Commentaries on Viewpoint: A paradigm shift for local blood flow regulation

TO THE EDITOR: The proposed role of O$_2^-$ produced by NAD(P)H oxidase acting in concert with changes in mitochondrial O$_2$ on regulating local blood flow hypothesized by Golub and Pittman (5) could very well be a contributing factor in the fascinatingly complex biology of the NO pathway. A delayed increase in O$_2^-$ production might explain the frequently observed undershoot in blood flow after reactive hyperemia. However, it is far too simplistic to attribute a major role to a single mechanism, as recognized in my review paper on NO (1) and demonstrated in an earlier mathematical model showing theoretical effects of NO scavenging by O$_2^-$ (4) and more thoroughly discussed in updated reviews (2, 3) for developments that need to be incorporated into mathematical models for NO biotransport. In my view, it is unlikely that a single “set point” for NO flux exists, because many other mechanisms, some of which are dependent on NO whereas others are not, can significantly modify NO-related feedback signaling. Indirect effects of NO, for example by nitrosylation of various signaling proteins, can also alter the sensitivity of blood flow regulation. Furthermore, because NO is known to inhibit the mitochondrial respiration chain and there is evidence in the literature that cytochrome oxidase can act either as an O$_2$ reductase or a NO oxidase, it is difficult to precisely define tissue hypoxia without knowing the extent of metabolic inhibition and net ATP production. A comprehensive, dynamic model for regulating blood flow and metabolism remains to be developed and experimentally verified.

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SKELETAL MUSCLE FUNCTIONAL HYPEREMIA: ROS GENERATION AND REDUNDANT MECHANISMS

TO THE EDITOR: The Bang-Bang model for regulation of local blood flow advanced by Golub and Pittman (2) proposes that the interaction between two signaling radicals (nitric oxide and superoxide) promotes the matching between tissue oxygen delivery and utilization. According to this model, the predominant (if not the sole) mechanism underlying skeletal muscle functional hyperemia is based on diminished superoxide generation after contractions onset, which results in increased nitric oxide bioavailability within the interstitial space. However, it is difficult to envisage such regulation given that a plethora of experimental evidence does not support the core postulates of the Bang-Bang model: 1) intracellular and interstitial superoxide content actually increase during contractile activity (rev. 3); 2) administration of antioxidants (including the superoxide dismutase mimetic tempol) does not increase but rather reduces skeletal muscle blood flow both at rest and during contractions in healthy young animals (1); 3) inhibition of the enzyme nitric oxide synthase does not abolish the hyperemic response (4); and 4) multiple metabolic signals participate in the hyperemic response because the early phases of skeletal muscle arteriolar vasodilation (5). Importantly, the last two findings are also consistent with the notion that substantial redundancy exists in the control of blood flow during transitions in metabolic demand and that the relative importance of distinct vasodilatory signals may vary to facilitate oxygen delivery-utilization matching when one or more mechanisms is altered/impaired. Therefore, at present, compelling experimental evidence refutes the need for a paradigm shift in the regulation of contracting skeletal muscle blood flow.

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REGULATION OF LOCAL BLOOD FLOW

TO THE EDITOR: Quantity of blood flow to tissues is precisely matched to their functional needs by altering the vascular tone of resistance vasculature. Modulation of vascular tone depends, among other factors, on humoral, metabolic, mechanical, paracrine, and endothelial inputs, implying its importance and highly complex nature in the control of local blood flow. Authors (2) corroborate the role NO and O$_2^-$ in local blood flow regulation. In addition to NO, other gases derived from endothelium such as CO and H$_2$S along with endothelium-derived hyperpolarizing factors (EDHF) are reported to cause vasodilation. The exact identity of EDHF is unknown but suspected to be H$_2$O$_2$, K$,^+$, epoxyeicosatrienoic acids, or even electrical signals causing vasodilation (3). Also, epoxyeicosatrienoic (EETs) activates BK$_{Ca}$ channels, whereas H$_2$S activates IK$_{Ca}$ and SK$_{Ca}$ channels, leading to vasodilation (5). To be more accurate, a blood vessel of finite length should be modeled as a nonlinear conduit governed by...
differential model parameters varying with location and tissue type. For example, the inhibition of eNOS decreases blood flow to oxidative fibers more than glycolytic fibers (3). Also a concerted effort by these mediators is required to cause changes in blood flow (3). In some animal models, attenuation in the increased blood flow to a contracting muscle is brought by a simultaneous blockade of KATP channels, adenosine receptors, and NOS (4). Thus, although NO and $O_2^-$ are proved to affect hemodynamics, one should also consider myriad related factors before making a paradigm shift.

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COMMENT ON “VIEWPOINT: A PARADIGM SHIFT FOR LOCAL BLOOD FLOW REGULATION”

Local metabolic regulation of blood flow requires mechanisms to sense oxygen or metabolite levels and to respond by modulating blood flow. Mechanisms for metabolic sensing remain controversial. Tissue hypoxia, i.e., inadequate oxygen supply for oxidative metabolism, with partial pressures $\sim$1 mmHg or less, is often assumed to drive the metabolic signal. This hypothesis is flawed because it implies that flow regulation requires tissue hypoxia (3). Effective regulation without hypoxia requires sensitivity at higher oxygen levels, for which one possible mechanism is oxyhemoglobin saturation-dependent ATP release by erythrocytes (2). Theoretical simulations showed that this may be effective as a sole mechanism in networks with multiple equivalent flow pathways (1) but fails in heterogeneous network structures because of uneven hematocrit partition at diverging bifurcations and formation of plasma channels (4).

Golub and Pittman (3) propose a model based on the balance between endothelial nitric oxide and its neutralization by parenchymal cell superoxide release. This model is attractive, because nitric oxide is a common final pathway for many vasodilatory mechanisms. Moreover, it provides an appealing mechanism to increase the range of responsiveness to hypoxia, because superoxide production by NADPH oxidase is oxygen-dependent and half-maximal at partial pressure $\sim$13 mmHg (5). However, this proposal does not exclude other mechanisms of metabolic regulation, including generation of vasodilator substances in hypoxic regions and ATP release by erythrocytes. Considering the complexity of evolution and the redundacy in many biological systems, we suggest that multiple mechanisms are important in the local metabolic regulation of flow.

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