PERSPECTIVES IN PHYSIOLOGY

Sympathetic nerves continue to regulate blood flow in exercising muscles

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In humans, rhythmic exercise like running or cycling causes an increase in total systemic vascular conductance as a result of vasodilatation in the contracting skeletal muscles. At the same time, mean arterial pressure increases modestly. How do these two physiologically 'contradictory' events occur? First, cardiac output rises as a result of increased heart rate and stroke volume. Second, there is sympathetically mediated vasoconstriction in 'non-exercising' skeletal muscle and also in the renal and splanchnic vascular beds. However, a number of questions remain concerning the extent to which sympathetic nerves regulate blood vessels in the active muscles during exercise. The paper by Puvi-Rajasingham *et al.* (1997) in this issue of *The Journal of Physiology* highlights a variety of related issues and also provides definitive insight into a number of them.

The authors studied the arterial blood pressure, cardiac output and visceral blood flow responses in patients with neurogenic orthostatic hypotension during mild supine cycle exercise. When these patients exercised, mean arterial pressure fell in spite of the fact that cardiac output appeared to rise normally. Additionally, no major differences in visceral blood flow were seen between control subjects and individuals with autonomic denervation. These latter findings, along with the fact that visceral beds contribute only a small fraction of the total vascular conductance during exercise, challenge the older suggestion that inadequate vasoconstriction in the splanchnic and renal vascular beds is the 'cause' of hypotension during exercise in these patients. Therefore, a lack of sympathetic vasoconstrictor 'restraint' of blood flow to the active muscles must contribute to the fall in pressure during exercise in the patients. This observation challenges the long-held belief that vascular conductance in exercising muscles is governed exclusively by the release of local vasodilatory factors.

The previously held view was that factors released by the active muscles have two important roles in vascular control during exercise (for discussion see Rowell, 1997). First, they cause local vasodilatation. Second, they limit the ability of vasoconstrictor nerve traffic to regulate vascular tone in the dilated vessels. While several lines of evidence from isolated preparations can be interpreted to favour this second concept, other evidence suggests that vasoconstriction in active muscles must be present. During exercise of a small muscle mass, vasodilatation far in excess of that seen during large muscle mass exercise is observed and blood flow values of $\sim$250 ml (100 g)$^{-1}$ min^{-1} can be seen (Andersen & Saltin, 1985). If this dilatation were extended to 20 kg of muscle, either a cardiac output in excess of 50 l min^{-1} would be needed or the resultant vasodilatation would overwhelm the capacity of the heart to pump blood and arterial pressure would fall during dynamic exercise. Thus, sympathetic restraint of vasodilatation in active muscles is necessary for the maintenance of arterial pressure during large muscle mass rhythmic exercise in humans (Rowell, 1997). The fall in blood pressure seen during mild supine exercise in the autonomic failure patients demonstrates the clinical relevance of this concept.

There is other evidence for sympathetic 'restraint' of blood flow to active muscles in humans. These include the fact that both directly mediated muscle sympathetic nerve activity and noradrenaline spillover to active muscles can increase during exercise and the observation that limiting sympathetic outflow to active muscles raises vascular conductance in the muscle (Rowell, 1997).

Several important issues remain to be resolved with the concept of sympathetic restraint of vasodilatation in active skeletal muscles (Rowell, 1997). What regulatory mechanisms govern sympathetic outflow to active skeletal muscles? One possibility is that chemosensitive afferents in the active muscles are stimulated by muscle metabolites and evoke a reflex increase in sympathetic outflow to the active muscles. While the neural pathways for such a scheme are well known, this 'muscle chemoreflex' might have the paradoxical effect of actually causing vasoconstriction in skeletal muscle that is already 'under-perfused' and metabolically stressed. Additionally, there is evidence that sympathetic 'restraint' occurs prior to a build-up of the metabolites known to stimulate the chemosensitive afferents. Another hypothesis is that the arterial baroreflexes operate to limit any mismatches between cardiac output and vascular conductance so that arterial pressure remains regulated during whole body exercise. This idea is attractive and relies on well-known reflex mechanisms; however, direct experimental evidence to support it is not yet available in humans.

In addition to these two mechanisms it also appears that dilatory substances from active muscles can interfere with sympathetic α_2-mediated postsynaptic vasoconstriction in the skeletal muscle microcirculation (Thomas *et al.* 1994). Since α_1-receptors appear to predominate upstream in skeletal muscle arterioles, and α_2-receptors downstream in the arterioles closest to the tissue, this means that α_1-mediated vasoconstriction might limit the increase in total blood flow to the active muscles, but that competition between dilatory substances and α_2-receptors in close proximity to the active muscle fibres might operate to distribute flow towards the most 'metabolically stressed' areas within a given active muscle. This scheme would permit both sympathetic restraint of blood flow to active 'muscles' while optimizing the distribution of blood flow within the muscle to the most metabolically active fibres. Understanding how sympathetic restraint of blood flow to active muscles contributes to arterial pressure regulation and simultaneously optimizes blood flow within a given muscle is an important emerging question.

The paper by Puvi-Rajasingham and colleagues (Puvi-Rajasingham *et al.* 1997) also highlights the continued importance of patient-oriented research and integrative physiology in the era of molecular biology and reductionism (Goldstein & Brown, 1997). Patients with a variety of diseases are likely to continue to provide important 'experiments in nature' that will permit us to understand better the integrative contribution of various micromechanisms and factors that are being identified on a daily basis with reductionist tools. For this mass of information to be either intellectually satisfying or clinically useful it will have to be integrated into a coherent scheme by systems physiologists.

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