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VIEWPOINT

Commentaries on Viewpoint: Managing the power grid: How myoglobin can regulate P_{O_2} and energy distribution in skeletal muscle

EXERCISE, MYOGLOBIN, AND P_{O_2}: WHAT LIES BEYOND THE "GRID"?

TO THE EDITOR: A recent article by Clanton (1) highlights an insightful Viewpoint regarding the emerging role of myoglobin (Mb) as an interstitial P_{O_2} (Pi_{O_2}) regulator during exercise by switching from a nitric oxide (NO) consumer to an NO producer. We propose a point of contention that the now well-known role of NO in regulating Pi_{O_2} during exercise may include mechanisms independent of the mitochondrial "power grid." The reduction of nitrite to NO during periods of low-Pi_{O_2} by deoxyMb has been increasingly discussed over the past decade in the context of inorganic nitrate supplementation. Indeed, dietary supplementation of inorganic nitrate (e.g., beetroot juice) increases circulating NO bioavailability through serial reduction facilitated by deoxyMb (4). Here, NO boosts cGMP within arteriolar vascular smooth muscle increasing local Pi_{O_2}. Recent works supporting this notion demonstrated that 8 weeks of inorganic nitrate supplementation improved blood flow and vasodilation (i.e., O_2 delivery) during exercise in patients with peripheral artery disease (3). A second mechanism by which inorganic nitrate supplementation increases Pi_{O_2} may include suppressing α-mediated vasoconstriction during exercise (functional sympatholysis) (2). Previous works by Nelson and colleagues (5) demonstrated a single dose of inorganic nitrate can improve functional muscle oxygenation in patients with ischemia by blunting sympathetic vasoconstriction. Collectively, regulating Pi_{O_2} during exercise may not rest solely on the shoulders of mitochondria, especially in clinical populations. Thus, the role of Mb in regulating Pi_{O_2} via NO during exercise may not be exclusive to skeletal muscle mitochondria and it could be time to think beyond the "grid."

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MANAGING THE POWER GRID: HOW MYOGLOBIN CAN REGULATE P_{O_2} AND ENERGY DISTRIBUTION IN SKELETAL MUSCLE

TO THE EDITOR: Clanton (1) concluded that the role of myoglobin, in the setting of intracellular distribution of mitochondrial function in active myofibers, is to optimize the effectiveness of the mitochondrial reticulum network for generating proton gradients and ATP by tuning regional mitochondrial activity to intracellular P_{O_2} gradients (Pi_{O_2}]. Myoglobin's role in metabolic control must be put in the perspective of the heterogeneity of skeletal muscle fibers and tissue before generalizing conclusions.

During exercise, skeletal muscles are not homogenous with respect to their contribution to the work performed, recruitment patterns, fiber type composition, distribution of blood flow, and $\dot{V}O_2$ (2). Thus it is inappropriate to extrapolate mean tissue measurements (e.g., Pi_{O_2}) to that in a single muscle fiber beyond developing underlying principles (1).

For example, skeletal muscle fibers display heterogeneity in glycogen storage, the predominant fuel source during high-intensity exercise (3). The subsarcolemmal region where Clanton suggests myoglobin directs the highest Pi_{O_2}during high-intensity exercise to facilitate generation of a proton gradient within the mitochondrial "power grid" (1, 4) contains a glycogen store (3). The concept that the proton-motive force is generated by mitochondria in the region with the highest Pi_{O_2}, a glycogen store, and where O_2 and glucose delivery are privileged is intuitively satisfying. However, exercise-induced changes in other regions of the network [e.g., depletion of glycogen within the myofibrils, which alters sarcoplasmic reticulum Ca^{2+} release and muscle contraction (3)] can alter metabolism. These observations suggest that both reductionist and integrative approaches are now needed to unravel the complex and fascinating role of myoglobin in skeletal muscle metabolic control.

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COMMENTARY ON VIEWPOINT: MANAGING THE POWER GRID: HOW MYOGLOBIN CAN REGULATE P_{O_2} AND ENERGY DISTRIBUTION IN SKELETAL MUSCLE

TO THE EDITOR: Oxygen diffusion from the red blood cell (RBC) to skeletal muscle mitochondria is governed by Fick's law: $\dot{V}_{O_2} = D_{O_2} \times \Delta P_{O_2}$; where $\dot{V}_{O_2}$ is oxygen flux, D_{O_2} is the diffusion capacity, and ΔP_{O_2} is the oxygen partial pressure gradient between physiological compartments (i.e., microvascular, interstitial, and intracellular). Increased $\dot{V}_{O_2}$ imposed by muscle contractions is thus determined by commensurate alterations in effective D_{O_2} and/or ΔP_{O_2}. Our recent phosphorescence quenching investigation of both microvascular and interstitial spaces revealed that the transcapillary ΔP_{O_2} seen at rest is largely maintained (rather than increased) during submaximal contractions (2). This indicates that transcapillary $\dot{V}_{O_2}$ is contingent on elevations in effective D_{O_2} in already-flowing capillaries as evidenced previously using intravital microscopy (i.e., ↑ RBC flux, velocity, and hematocrit from rest to contractions) (4). Further down the O_2 transport pathway, reductions in both interstitial (2) and intracellular P_{O_2} (5) during contractions compounded with low attained intracellular P_{O_2} (~2–5 mmHg) (5) minimize the potential of transsarcolemmal ΔP_{O_2} to facilitate O_2 transport into the myocyte. Enhanced D_{O_2} with contractions thus likely drives the bulk of the $\dot{V}_{O_2}$ increase across the sarcolemma. Within the myocyte, it is traditionally considered that O_2 diffusion is facilitated by myoglobin desaturation during contractions, which reduces the so-called "functionally carrier-depleted region," thus enhancing intracellular D_{O_2} (3). The fascinating model advanced by Clanton (1) proposes additional mechanisms by which myoglobin accommodates $\dot{V}_{O_2}$ increases with contractions. However, a concern is that this thesis presumes constant D_{O_2} during contraction transients. Consequently, a hybrid model incorporating the above mechanisms (i.e., including ↑ D_{O_2} with contractions) might reflect better our current understanding of microcirculatory and intracellular O_2 transport.

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COMMENTARY ON VIEWPOINT: MANAGING THE POWER GRID: HOW MYOGLOBIN CAN REGULATE P_{O_2} AND ENERGY DISTRIBUTION IN SKELETAL MUSCLE

TO THE EDITOR: Oxygen exchange between myoglobin and the electron transport chain is a complex and highly regulated interaction, and as Dr. Clanton highlights (2), this level of the oxygen cascade has a marked influence on diffusive oxygen conductance and ultimately exercise capacity. ^{1}H magnetic resonance spectroscopy (MRS) has indeed provided important in vivo, insight into deoxymyoglobin dynamics during exercise (4). Until recently, however, assessment of cytochrome C oxidase activity has remained largely limited to in situ preparations and cellular models. With the advent of broadband near infrared spectroscopy (bb-NIRS), it is now possible to study the redox state of cytochrome C oxidase in vivo (5). NIRS is also known to derive at least part of its tissue saturation signal from myoglobin, potentially addressing some of the limitations associated with large-scale MRS investigations. Finally, diffuse correlation spectroscopy has emerged as a powerful noninvasive tool for the direct assessment of microvascular perfusion (1). Taken together, we contend that by combining bb-NIRS with diffuse correlation spectroscopy and clinically approved methods to manipulate nitrate-nitrite bioavailability (3), the opportunity to translate the intriguing mechanisms described by Dr. Clanton has never been so ripe.

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MYOGLOBIN/MITOCHONDRIA COUPLING—IS THERE A BACKUP? VIEWPOINT ON VIEWPOINT

TO THE EDITOR: Myoglobin (Mb), small monomeric oxygen binding heme protein, is expressed exclusively in heart and skeletal muscle. In his recent Viewpoint (1), Clanton proposes a mechanism of Mb/mitochondria coupling, in which Mb plays vital role in regulation of mitochondrial respiration, serving as a hypoxia sensor and protective switch. In hypoxia, Mb temporary disables respiration chain in more hypoxic regions by halting electron flow on cytochrome c oxidase (CcO) site, using its nitrite reductase activity to produce nitric oxide (NO) that temporary inhibits CcO activity. Because only deoxyMb reduces nitrite, this reaction, followed by CcO-NO binding, selectively protects mitochondria in more hypoxic regions and increases access to oxygen for mitochondria in the regions of highest oxygen availability. Mb structure, its colocalization with mitochondria, and greater abundance in fast oxidative fibers are highly conserved among species. Yet, interestingly, this simple, but sophisticated mitochondria-protecting mechanism is absent from Mb knockout mouse (2) and Antarctic hemoglobin/myoglobin-lacking icefish (3). Neither of these exhibits mitochondrial damage at normoxia, and functional and molecular adaptations in Mb-lacking mouse (4) allow it to support hypoxia without profound mitochondrial damage (5). Increased capillary density and shift toward the higher amount of slow-twitch fiber type, characteristic for Mb knockout mouse, can perhaps be considered a reversal to simpler, but still effective, backup mechanism of protecting mitochondria against stress. It would be interesting to examine possible hypoxic adaptation, if any, caused by disruption of NO/nitrite/nitrate cycle in the skeletal muscle.

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IN VITRO MEASUREMENTS OF MUSCLE OXIDATIVE CAPACITY UNDERESTIMATE IN VIVO VALUES EVEN MORE WHEN THE MITOCHONDRIAL RETICULUM OPERATES REGIONALLY

TO THE EDITOR: Across the upper half of skeletal muscle's expansive dynamic range, the sarcolemma-to-cytochrome oxidase (CcO) O_2 diffusion gradient apparently changes little, implying the diffusion distance is halved as $\dot{V}_{O_2}$ rises toward maximum. Tom Clanton (2) integrates recent discoveries related to myoglobin (Mb) catalytic activity and mitochondrial structure (1, 3) to offer a compelling explanation for this fundamental problem. In his model, Mb senses O_2 availability and modulates CcO activity via nitric oxide (NO). Briefly, rising ATP turnover decreases P_{O_2} in the fiber interior toward the Mb P_{50}, which switches catalytic activity toward NO production and inhibits CcO in the intermyofibrillar region of the reticulum. In turn, cable properties recruit greater electron transport in the subsarcolemmal (SS) region to defend the protonmotive force, as hypothesized decades ago by Skulachev and coworkers (1). Clanton's elegant synthesis is supported by the recent work of Glancy, Balaban, and coworkers, which has substantially extended Skulachev's original findings, in addition to showing a relative concentration of CcO activity in the SS region (3). Thus, Clanton's clever model suggests that a subset of tissue mitochondria should be able to account for in vivo maximum oxidative flux. Unfortunately (for in vitro "mitochondriacs"), even whole tissue mitochondrial content assayed in vitro can account for only slightly more than half of in vivo values (5), despite the observation (4) that isolated mitochondria can generate thermodynamic forces similar to non-invasive in vivo assessments.

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COMMENTARY ON VIEWPOINT: MANAGING THE POWER GRID: HOW MYOGLOBIN CAN REGULATE P_{O_2} AND ENERGY DISTRIBUTION IN SKELETAL MUSCLE

TO THE EDITOR: The discovery of mitochondrial reticulum (MR) network in skeletal muscle puts forward the hypoth-

esis that MR may function to transport oxygen. This model was supported by Glancy et al. (3) who showed that the efficient energy distribution is achieved through the conduction of membrane potential via MR system in myocytes. In this Viewpoint (2), the concept of MR was further discussed in the context of intracellular hypoxia such as during the intense exercise.

We agree that myoglobin may play a critical role in maintaining a relatively constant intracellular P_{O_2} in skeletal muscle by regulating the nitric oxide (NO) levels. NO produced at low P_{O_2} acts as an inhibitor for cytochrome *c* oxidase (CcO), thus preventing the consumption of oxygen (O_2) (1). The electron chain is interrupted at low P_{O_2} regions while kept active at high P_{O_2} regions of MR. This mechanism ensures a relatively uniform P_{O_2} across the muscle fibers and simultaneously increases the efficiency of O_2 utilization.

Myoglobin has shown to be able to generate reactive oxygen species (ROS) in myocytes under low-oxygen conditions (4). Furthermore, the dysfunction of CcO may also exacerbate the electron leakage from the respiratory chain and subsequently the formation of ROS. For instance, Zuo et al. (5) observed ROS burst in the diaphragm in transition to hypoxia. The increased ROS formation may likely be attributed to CcO disruption by NO and comprise myoglobin regulation of both P_{O_2} and energy in myocytes.

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THE IMPORTANCE OF DIFFUSION COEFFICIENT AND TEMPERATURE IN MUSCLE O_2

TO THE EDITOR: According to the Fick's law of diffusion, the flux of a molecule is proportional to its concentration gradient. During exercise, this gradient for muscle oxygen apparently decreases because intramuscular and interstitial values become similar. Hence, how it is possible to explain that, in this condition, the O_2 flow is doubled. To answer this paradox, Clanton (1) offers one elegant model focusing on the role of the myoglobin as sensor and controller of the mitochondrial reticular network. While this presents a fine mechanism from a valid biochemical approach, this model assumes constancy in the diffusion coefficient, which minimizes the role of other physical factors and results in an incomplete picture of this phenomenon. In addition to the O_2 gradient, another factor affecting O_2 diffusion is temperature (2), which changes drastically during exercise (3). Kenny et al. (4) showed in humans that exercise levels as low as 15 min at 60% $\dot{V}_{O_2}$ could generate increases of up to 3°C, which can translate into an increase in diffusion around 11%. It would be expected that at higher duration and values of $\dot{V}_{O_2}$, and according to the depth of the muscle, these changes could have been even higher. In fact, Bentley et al. (5) have been able to show even stronger changes in isolated muscle of hamsters. Of course, Clanton's model and the role of temperature are not mutually exclusive considering that, as recently shown, the temperature is not just changing diffusion coefficient but also the mitochondrial adaptation.

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