Aerobic performance and the function of myoglobin in human skeletal muscle

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THE ROLE OF MYOGLOBIN as an oxygen storage protein in the muscles of diving birds and mammals is well-established (8). In contrast, the function of the lower myoglobin content in striated muscles of humans and other terrestrial vertebrates has long been a subject of debate. In a seminal review published in 1939, Millikan (13) identified three potential functional roles for myoglobin in the aerobic muscles of terrestrial animals: first, “as an agent in oxygen transport”; second, “as an intracellular catalyst”; and third, “as an oxygen store.” Largely by elimination of the first two possibilities, Millikan concluded that myoglobin acted primarily as “a short term oxygen store, tiding the muscle over from one contraction to the next.” This conclusion is consistent with the observation that myoglobin content is higher in more aerobic muscles and is highest in aerobic muscles with long contraction duration (e.g., in muscles of large vs. small quadrupeds) and hence more prolonged impedance of blood flow during contractions.

Millikan dismissed the importance of myoglobin in oxygen transport, in part because it was not clear how “the presence of the pigment in an equilibrium state” of oxygen saturation could aid oxygen transport. However, after the demonstration by Wittenberg (16) in 1959 that myoglobin enhances the diffusive flux of oxygen in vitro, Wyman (18), Wittenberg (17), Kreuzer (9), Murray (14), and others showed that it is precisely the fast, near-equilibrium nature of myoglobin’s binding kinetics, along with its oxygen dissociation constant near the PO2 of active muscle and its high concentration compared with dissolved oxygen, that enables myoglobin to facilitate oxygen diffusion. Subsequent experiments demonstrated that inhibition of myoglobin oxygen binding, for example, with H2O2 (1), decreased maximum oxygen consumption (\(\dot{V}O_2 \text{max}\)) in isolated muscles, and by 1990, the importance of myoglobin to oxygen transport in aerobic muscle was widely accepted. This consensus suffered an apparent setback in 1998, when Garry et al. (5) reported that genetic knockout of myoglobin expression in mice had no effect on exercise performance. However, less than a year later, Godecke et al. (6), using an independently developed knockout line, reported cardiac adaptations (e.g., increased capillarity and blood flow) that could have compensated for the loss of myoglobin’s transport function. Using this knockout as a control, the same group showed that the effects of CO poisoning on performance and \(V_0_2\) in cardiac muscle of wild-type mice were specific to its effect on myoglobin (11).

Furthermore, recent studies of cardiac muscle from the same myoglobin knockout mouse line have resurrected catalytic roles for myoglobin, first as an NO scavenger (4), and more generally, as an antioxidant (3). Thus all three of the myoglobin functions listed by Millikan remain credible, although perhaps not universally accepted (7).

Of course, the three functions of myoglobin are not mutually exclusive. In particular, the properties of myoglobin that suit it for a role in oxygen transport (high concentration, half-saturation near the in vivo Po2, and fast kinetics) suit it equally well for short-term oxygen storage. Thus, just as for the creatine kinase system (12), the spatial and temporal buffering functions of myoglobin are inseparable, and sorting out their relative importance in a single physiological context can be difficult. Defining the role of myoglobin in human skeletal muscle during exercise has been particularly difficult. Despite the well-known correlation between muscle myoglobin content and aerobic capacity across species, little correlation was reported across human individuals (15), and aerobic training appeared to have little effect (10).

The paper by Duteil et al. (2) in this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology is a long stride down the road to understanding the functions of myoglobin in human muscle. Using a unique combination of interleaved, state-of-the-art nuclear magnetic resonance techniques, these authors show that myoglobin content is significantly higher in calf muscles of endurance- vs. sprint-trained human subjects. More importantly, they demonstrate a good correlation across individuals between myoglobin content and muscle-specific functional aerobic capacity, estimated from the kinetics of phosphocreatine recovery after exercise. In the same experiment, they measure the rate of myoglobin resaturation and the time course of muscle perfusion after ischemic exercise, both of which are also correlated with myoglobin content. Thus the association between myoglobin content and indexes of aerobic function in human muscle now seems established. Does this result prove that myoglobin plays a role in oxygen transport in human muscle? Alas, no, because the temporal and spatial aspects of oxygen buffering by myoglobin are equally relevant in the context of aerobic exercise. However, further studies using these advanced magnetic resonance techniques should be rewarding. For example, it should be possible to gate the measurements of myoglobin saturation and perfusion to individual contractions during a steady-state, repetitive exercise bout and directly measure the extent to which buffering of oxygen by myoglobin “tides” the muscle over from one contraction to the next” in humans.

REFERENCES


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