MUSCULAR CONTRACTIONS LEAD to a large (2) and rapid (14) increase in muscle perfusion, providing a challenging field of research for over a century. A particular challenge has been deciphering the mechanism(s) that regulate the increase in vascular conductance that, in turn, enables the large change in muscle perfusion. To further complicate the problem, the mechanism(s) regulating blood flow control appear to change over the course of an exercise bout with some affecting the rapid vasodilation at the exercise onset and others contributing to the steady-state conditions. The potential physiological determinants that are purported to affect the rapid vasodilation at the exercise onset have included mechanical factors such as the muscle pump, myogenic and vascular compression, endothelial factors, muscle metabolites, the red cell, and acetylcholine from the neuromuscular junction [e.g., see (7) for review]. In addition, the concept of neurally mediated vasodilation in skeletal muscle has teased the physiological community over the last century. With a need for speed, a neural mechanism fits well within the concept of central command (12) whereby motor, respiratory, and cardiovascular strategies are coordinated centrally to enable rapid adjustments to the exercise onset.

The first suggestion of sympathetic vasodilator nerves in skeletal muscle was provided by Bulbring and Burn in 1935 (6). The cholinergic basis of such a mechanism has been supported (5), inferring acetylcholine released from sympathetic neurons. Additional experimental work in the 1960–1980 period provided support for a centrally driven neurogenic (1) and cholinergic vasodilatory effect (9, 10).

Nonetheless, debate on this concept of sympathetic cholinergic vasodilation has focused around two issues. First, does the machinery exist in humans to support such a mechanism, and second, does it have any place in exercise blood flow control, particularly at the exercise onset? In the 1950s, a closer comparative look at this question indicated that functional dilatory signals, supported by immunohistochemical analysis of cholinergic and adrenergic neurons, could be achieved in the muscle of rats and cats and dogs, but not in primates (4, 15).

Also, any attempts to isolate such a mechanism with direct measures of sympathetic outflow in humans have not supported the general hypothesis to date; rather, sympathetic withdrawal has been observed accounting for most, but not all, of dilation in skeletal muscle [e.g. (8)] under conditions where neurally mediated vasodilation was proposed.

Within the context of human exercise, the dynamics of muscle blood flow adaptation at the exercise onset, or maintenance during steady-state conditions, were not modified by muscarinic receptor blockade in healthy humans (13). Moreover, hindlimb exercise hyperemia was not modified with atropine in a rat model (3), despite the previously documented existence of a neural dilatory mechanism in this species. These results challenge the hypothesis of a cholinergic sympathetic signal that produces an effective vasodilation during exercise in skeletal muscle. Nonetheless, the very large dilatory response that occurs within the complex environment created by the contractions of skeletal muscle may obscure any neurogenic contributions that operate on a smaller scale.

So, another decade or two has passed and new information has been published that challenges us to consider the possibility of neurogenic vasodilation once again. In this issue of the Journal of Applied Physiology, Ishii and colleagues (10a) have continued their pursuit of the question regarding neurogenic vasodilation in skeletal muscle by examining rapid functional changes in muscle oxygenation in the vastus lateralis muscle of humans during volitional, passive, and imagined cycling exercise. The issue of local vasodilation being associated with central command separates this paper from others exploring a neurogenic mechanism during steady-state exercise or during other sympathoexcitatory maneuvers such as mental stress or syncope (8). Anticipating that sympathetic outflow may increase during the initiating moments of exercise by central command or the muscle mechanoreflex and thereby affect an initial vasodilatation of noncontracting muscle, the authors compared the relative changes in concentration of oxygenated-hemoglobin (Oxy-Hb) in the noncontracting vastus lateralis (VL) muscle with near-infrared spectroscopy (NIRS), as an estimate of muscle tissue blood flow, and femoral blood flow to the nonexercising leg with Doppler ultrasound between voluntary and passive one-legged ergometer exercise. Oxy-Hb and femoral blood flow increased in the noncontracting VL muscle at the start of the voluntary cycling, but not the passive cycling. To further test the hypothesis, they examined the responses of Oxy-Hb in the noncontracting muscle during imagery of the voluntary one-legged exercise on the presumption that descending vasomotor neural outflow would be transmitted not only to the nonexercising limb but also to the exercising limb during one-legged exercise. The important observation was that Oxy-Hb increased in both right and left leg VL muscle during motor imagery of the voluntary one-legged cycling but not of other cognitive tasks. Furthermore, an increase in Oxy-Hb of the contracting VL, which was observed at the start period of voluntary one-legged cycling, had the same time course and magnitude as the increase in Oxy-Hb of the noncontracting muscle. On the basis of these observations, the
authors conclude that a neural signal associated with central command caused vasodilation in the leg muscles. The lack of change in the electromyogram argues against the concern that concurrent small-scale muscle activation developed with exercise imagery that could cause dilation.

These data reinstitute the provocative idea that neurally mediated vasodilation has a place in the physiology of human skeletal muscle blood flow control. Previously, functional observations of blood flow patterns have led to similar conclusions, only to be refuted by direct measures of neural activity and mechanistic experiments with receptor blockade or immunohistochemistry (11), understandably difficult in the human model. However, the emphasis on the early moments of exercise may present a different scenario. The results provided by Ishii and colleagues calls for additional information regarding the neural signal involved (is it cholinergic or undetectable motor activation?) as well as for receptor blockade studies to establish the neurovascular and receptor-based mechanism involved. Furthermore, the absolute levels of increase in blood flow and overall impact on leg vasodilation during volitional work would be of interest.

The existence of such a neural mechanism, even if small in scale, has important implications for our understanding of neurovascular physiology, exercise science, and clinical aspects of exercise tolerance. We still have not settled on an algorithm that explains the rapid increase in muscle vascular conductance at the exercise onset. The debate regarding the impact of such rapid changes on oxygen uptake and muscle metabolism is only part of the larger issue regarding the impact of rapid oxygen delivery to support muscular contraction and how this feature factors into exercise intolerance by patients with vascular disease and neural impairments such as advanced age, diabetes, peripheral vascular disease, and others. Finally, exercise training and detraining elicit neuroplastic responses that, based on the observations of Ishii et al., may further impact vasomotor control in muscle and other organs.

**Disclosures**

No conflicts of interest, financial or otherwise, are declared by the author.

**Author Contributions**

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