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Autonomic control of the heart during exercise in humans: role of skeletal muscle afferents

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NEW FINDINGS

1. What is the Topic of this review?

The autonomic nervous system plays a key role in bringing about the cardiovascular responses to exercise necessitated by the increased metabolic requirements of the active skeletal muscle. The complex interaction of central and peripheral neural control mechanisms evoke a decrease in parasympathetic activity and an increase sympathetic activity to the heart during exercise.

2. What advances does it highlight?

This review presents some of the recent insights provided by human studies into the role of mechanically and metabolically sensitive skeletal muscle afferents in the regulation of cardiac autonomic control during exercise

ABSTRACT

The autonomic responses to exercise are orchestrated by the interactions of several central and peripheral neural mechanisms. This short report will focus on the role of peripheral feedback from skeletal muscle afferents in the autonomic control of the heart during exercise in humans. Heart rate responses to passive calf stretch are abolished with cardiac parasympathetic blockade, indicating that the activation of mechanically sensitive skeletal muscle afferents (muscle mechanoreceptors) can inhibit cardiac parasympathetic activity and likely contribute to the increase in heart rate at the onset of exercise. Recent experiments show that the partial restriction of blood flow to the exercising skeletal muscles, to augment the activation of metabolically sensitive skeletal muscle afferents (muscle metaboreceptors) in humans, evokes an increase in heart rate that is attenuated with β_1-adrenergic blockade thus suggesting that this response is principally mediated via an increase in cardiac sympathetic activity. Heart rate remains at resting levels during isolated activation of muscle metaboreceptors with post-exercise ischemia following handgrip; unless cardiac parasympathetic activity is inhibited, whereupon a sympathetically mediated increase in heart rate is unmasked. During post-exercise ischemia following leg cycling exercise heart rate appears to remain elevated due to withdrawal of parasympathetic tone and/or the activation of sympathetic activity to the heart. Although the importance of skeletal muscle afferent feedback to the autonomic control of the heart during exercise is incontrovertible, the complexity of cardiac sympathetic-parasympathetic interactions and the absence of direct intraneural recordings in humans mean that it remains incompletely understood.

Introduction

The autonomic nervous system plays a key role in bringing about the cardiovascular responses to exercise necessitated by the increased metabolic requirements of the active skeletal muscle. Exercise is accompanied by a well established reduction in cardiac parasympathetic activity and increase in sympathetic activity to the cardiac, renal and splanchinc regions that together increase heart rate, stroke volume and cardiac output, and facilitates the redistribution of blood flow to the active skeletal muscles (Mitchell, 1990). Such autonomic responses to exercise are orchestrated by the interactions of several central and peripheral neural mechanisms. The parallel activation of somatomotor centres and autonomic nuclei of the brainstem (e.g., nucleus tractus solitarius) referred to as 'central command' provides a feed-forward coupling of skeletal muscle contraction and adjustments in cardiovascular control (Krogh & Lindhard, 1917; Goodwin *et al.*, 1972). In addition, group III and IV afferents converge on autonomic nuclei within the brainstem and provide sensory feedback in response to mechanical (mechanoreflex) and metabolic (metaboreflex) perturbation within the exercising muscle (Coote *et al.*, 1971; McCloskey & Mitchell, 1972; Kaufman *et al.*, 1996). The arterial baroreceptors, cardiopulmonary baroreceptors and carotid chemoreceptors also modulate autonomic nervous system activity during exercise (Raven *et al.*, 2006; Stickland *et al.*, 2008; Fadel & Raven, 2012). This broad topic has been the subject of several comprehensive reviews (e.g., (Mitchell, 1990; Kaufman *et al.*, 1996; Murphy *et al.*, 2011)) therefore the present article will provide a focused report on recent advances in our understanding of the role of skeletal muscle afferents in the autonomic control of the heart during exercise in humans.

Autonomic control of heart rate during exercise

The autonomic nervous system contributes to the regulation of cardiac chronotropic, inotropic and lusitropic function. Given that it is not possible to make direct intraneural recordings of cardiac autonomic efferent activity in humans our understanding of the autonomic control of heart rate during exercise in humans is largely based on the results of investigations utilizing heart rate variability analyses and/or administration of pharmacological agents to antagonise cardiac autonomic receptors. The strengths and weaknesses of these experimental approaches at rest and during exercise have been discussed extensively elsewhere (Casadei *et al.*, 1995), but one pertinent limitation is that using either it is challenging to elucidate the true complexity of reciprocal sympathetic-parasympathetic interactions (e.g., excitatory facilitation, accentuated antagonism).

Using separate and combined β-adrenergic blockade (propranolol) and cholinergic blockade (atropine) in four young subjects, (Robinson *et al.*, 1966) provided early experimental evidence to suggest that withdrawal of cardiac parasympathetic activity is principally responsible for the cardiac acceleration observed during low intensity dynamic exercise, and that increases in sympathetic activity are principally responsible for further increases in heart rate once exercise becomes more strenuous. The initial heart rate response to exercise has also been shown to be atropine sensitive suggesting that it is mediated by cardiac parasympathetic withdrawal (Freyschuss, 1970). Such findings are in part supported by studies employing heart rate variability analyses, in which exercise intensity-dependent reductions in indices of cardiac parasympathetic activity have been identified at both the onset and during steady-state exercise (Arai *et al.*, 1989; al-Ani *et al.*, 1996). However, the utility of heart rate variability analyses in assessing cardiac sympathetic activity, particularly during exercise, remains controversial (Casadei *et al.*, 1995).

Central command and cardiac autonomic control

Central command is traditionally viewed as mediating the increase in heart rate at the onset of exercise (Krogh & Lindhard, 1917). In an influential study (Mitchell *et al.*, 1989) reported that the augmented increase in heart rate observed during attempted static handgrip with partial neuromuscular blockade to enhance central command, was significantly reduced by cardiac parasympathetic blockade (from 15 to 4 $b \cdot min^{-1}$) but was not affected by β-adrenergic blockade. The concept that the withdrawal of cardiac parasympathetic activity due to the activation of central command elicits the initial heart rate response to exercise and the cardiac acceleration observed during low and moderate intensity exercise has recently been challenged. In an elegant series of studies using direct recordings of cardiac efferent activity in cats Matsukawa and colleagues have observed that cardiac sympathetic activity increases rapidly at the onset of low intensity treadmill exercise in conscious animals (Tsuchimochi *et al.*, 2002) and during spontaneous fictive motor activity in paralysed animals decerebrated at the level of the precollicular-premammillary body, while cardiac parasympathetic activity remained unchanged (Kadowaki *et al.*, 2011). However, further studies are required to better understand whether such alterations in autonomic regulation are unique to the experimental models utilised and whether hitherto the contribution of cardiac sympathetic nerve activity to the initial heart rate response to exercise in humans has been underappreciated.

Muscle mechanoreceptors and cardiac autonomic control

Notwithstanding the importance of central command to the heart rate response to muscular contraction its presence is not requisite. Indeed, a rapid increase in heart rate is evoked

during electrically stimulated contractions (Krogh & Lindhard, 1917; Coote *et al.*, 1971; McCloskey & Mitchell, 1972) where peripheral feedback is present, but the parallel activation of somatomor and cardiovascular centres is missing (i.e., central command is bypassed). Almost instantaneous decreases in cardiac parasympathetic activity (McMahon & McWilliam, 1992) and increases in sympathetic activity (Matsukawa *et al.*, 1994; Tsuchimochi *et al.*, 2002; Tsuchimochi *et al.*, 2009) are elicited by static contraction evoked using ventral root stimulation in decerebrate cats. In humans a brief (5 s) electrically evoked contraction of the biceps brachii elicits an increase in heart rate that is more pronounced when triggered during expiration than during inspiration, suggesting that muscle afferent feedback inhibits cardiac parasympathetic activity (al-Ani *et al.*, 1997). The distinct contributions made by mechanically and metabolically sensitive skeletal muscle afferents is difficult to precisely determine using electrically evoked contractions, although given the rapidity of the autonomic responses a role for muscle mechanoreceptors is likely. Indeed, (Williamson *et al.*, 1995) observed that passive limb movement combined with electrical stimulation evoked an instantaneous shortening of the R-R interval providing the movement began in the first 1/3 of the cardiac cycle.

Selective activation of mechanically sensitive skeletal muscle afferents in anaesthetised animals using hindlimb stretch elicits a brief increase in sympathetic activity and a longer lasting decrease in parasympathetic activity to the heart (Matsukawa *et al.*, 1994; Murata & Matsukawa, 2001). Sustained passive stretch of the triceps surae in humans also elicits a transient increase in heart rate (~5-6 $b \cdot min^{-1}$) (Gladwell & Coote, 2002). This manoeuvre also reduces a heart rate variability derived index of cardiac parasympathetic activity (i.e., standard deviation of successive differences in R-R interval) during the first 20 cardiac cycles of application. Furthermore, in a subsequent report these investigators showed that the heart rate response to

passive calf stretch was virtually abolished by administration of a muscarinic cholinergic blocker, implying that muscle mechanoreceptor activation elicits an increase in heart rate by inhibiting cardiac parasympathetic activity (Gladwell *et al.*, 2005).

The firing rate of mechanically sensitive muscle afferents during muscular contraction may be potentiated by ischemia or the presence of bradykinin, arachidonic acid, ATP or cyclooxygenase products (Kaufman *et al.*, 1996; Murphy *et al.*, 2011). We investigated if the cardiovascular response to calf muscle stretch is augmented when performed with concurrent elevation of muscle metabolites (Fisher *et al.*, 2005). Contrary to expectation the heart rate response to calf stretch was independent of the presence of muscle metabolites. In contrast, the modest increase in muscle sympathetic nerve activity elicited by passive wrist extension is augmented the concentration of muscle metabolites is elevated (Cui *et al.*, 2008). This is perhaps indicative of the differential effects of muscle mechanoreceptor activation on autonomic outflow to the heart and skeletal muscle vasculature. However, passive muscle stretch is reported to activate a population of afferent fibres of which less than half are engaged by static muscular contraction (Hayes *et al.*, 2005).

Muscle metaboreceptors and cardiac autonomic control

The contribution of metabolically sensitive skeletal muscle afferents to the regulation of cardiac autonomic activity during exercise in humans is not as well elucidated as its role in the sympathetic regulation of the skeletal muscle vasculature (Mark *et al.*, 1985). This is likely in part a consequence of the experimental approaches used to investigate it. As originally described by (Alam & Smirk, 1937), the two main approaches used to examine the muscle metaboreflex have been to, 1) occlude or partially reduce the blood flow to the exercising skeletal muscle, and

2) occlude the circulation to the active muscles just prior to the cessation of exercise and maintain the occlusion during exercise recovery (post-exercise ischemia). In the first manoeuvre the hypoperfusion induces a mismatch between oxygen delivery and demand such that exercise-induced metabolites accumulate and activate metabolically sensitive skeletal muscle afferents, whilst central command and muscle mechanoreceptors are also activated. In the second manoeuvre exercise-induced metabolites are trapped within the quiescent muscle and thus the muscle metaboreceptors are activated without concurrent central command and muscle mechanoreceptor activation. While blood pressure and sympathetic vasoconstrictor outflow are elevated above resting levels during either manoeuvre (Mark *et al.*, 1985; Victor *et al.*, 1987), whether the muscle metaboreflex is activated during or after exercise has a major influence on the resultant heart rate response. When muscle metaboreflex activation is evoked during exercise a notable increase in heart rate is elicited (O'Leary, 1993; Fisher *et al.*, 2013); however with isolated muscle metaboreflex activation during post-exercise ischemia heart rate typically returns toward resting levels following static leg extension (Iellamo *et al.*, 1999) or handgrip (Mark *et al.*, 1985; Nishiyasu *et al.*, 1994; Fisher *et al.*, 2010). Such findings imply that the autonomic control of the heart is differentially modified during these manoeuvres.

(O'Leary, 1993) demonstrated that the increase in heart rate elicited by partial restriction of terminal arterial blood flow in dogs exercising on a treadmill was significantly attenuated following β-adrenergic blockade, although the response was not completely abolished. In contrast, the heart rate response was unaffected by cardiac parasympathetic blockade. In humans, (Iellamo *et al.*, 1999) proposed that the muscle metaboreflex increases a heart rate variability derived index of cardiac sympathetic activity during static knee extension exercise. However, leg cycling with experimental flow restriction reduces indices of cardiac parasympathetic activity

derived from heart rate variability and cardiovagal baroreflex sensitivity analyses (Hartwich *et al.*, 2011). Given these conflicting findings in humans and to better understand the influence of muscle metaboreflex activation during dynamic exercise on the autonomic control of the heart we examined the cardiovascular responses to moderate intensity leg cycling with partial flow restriction under control conditions, and with β_1-adrengeric blockade and cholinergic muscarinic blockade (Fisher *et al.*, 2013). As anticipated enhanced muscle metaboreflex activation during leg cycling with partial flow restriction increased heart rate and while this was unaffected by parasympathetic blockade, it was attenuated with β_1-adrengeric blockade by ~50%. Thus, it seems that the chronotropic response to muscle metaboreflex activation with partial flow restriction principally occurs via an increase in sympathetic activity. However, the failure of β-adrenergic blockade to completely abolish the heart rate response partial flow restriction in either dogs or humans hints at the potential for the muscle metaboreflex to inhibit cardiac parasympathetic activity under certain circumstances. Administration of intrathecal fentanyl to block muscle afferent feedback has recently been shown to attenuate heart rate during moderate-to-high intensity voluntary leg cycling (Amann *et al.*, 2010). This is presumably attributable to a reduction in cardiac sympathetic activity; however alterations in parasympathetic activity cannot be definitively excluded.

Given that the muscle metaboreflex can increase cardiac sympathetic activity, it is intriguing that several studies have reported that heart rate remains at resting levels during post-exercise ischemia where muscle metaboreflex is isolated (Mark *et al.*, 1985; Nishiyasu *et al.*, 1994; Fisher *et al.*, 2010). A potential explanation for this observation is that at the cessation of exercise there is a reactivation of cardiac parasympathetic activity which overpowers the potential sympathetically mediated increase in heart rate by the metaboreflex (O'Leary, 1993;

Nishiyasu *et al.*, 1994; Iellamo *et al.*, 1999; Fisher *et al.*, 2010). Such a reactivation of cardiac parasympathetic activity may occur due to the removal of inhibitory inputs from central command (Mitchell *et al.*, 1989) and the muscle mechanoreceptors (Gladwell *et al.*, 2005) and/or a baroreflex mechanism. In support of this proposition (O'Leary, 1993) demonstrated that following cardiac parasympathetic blockade heart rate remained elevated during post-exercise ischemia following treadmill running in dogs, presumably due to an unmasking of a muscle metaboreflex mediated increase in cardiac sympathetic nerve activity. In humans, (Nishiyasu *et al.*, 1994) reported that a time domain heart rate variability index of cardiac parasympathetic tone (i.e., standard deviation of successive differences in R-R interval) was elevated during post-exercise ischemia. In contrast, (Iellamo *et al.*, 1999) observed that another index of cardiac parasympathetic tone (i.e., high frequency heart rate variability) was unchanged from rest during post-exercise ischemia, although an index of cardiac sympathetic activity was elevated (i.e., low frequency heart rate variability). To more directly evaluate the influence of the muscle metaboreflex on cardiac autonomic control we examined the heart rate response to post-exercise ischemia following low and moderate intensity handgrip under control conditions and with β-adrenergic and muscarinic cholinergic blockade (Fisher *et al.*, 2010). Cardiac parasympathetic blockade unmasked a modest elevation in heart rate during post-exercise ischemia following low intensity handgrip under control conditions (no drug), indicative of a muscle metaboreflex mediated increase in cardiac sympathetic activity. During post-exercise ischemia following moderate intensity handgrip a small elevation in heart rate was observed which was abolished with β-adrenergic blockade, indicating that with robust muscle metaboreflex activation increases in cardiac sympathetic activity can prevail over the reactivation of cardiac parasympathetic activity. Of note, we observed that following cardiac parasympathetic blockade heart rate fell

from end-exercise levels (~30 b·min^{-1} above rest) during post-exercise ischemia (~9 b·min^{-1} above rest). This is in contrast to the findings of (O'Leary, 1993) where in dogs, atropine maintained the end-exercise heart rate during post-exercise ischemia following treadmill running. This might suggest that the exercise induced increase in heart rate elicited by augmented cardiac sympathetic activity in humans is not wholly attributable to the muscle metaboreflex, and perhaps points to a contribution from central command and/or muscle mechanoreceptors. In support of this idea (Tsuchimochi *et al.*, 2009) have identified that both central command and muscle mechanoreceptors can increase cardiac sympathetic nerve activity in decerebrate cats.

The effects of isolated muscle metaboreflex activation with post-exercise ischemia on heart rate appear to depend on the exercise modality utilized. (Alam & Smirk, 1938) demonstrated that heart rate remained significantly elevated during post-exercise ischemia following dynamic calf plantar flexion exercise performed with both legs, whereas during post-exercise ischemia following forearm exercise heart rate returned to resting levels. To investigate whether the elevation in heart rate observed during isolated muscle metaboreflex activation is attributable to sympathetic activation and/or parasympathetic withdrawal we have utilized both heart rate variability analyses and autonomic blocking agents. The elevation in heart rate during post-exercise ischemia following leg cycling exercise was found to be accompanied by a reduction in heart rate variability derived indices of cardiac parasympathetic nerve activity (Hartwich *et al.*, 2011). Intriguingly, this elevation in heart rate was maintained with either β-adrenergic or cardiac parasympathetic blockade, indicating that either sympathetic activation or parasympathetic withdrawal may increase heart rate in these conditions (Fisher *et al.*, 2013) and again highlights the complexity and redundancy of the autonomic control of the heart during

exercise. Furthermore, (Kjær *et al.*, 1999) observed that electrically induced cycling in individuals with spinal cord injury elicited an increase in heart rate that was abolished by the inflation of thigh cuffs to occlude the circulation to the lower limbs. Such findings indicate the potential importance of temperature and/or hormones (e.g., adrenaline) on the heart rate responses to exercise.

Conclusion

Accumulating evidence in humans suggests that along with central command the muscle mechanoreceptors inhibit cardiac parasympathetic activity and increase heart rate at the onset of exercise and during low intensity steady-state exercise. Recent experiments suggest that the activation of metabolically sensitive skeletal muscle afferents (muscle metaboreceptors) with partial flow restriction to the exercising skeletal muscles evokes an increase in heart rate that is attenuated with β_1-adrenergic blockade, but unaffected by cardiac parasympathetic blockade. This suggests that under these conditions the heart rate response is principally mediated via an increase in cardiac sympathetic activity. During isolated activation of muscle metaboreceptors with post-exercise ischemia following moderate intensity handgrip, heart rate remains at resting levels, unless cardiac parasympathetic activity is inhibited whereupon a sympathetically mediated increase in heart rate can be unmasked. However, during post-exercise ischemia following leg cycling exercise heart rate may remain elevated due to withdrawal of parasympathetic tone and/or the activation of sympathetic activity to the heart. In light of recent work in animals, additional studies in humans are required to better understand the control of cardiac sympathetic activity by the muscle mechanoreceptors and central command with particular reference to the influence of exercise intensity and phase (e.g., onset, steady-state).

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