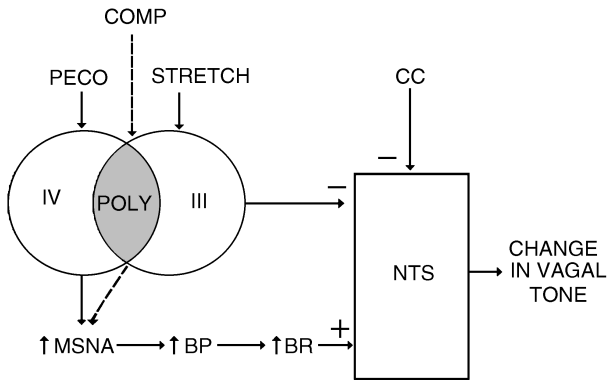

Figure 1. Possible pathways of muscle afferent activation by postexercise circulatory occlusion (PECO), compression and muscle stretch and the resultant cardiovascular change
The net change in vagal tone is dependent upon the magnitude and sign of the inputs to the nucleus tractus solitarii (NTS). IV, muscle metaboreceptors; III, muscle mechanoreceptors; Poly, polymodal muscle afferents; CC, central command; MSNA, muscle sympathetic nerve activity; BP, blood pressure; BR, baroreflex; –, inhibitory effect; +, excitatory effect; dashed lines, putative mechanism for the effect of compression.

Training

Training studies have provided some insight into the plasticity of resting and exercising heart rate, blood pressure and MSNA, with equivocal results. Several studies have argued that whole-body training has little effect on the autonomic nervous system at rest or during exercise (Svedenhag *et al.* 1984; Seals, 1991). For example, Seals (1991) found no differences in the cardiovascular responses to three types of acute physical stress in highly endurance-trained athletes compared to untrained control subjects. Furthermore, Saito *et al.* (1993) found no significant differences between MSNA responses produced by the dominant and non-dominant arm in either isometric or dynamic exercise in racket sport players. This is surprising because the metabolic profiles (Saltin *et al.* 1976) and motor recruitment patterns (Sale, 1987) of the dominant and non-dominant limbs might be expected to lead to a delay in metabolite accumulation and reduction of the muscle metaboreflex in the dominant arm.

Contrary to the findings of Seals (1991) and Saito *et al.* (1993), Somers *et al.* (1992) demonstrated that unilateral handgrip training decreased the MSNA response to isometric handgrip in normal human subjects, which persisted during PECO. Furthermore, Mostoufi-Moab *et al.* (1998) demonstrated that ischaemic forearm training reduced the mean arterial pressure, venous lactate and the pH response to isometric exercise. Thus, the attenuated muscle metaboreflex could be accounted for by a reduction in metabolite accumulation. Alternatively, Sinoway *et al.* (1989) suggested that the blunting of the MSNA response by forearm training might be due to an alteration in the sensitivity of the muscle afferents. Fatiguing ischaemic handgrip exercise in the dominant arm was found to produce an increase in MSNA that was over twice as great in untrained subjects compared to weightlifters. However, the fall in pH was greater in the weightlifters, suggesting that the attenuated MSNA response was due to a desensitization of the metabolically sensitive muscle afferents caused by their chronic exposure to the products of anaerobic metabolism. Furthermore, Carrington *et al.* (1999) demonstrated that during electrically evoked exercise, where central command is absent, 400 m runners experienced an attenuated blood pressure response when compared to that elicited in 100 and 200 m sprinters. As in the weightlifters, the training regime of the 400 m sprinters, with very high, chronic exposure to the products of anaerobic metabolism, may have caused a reduction in the muscle afferent input to the pressor

response. In a longitudinal study from the same laboratory Fisher & White (1999) demonstrated that 6 weeks of calf-raise training significantly attenuated the diastolic blood pressure response to ischaemic electrically evoked isometric contraction (by 27%). By analogy to the effect of chronic capsaicin pretreatment of the nasal mucosa and subsequent attenuation of the hypertensive response produced by exposure to capsaicin (Lundblad *et al.* 1984; Joyner, 1992), it might be hypothesized that a similar change occurs in skeletal muscle afferents in relation to repeated exposure to low pH. Chronic exposure to muscle acidosis induced, for example by weightlifting or 400 m running, could attenuate the afferent response to a reduction in pH.

In summary, it appears that the effect of training on the pressor response and MSNA depends largely on what type of training is performed. With whole-body training, there appears to be little effect on MSNA (Seals, 1991). With local muscle training, however, the MSNA response to exercise can be attenuated (Somers *et al.* 1992; Mostoufi-Moab *et al.* 1998). This may be due to a decrease in metabolite production (Mostoufi-Moab *et al.* 1998) or a desensitization of either chemically or mechanically sensitive muscle afferents (Sinoway *et al.* 1989; Carrington *et al.* 1999).

Disease and deconditioning

At the other end of the activity spectrum from athletic groups are patient populations whose activity patterns are limited by disease, such as in CHF and those with chronic obstructive pulmonary disorder. CHF is a complex syndrome, in which left ventricular dysfunction leads to pathophysiology in other organs, producing characteristic symptoms of breathlessness, exertional fatigue and exercise intolerance. Typically, atrophy of skeletal muscle and a shift towards faster fibre types (Massie *et al.* 1987) occurs, causing an early dependence on anaerobic metabolism and excessive intramuscular acidification during exercise (Sullivan *et al.* 1988), which leads to increased fatigability. Parallels could be drawn between the skeletal muscles of a heart failure patient and of a healthy subject working at maximal exercise intensity. In both, aerobic exercise is limited by insufficient cardiac output. Thus, the importance of the muscle metaboreflex and mechanoreflex in CHF patients is a hotly debated topic.

It has been hypothesized that the increased reliance on anaerobic metabolism in CHF patients and the subsequent chronic sympatho-excitation and vasoconstrictor response during exercise could lead to a persistent and adverse increase in afterload exerted on the left ventricle. This has been termed the 'muscle hypothesis' of chronic heart failure (Coats *et al.* 1994). This theory proposes that an increase in the afferent feedback arising from the active skeletal muscle, or 'exaggerated ergoreflex', links the symptoms of CHF. Piepoli *et al.* (1996) demonstrated that CHF patients showed greater muscle afferent activity than control subjects as evidenced by significantly elevated ventilation, diastolic blood pressure, heart rate and vascular resistance during PECO. After 6 weeks training afferent activity was decreased to a greater extent in CHF patients than in control subjects, so that during the PECO phase of the experiment there was no significant difference in the measured variables between the subject groups. It was concluded that training could decrease the exaggerated muscle afferent activity demonstrated in CHF patients.

Contrary to the hypothesis of an exaggerated reflex arising from the muscle afferent in CHF patients, Sterns *et al.* (1991) argued that a desensitization occurred. The MSNA response of CHF patients and age-matched controls was not different during static handgrip exercise; however, during PECO, CHF patients demonstrated a pronounced MSNA attenuation. Since intramuscular hydrogen ion accumulation was not different between the groups during PECO, a desensitization of the muscle metaboreflex was hypothesized. Additionally, Carrington *et al.* (2001) argued for a desensitization of the muscle mechanoreflex in CHF patients, because they found that the pressor response during electrically evoked isometric exercise of the calf was attenuated in CHF patients when compared with age-matched controls, but not during PECO. Since central command was inactive during exercise and the PECO response indicates that the metaboreflex was equal, a decreased mechanoreflex was indicated.

Despite the potential for differences in the afferent feedback arising from the active muscles in CHF patients, Scott *et al.* (2002) argued that the muscle metaboreflex is systemically overactive in CHF patients. Interestingly, when the magnitude of the muscle metaboreflex is compared during PECO following standardized isometric calf and forearm exercise in CHF patients, an attenuated response is elicited from the calf muscles (Carrington *et al.* 2004). This finding indicates that, contrary to the contention of Scott *et al.* (2002) of a systemically overactive metaboreflex in CHF patients, muscle fibre type or the typical activity pattern of the weight-bearing calf muscles can produce a muscle group-specific attenuation of the metaboreflex arising from the calf muscles. However, along with altered afferent input in CHF there may also be changes in the way that feedback from the periphery is processed in the brain (Zucker *et al.* 2004).

The differences between these studies may be due to the different muscle groups used and specifically the training status and fibre types of these muscles. As in the weightlifter (Sinoway *et al.* 1989) and 400 m sprinter (Carrington *et al.* 1999), the chronic low-exercise blood flow routinely experienced by the CHF patient's muscle may cause a

chronic exposure to the products of anaerobic metabolism and a desensitization of their muscle afferents.

A general limitation of the studies discussed above is that measurements of muscle interstitial pH and metabolites were not made. Without this information, a definite conclusion cannot be reached as to whether desensitization of the muscle afferent has occurred or there is a decrease in metabolic byproduct accumulation during exercise.

Conclusion

From this review of the literature it is clear that during isometric exercise the afferent feedback from active muscle can depend upon the skeletal muscle fibre type, muscle group and training status of the muscle exercised. It is important that future studies control for the confounding effects of muscle blood flow and central command when examining the importance of muscle afferent feedback. Provided that this is done, the powerful and varying role of muscle afferent feedback in human cardiovascular control will be revealed.

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