

## HIGHLIGHTED TOPIC | *Skeletal and Cardiac Muscle Blood Flow*

For more than 100 years, it has been known that exercise increases blood flow to the myocardium and active skeletal muscles, and a number of underlying mechanisms have been proposed to govern this response. This *Highlighted Topic* series on “Skeletal and Cardiac Muscle Blood Flow” reviews these mechanisms and discusses them in several contexts. In the July through September 2004 issues, this series will feature original research and invited mini-reviews that will address the issues associated with this very stimulating area of investigation.

In the July issue, in a *Historical Perspective* article entitled “Ideas about control of skeletal and cardiac muscle blood flow (1876–2003): cycles of revision and new vision,” Dr. L. Rowell briefly examines the origins of key ideas central to the major issues addressed in each of the six mini-reviews in this series. Such issues concern how metabolic, mechanical, and neural (reflex) controls might act to regulate skeletal and cardiac muscle blood flow by reinforcing or opposing effects, especially in the case of reflex control of muscle vascular conductance and arterial blood pressure during dynamic exercise. An important lesson revealed by this article is that “older” original ideas, which are often disputed, have persistent value and that we can use such ideas as a foundation to build and advance our understanding of skeletal and cardiac muscle blood flow.

In a mini-review entitled “Vasodilatory mechanisms in contracting skeletal muscle,” Drs. P. Clifford and Y. Hellsten explore the complex and perplexing problem of identifying the mechanism or vasoactive compound responsible for initiating vasodilatation in skeletal muscle. Several vasoactive compounds, and several cellular sources of these compounds, are found in skeletal muscle, vascular endothelium, and red blood cells. However, identifying a single vasodilatory mechanism capable of responding rapidly enough to explain the prompt increase in blood flow at the onset of exercise has been a particularly difficult problem. Because metabolic processes are too slow to account for the initial blood flow response, it seems that the mechanism or vasoactive compound that initiates vasodilation is different from that which sustains it. Numerous inhibitor studies have been performed to date, but none of the compounds studied thus far appears to be essential for exercise hyperemia, as the effect of one vasodilator can generally be blocked without affecting a change in blood flow. Nevertheless, these observations do not exclude the possibility of redundancy, such that the lack of effect of one vasodilator could be explained by a compensatory effect of another.

Also in the July issue, in a mini-review entitled “Matching coronary blood flow to myocardial oxygen consumption,” Dr. E. Feigl and colleagues review several mechanisms that have been proposed to control coronary blood flow. Cardiac contraction is dependent on adequate supply of oxygen from coronary blood flow. Interrupting coronary blood flow causes contraction in the affected cardiac segment to cease after only a few beats. At rest, the myocardium extracts ~75% of the oxygen delivered by coronary blood flow, leaving little reserve capacity. Therefore, because myocardial oxygen consumption increases severalfold during the tachycardia associated with exercise, coronary blood flow must also increase. Although

sympathetic  $\beta$ -adrenoceptors are known to mediate feed-forward coronary vasodilation during exercise, the powerful local metabolic mechanism of vasodilation in the coronary circulation remains unknown.

In the August issue, in a mini-review entitled “Neural control of muscle blood flow during exercise,” Drs. G. Thomas and S. Segal review the progress made toward understanding the neural control of circulation in exercising muscle. Specifically, these investigators examine the interaction between vasodilation generated by somatic nerve activity and vasoconstriction induced by sympathetic nerve activity, as well as how this interaction regulates blood flow distribution to exercising muscle. During dynamic exercise, increases in somatic motor nerve activity are accompanied by increases in skeletal muscle blood flow that are graded to the metabolic demands of active muscles. Exercise is also a potent stimulus for sympathetic vasoconstrictor nerve activity, which can paradoxically reduce muscle blood flow. The interaction between somatic vasodilation and sympathetic vasoconstriction plays an essential role in the integrated cardiovascular response to exercise, and this interaction has intrigued physiologists for more than 70 years. Disrupting this interaction is detrimental and may contribute to the exercise intolerance observed in such disease states as hypertension and heart failure.

Also in the August issue, in a mini-review entitled “Immediate exercise hyperemia: contributions of the muscle pump vs. rapid vasodilation,” Drs. M. Tschakovsky and D. Sheriff describe the physics of blood flow and the muscle pump theory. These investigators examine evidence both for and against the muscle pump, concluding that muscle contractions appear to be capable of elevating blood flow independently of causing vasodilation and that this mechanism is contraction frequency, but not intensity, dependent. These investigators also examine evidence for rapid vasodilation and conclude that vasodilation can occur “immediately.” A critical area of exploration is that of vasodilation induced by muscle mechanical distortion, which results in smooth muscle cell hyperpolarization. It appears that, although the muscle pump and rapid vasodilation can act in concert at the onset of exercise, the relative contribution of each is dependent on exercise mode and conditions. Considerable controversy exists among the views regarding mechanisms that underlie blood flow elevation at the onset of exercise. This mini-review clarifies the most recent evidence and offers direction for further research.

In the September issue, in a mini-review entitled “Integrative control of the skeletal muscle microcirculation in the maintenance of arterial pressure during exercise,” Drs. M. Delp and D. O’Leary highlight the integration of central and local cardiovascular control mechanisms involved in the regulation of skeletal muscle blood flow and vascular conductance during dynamic steady-state exercise. Although skeletal muscle receives the largest fraction of cardiac output during high-intensity exercise, the muscle retains a vasodilator reserve capable of producing further elevations in blood flow and vascular conductance. Reflex-mediated increases in sympathetic nerve activity impose limits on muscle perfusion, preventing large elevations in muscle vascular conductance from leading to a fall in arterial pressure. Understanding the coor-

dinated control of cardiac output and peripheral vascular conductance in the maintenance of arterial pressure during exercise provides unique insight into how the cardiovascular system responds to physical stresses and how failures of key regulatory processes could adversely affect arterial pressure regulation and tissue homeostasis.

Also in the September issue, in a mini-review entitled "What makes blood vessels grow with exercise training?," Dr. R. Terjung explores angiogenesis during exercise. During exercise and muscle contraction, increased blood flow velocity enhances shear stress within vessels, thereby stimulating vasodilation as well as structural remodeling of the vasculature. In the absence of contraction, increased blood flow within skeletal muscle enhances capillarity by intussusceptive angiogenesis, by which intraluminal longitudinal division causes capillary splitting. Sprouting angiogenesis, in contrast, occurs during adaptation to chronic muscle contraction and/or muscle overload and depends on extensive endothelial cell proliferation and degradation of extracellular matrix to permit migration and tube formation. Recent investigations have identified hemodynamic and mechanical stimuli responsible for upregulating angiogenesis and have illustrated the complex nature of the interactions between growth factors and their receptors. Additionally, such studies have detected an interaction between

cellular signaling events and have identified tissue reorganization processes, coordination of which is vital to vascular remodeling. The findings of such studies almost certainly relate to the vascular remodeling response to exercise and muscle contraction.

The articles featured in this *Highlighted Topics* series bring us up to speed with respect to what has become known, and what remains unknown, about skeletal and cardiac muscle blood flow in light of over 100 years of investigation. This series also seeks to integrate events occurring at the molecular level with events occurring in the systemic circulation. Finally, this series demonstrates how ideas in science come, go, and return to prominence. With these thoughts as background, the coming years promise to be an exciting time for investigations that attempt to uncover the mechanisms that govern skeletal and cardiac muscle blood flow. The Associate Editors and I hope that the work featured in this *Highlighted Topic* series serves to encourage the submission of future work addressing this very important area of investigation to the *Journal of Applied Physiology*.

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