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 Ca2+ 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 importance of membrane potential for myogenic reactivity, but this time in a resistance artery from a striated muscle bed (the rat cremaster muscle, pressurized arteries with a passive diameter of ~140 μm at 70 mmHg). This is the first study in a muscle resistance artery that has attempted to assess the effect of a stepwise increase in luminal pressure on smooth muscle membrane potential and arterial diameter. In addition, the authors have compared their data with published data from rat isolated cerebral arteries [distal posterior, passive diameter of ~200 μm at 70 mmHg (19)] to attempt to reveal how closely arteries from vascular beds with quite distinct roles may or may not share the mechanisms responsible for myogenic tone.

Of course, a key question is “What are the physiological pressures in each bed?” While we cannot answer this absolutely, measurement of arterial pressure in anesthetized animals has shown that the pressure at small cerebral arteries [including 180-μm feline pial arteries (10)] is only about 50–60% of systemic (14). In contrast, even in skeletal muscle arteries and arterioles with diameters <100 μm, the pressure is still 75–95% of systemic [a staggering 90–95% in 70- to 100-μm feline tenuissimus muscle arteries! (11)] (14). However, it is not known what these relative pressures are during exercise, such delicate measurements not being feasible in moving tissue.

Given these approximate values for pressure in vivo, and a mean systemic blood pressure of ~100 mmHg (15), what would the corresponding arterial smooth muscle membrane potential be in the respective vascular beds? These values must be estimated, as there are no available direct measurements in rat distal posterior cerebral or cremaster arteries. However, by using data from isolated arteries (19, 21), the predicted values would be near −45 mV (at 60 mmHg) in the cerebral artery and −37 mV (at 80 mmHg) in the muscle arteries. At these (nonexercise resting) levels, active myogenic tone (defined as the percentage of passive diameter) would be near 40% in cerebral arteries and closer to 50% in the muscle arteries (taken from Ref. 21). In effect, “resting” resistance to blood flow would be somewhat greater in the muscle arteries, which is of course what we might predict. To put this into some sort of context, based on the present data, a hyperpolarization of 10 mV (e.g., during exercise) would dilate the cerebral artery by only 15%, whereas the cremaster artery would dilate by 50% [taken from Fig. 8 (21)]. So it seems difficult to deny the conclusion that the intrinsic nature of the arteries underlies the more dramatic increase in blood flow to striated muscle during exercise.

Although direct electrophysiological recording from striated muscle arteries in vivo is difficult, it is possible to see that the arteries and arterioles in the cremaster muscle of anesthetized animals have active tone (which is partly dependent on tissue PO2) (12). Furthermore, arterial diameter and blood flow can be increased by contracting a subset of muscle fibers (1, 12). The exact nature of the dilator factors that are active during exercise is not clear (27). Some data do suggest a key role for arterial hyperpolarization, such as the sensitivity of muscle fiber contraction-mediated dilation to glibenclamide (4, 24), an inhibitor of ATP-sensitive K+ channels (and ABC transporters), and the release of ATP into the lumen of arteries during exercise (26). ATP is released in response to low PO2 [from red blood cells (8, 9)] and may have a key role in regulating tissue perfusion. 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-
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
dilatation [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 Po2 and thus help to balance flow with
metabolic demand (18, 27, 28). Thus the ability of a hyperpo-
larizing stimulus readily to cause local dilatation, but also to
evoke extensive spread of that dilatation, 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 com-
pared 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 mecha-
nisms. 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 impor-
tant modulators of systemic blood pressure, because in BK\(_{Ca}\)
\(\beta_1\)-subunit knockout mice, resting blood pressure (measured in
conscious mice) is quite elevated (2, 25). Interestingly, resting
myogenic tone in cerebral arteries isolated from \(\beta_1\)-subunit
knockout mice is greater than those from control mice (2).
In contrast, the addition of a selective inhibitor of BK\(_{Ca}\), iberio-
toxin, 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
to greater than at the pressure of 70
arteries at 40 mmHg (resting membrane potential approxi-
\text{mately} –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 microcircu-
lization in vivo, where inhibition of BK\(_{Ca}\) does not alter resting
diameter (17) but does augment contraction to raised Po2
(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 Knot 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 (es-
pecially 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 dilatation; 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 them-

selves have evolved differentially to help regulate their inher-
ent 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.

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