PERSPECTIVES

Metaboreflex control of the heart

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The cardiovascular responses to exercise include cardioacceleration and vasoconstriction. When the exercise is static, such as that performed during weightlifting, these responses are comprised of relatively large increases in arterial blood pressure caused by sympathetic vasoconstriction, and small increases in cardiac output caused by increases in heart rate. The relatively large increases in arterial pressure are believed to improve perfusion of muscles whose statically contracting fibres compress blood vessels. When the exercise is dynamic, such as that performed during running, the cardiovascular responses are comprised of small or no increases in arterial blood pressure, caused by sympathetic vasoconstriction and countered by metabolic vasodilatation, as well as by large increases in cardiac output caused by large increases in heart rate. The relatively large increases in cardiac output are believed to improve perfusion of working muscles which, when in the relaxation phase of their duty cycles, allow blood to flow through them.

Regardless of the type of exercise performed, the cardiovascular response to it is caused by neural mechanisms, which include central command, the exercise pressor reflex and the baroreflex. Central command is defined as the parallel activation of motor, autonomic and ventilatory circuits in the brain at the onset of exercise. Central command is not dependent on sensory input from exercising muscles, and its anatomical locus is believed to include the posterior hypothalamus (Eldridge *et al.* 1981). The exercise pressor reflex is initiated by metabolic and mechanical stimuli in contracting muscles that stimulate group III and IV afferents (Mitchell *et al.* 1983). The contribution of each neural mechanism to the cardiovascular response to exercise has been the subject of considerable investigation in both humans and animals. These investigations have yielded three conclusions. The first is that the baroreflex is suppressed during exercise, with both central command and the exercise pressor reflex contributing. The second is that central command at the onset of exercise increases heart rate by withdrawing vagal input to the heart, and the third is that during low to moderate levels of exercise that the exercise pressor reflex increases the sympathetic outflow to the vascular beds of the skeletal muscles. The role played by central command in evoking this increase in sympathetic outflow is only apparent at intense levels of exercise (Victor *et al.* 1995).

The metabolic component of the exercise pressor reflex has received particular attention because it is thought to provide an error signal to the central nervous system that blood supply to the working muscles in not adequate to meet metabolic demand. In humans, the role played by metabolic stimuli in evoking sympathetic vasoconstriction is well established (Victor *et al.* 1989), whereas the role played by metabolic stimuli in evoking any of the cardioacceleration is controversial. The metabolic component can be isolated and studied by occluding both the arterial inflow and venous outflow of an exercising limb by inflating a cuff placed around the limb to suprasystolic pressure. When this is done and the muscles are no longer contracting, metabolites produced by the contracting muscles are trapped within their circulation. These metabolites in turn exert a stimulatory effect on the thin fibre muscle afferents evoking the metabolic component of the exercise pressor reflex. As there is no contraction, there is no central command; likewise, there is no mechanical stimulus to the exercise pressor reflex, and as a consequence any cardiovascular effects are presumed to be evoked by metabolic stimuli and are reflex in origin.

In humans, the role played by the metabolic component of the exercise pressor reflex in the control of heart rate is controversial. Often, post-exercise ischaemia, initiated by inflating a cuff to suprasystolic pressure, increases both arterial blood pressure and muscle sympathetic nerve activity over baseline (i.e. resting) levels, but does not increase heart rate. These findings have led to the conclusion that the metabolic component of the exercise pressor reflex (called the metaboreflex) has no effect on heart rate.

In this issue of *The Journal of Physiology*, Fisher *et al.* (2010) have provided some fascinating data in humans that challenges this conclusion. Two aspects of the experiments by Fisher *et al.* were particularly significant, and which, in combination, have been notably absent from previous studies performed on humans. The first is that the authors employed two levels (25 and 40% of maximum voluntary contraction) of static handgrip exercise, and consequently two levels of post-exercise ischaemia, and the second is that the authors used autonomic blocking agents. Fisher *et al.* found that the cardioacceleration evoked by post-exercise ischaemia at both levels of handgrip exercise was significantly attenuated by β-adrenergic blockade, but was not attenuated by muscarinic blockade. These findings provide strong evidence that the muscle metaboreflex accelerates the heart by increasing sympathetic input to it. In addition, these findings confirm and extend to humans previous findings by O'Leary (1993) in dogs.

The use of established autonomic blocking agents by Fisher *et al.* is laudable, and contrasts with the reliance of other investigators on computational measures to assess parasympathetic and sympathetic input to the heart. The use of these measures is controversial (Taylor & Studinger, 2006), and one can speculate that they are used because of their convenience. One limitation of the study, and one which is recognized by the authors, is that the use of post-exercise ischaemia is an artificial intervention that rarely occurs in healthy people. Metaboreceptors are probably influenced by mechanical factors occurring in exercising muscles, and the removal of these factors is likely to underestimate the contribution of these afferents to the reflex responses observed. Despite this limitation, the experiments performed by Fisher *et al.* are an important advance, clarifying the role played by metaboreceptors in evoking the cardiac sympathetic component of the exercise pressor reflex.

References

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DOI: 10.1113/jphysiol.2010.189241

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