Does arterial myogenic tone determine blood flow distribution in vivo?

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Blood flow distribution at rest and during exercise is intricately controlled by centrally driven neuroeffector mechanisms and circulating hormones (particularly epinephrine), local autacoids, and metabolites, all superimposed on the inherent or “myogenic” reactivity of the arterial smooth muscle. During exercise, the cardiac output of a trained athlete can increase ~5-fold, and these mechanisms serve to coordinate a huge (~20-fold) increase in the amount of blood routed to the exercising muscle (3). The dramatic nature of this increase is illustrated by the fact that the proportion of the cardiac output diverted to skeletal muscle can change from 20% to ~80%! Importantly, and to the benefit of the individual, despite this enormous increase in the flow of blood to muscle, brain blood flow is not compromised (3). But to what extent do the inherent characteristics of the arteries of the brain and musculature explain these distinct changes?

As cerebral arteries are not particularly responsive to the sympathetic nerves surrounding them, myogenic reactivity is thought to be a fundamental determinant of the constant flow of blood to the brain and, as a consequence, has been extensively studied. The most direct studies have assessed how changes in intraluminal pressure links to smooth muscle contraction/relaxation in isolated arteries, where reflex and most local influences are absent and steady-state conditions can be achieved. It is technically extremely difficult to make intracellular recordings from the very small (<10 μm width) smooth muscle cells, particularly in isolated arteries under physiological pressure. However, a now classic study in 1984 by Harder (13) first showed that increasing pressure alone caused depolarization and as a result stimulated Ca^{2+} influx and vasoconstriction. Unfortunately, technology at the time did not allow accurate simultaneous measurement of diameter. This was achieved in later studies, notably from Nelson’s group (19), as the complexity of the myogenic control mechanism became apparent. It is now known that voltage-activated calcium entry is not the only mechanism responsible for changes in myogenic tone (16) and that the relative contributions from different mechanisms vary between and within vascular beds.

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Kotecha and Hill (21) are the latest to attempt the extremely difficult task of quantifying the exact nature of the dilator factors that are active during exercise (26). Stimulation of endothelial cell purinergic receptors evokes dilation that can spread upstream through the wall of arteries/arterioles and against the direction of blood flow (termed “spreading dilation”) (9, 22). In addition, an increase in vas-

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cular endothelial cell Ca\(^{2+}\) observed in response to muscle fiber contraction (7, 23) could stimulate endothelial cell Ca\(^{2+}\)-activated K\(^+\) channels (K\(_{Ca}\)), which would also evoke spreading dilation [similar to that observed with focally applied acetylcholine (6, 27)]. Overall, the reduction in resistance evoked by these mechanisms would increase blood flow to a localized area of low PO\(_2\) and thus help to balance flow with metabolic demand (18, 27, 28). Thus the ability of a hyperpolarizing stimulus readily to cause local dilation, but also to evoke extensive spread of that dilation, would work together to enhance overall blood flow to an exercising muscle.

Part of the reason why muscle blood flow can increase to such a large extent during exercise, particularly when compared with the relatively small change in the overall flow of blood to the brain, reflects the structure of arteries (14) and differences in activation of their intrinsic regulatory mechanisms. By comparing the active diameter of the muscle and cerebral arteries in response to stepwise increases in luminal pressure (10–100 mmHg), Kotecha and Hill (21) suggest that striated muscle arteries appear to have a much wider dynamic range for myogenic responsiveness. They then show that large-conductance Ca\(^{2+}\)-activated K\(^+\) channels (BK\(_{Ca}\)) have less influence in modulating resting membrane potential and thus diameter in the muscle arteries. The BK\(_{Ca}\) channels are important modulators of systemic blood pressure, because in BK\(_{Ca}\) β1-subunit knockout mice, resting blood pressure (measured in conscious mice) is quite elevated (2, 25). Interestingly, resting myogenic tone in cerebral arteries isolated from β1-subunit knockout mice is greater than those from control mice (2). In contrast, the addition of a selective inhibitor of BK\(_{Ca}\), iberiotoxin, to rat cremaster arteries failed to depolarize and contract these vessels much, and far less than in cerebral arteries, especially at the higher pressures (20, 21). Considering the steep relationship between active tone and membrane potential in the muscle arteries (21), the effect of iberiotoxin may be critically determined by the resting intraluminal pressure. Hence, the ability of iberiotoxin to depolarize and contract arteries at 40 mmHg (resting membrane potential approximately −45 mV) should be greater than at the pressure of 70 mmHg (resting membrane potential approximately −38 mV). But at the lower pressure, active myogenic tone is minimal (smooth muscle cells are less depolarized and have lower intracellular Ca\(^{2+}\) concentration), so BK\(_{Ca}\) would tend to be less active, minimizing their overall contribution. These data are consistent with observations in the cremaster microcirculation in vivo, where inhibition of BK\(_{Ca}\) does not alter resting diameter (17) but does augment contraction to raised PO\(_2\) (arteries likely more depolarized?) In cerebral arteries, it appears that the BK\(_{Ca}\) are more active at pressures >40 mmHg (at which pressure active tone is higher than in cremaster arteries), and resting membrane potential more depolarized than −53 mV. From rough calculations based on Kote et al. (20), iberiotoxin causes increases in cerebral myogenic tone to a level similar to that in the cremaster arteries (−60% passive diameter). However, quantifying this relationship precisely will require a more systematic study, to include membrane potential recording at different pressures in the presence of iberiotoxin, and excluding the potential variables that might be associated with gender, age, etc., of rats.

Thus it appears that the differential activation of BK\(_{Ca}\) reported in cerebral arteries cannot in itself explain the inherent differences in myogenic response seen in muscle arteries (especially at lower pressures). However, there are obviously a host of other candidates that may have an influence, for example, the relative formation of intracellular 20-HETE and other cytochrome P-450 metabolites; the role of other K\(_+\) channels such as K\(_{ATP}\) channels; the mechanisms for Ca\(^{2+}\) signaling, including the ability of Ca\(^{2+}\) sparks to activate BK\(_{Ca}\) channels and thus dilation; plus other mechanisms controlling diameter that are not necessarily influenced by membrane potential (reviewed in Refs. 5 and 16). However, from a purely empirical standpoint, the fact that blood vessels within themselves have evolved differentially to help regulate their inherent basal tone and in so doing help to match blood flow delivery to survival in distinct settings is an intriguing level of complexity. The late Neela Kotecha, through her elegant and technically demanding studies, did much to unravel these complexities.

**REFERENCES**


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