Exercise hyperemia: waiting for the reductionists?

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In the play, Waiting for Godot, Godot never arrives. In the context of the “reductionist” (cellular and molecular) wave that has swept over biomedical research during the last 20–30 years, the continuing puzzle of exercise hyperemia is one issue where we may be waiting for the reductionists to address a question that is fundamentally beyond their reach. Part of this is an intellectually combative response to the idea that integrative physiology is passé: “If reductionism is the answer to all unsolved questions, then why have you waited so long to enlighten us?” On the other hand, it is also unfortunate that the reductionists have not contributed more to the fundamental question of what makes blood flow to contracting muscles increase. Indeed, for more than 100 years, this most fundamental physiological phenomenon has been well known and at the same time poorly understood (3, 6, 7). So, what is known and how might the paper in this issue of American Journal of Physiology-Heart and Circulatory Physiology by Rogers and colleagues (5) help sort some of this mess out?

Blood flow to exercising muscle can increase up to 100-fold above the resting values (3, 4, 6). This increase in flow starts instantaneously, is proportional to the metabolic rate of the muscle, and can be sustained (3, 4, 7). Over the years, mechanical, neural, and chemical factors have all been described that, under some circumstances, might initiate, evoke, sustain, and/or otherwise contribute to exercise hyperemia (3, 4, 7). From time to time, it has been thought that a single factor or limited number of factors are responsible for most or all of the hyperemic response to exercise (4, 6, 7). More recently, the idea that there might be multiple redundant control/regulatory systems operating in concert has gained favor (6). The predominance of this perspective has perhaps as much to do with the failure to find a single or limited number of mechanisms that are obviously responsible for exercise hyperemia versus any especially strong evidence for a multifactorial or redundant control/regulatory system. Enmeshed in all of this are a host of important subsidiary questions like “do the factors that initiate the contraction also sustain it?” (3, 4, 6, 7).

These and related issues have been tested, evaluated, and sorted through repeatedly, and related ideas seem to come and go and are rediscovered or revisited over time. During the last 10–20 years, one idea that has influenced much of the thinking about exercise hyperemia is that the immediate rise in blood flow with contractions is simply too fast to be accounted for by “metabolic vasodilation.” That is, for metabolites to be generated in the contracting muscles, diffuse into the interstitial space, and relax the resistance vessels in the nearby skeletal muscle would take 5 s or longer (1, 3, 4, 6, 8).

In the absence of metabolic vasodilation, the options were a rapid, neurally mediated vasodilation or a rise in blood flow caused by mechanical interactions between the active muscles and their blood vessels (i.e., the muscle pump) (4, 8, 12). Recent ideas include the concept that the muscle pump—rhythmic opening and closing of veins (with their one-way valves) surrounded by contracting muscles—could effectively generate a negative pressure and augment muscle blood flow in the absence of changes in resistance vessel tone. Another idea is that acetylcholine released from the motor nerves might also stimulate the vascular endothelium and relax blood vessels in the active muscles (4, 8, 10).

However, in a series of human studies, investigators in Canada (first led by R. Hughson and later by his protégé M. Tschakovsky) have used forearm contractions in ways that minimized the potential contribution of the muscle pump on the initial blood flow responses to contraction (9–11) or a change in workload. In these studies, consistent (or is it persistent?) evidence for rapid vasodilation at the onset of contractions has been found.

In the most recent paper on this topic from the Tschakovsky laboratory, Rogers and colleagues (5) used Doppler ultrasound to make beat-to-beat measurements of brachial artery blood flow during rhythmic (20 contractions/min) handgrip exercise (5). Two workloads were used, and the subjects alternated between them at very short (every other contraction), short (every two contractions), or longer (every six contractions) intervals. Additionally, the lighter of the two workloads was heavy enough that any contribution from a forearm muscle pump would already be maximal. With the use of this approach, the total work done per minute and metabolic demand remained constant between the three conditions, and the questions were as follows: 1) how fast would blood flow change in response to a change in workload and 2) would the pattern of change be the same or different when the workload was increasing and decreasing?

When the workload was changed every other contraction, blood flow rose steadily to a plateau, and there was no discernible change in flow between the heavier and lighter contractions. When the workload was changed every two contractions, blood flow increased during the heavier workload and declined during the lighter workload, and no steady state was reached. When workload was changed every sixth contraction, blood flow increased during the heavier workload and declined during the lighter workload, and again no steady state was reached. Additionally, the pattern of increase and decrease in flow in response to the every other and every sixth contraction changes in workload was remarkably similar. These changes in flow were large, rapid, and not accompanied by major changes in perfusion pressure; hence, there was clear evidence for rapid (<5 s) changes in vascular tone.

When these data are put in the context of recent observations, the authors suggest that perhaps metabolic vasodilation can occur more rapidly than previously thought (1, 13). They also discuss evidence for and (mostly) against a neural mechanism that might explain their findings and highlight new (or at least new versions of) ideas postulating a rapid, mechanically mediated release of vasodilating substance from the resistance...
vessels. In this case, they focus on recent observations from the Clifford laboratory (2), suggesting a key role for K\(^+\) ions. However, most importantly, Rogers and colleagues (5) emphasize that what causes blood flow to go up must be reversible in a matter of seconds because the pattern of rise and fall in flow and vascular conductance is symmetrical. So, the signaling mechanism(s) responsible must be very fast and resistant to desensitization over time, and perhaps it is time for some version of mechanical/metabolic coupling to be thought about (again?) as a mechanism that plays a major role in exercise hyperemia.

Perhaps it is also wise to remember in a more general context that the mechanisms that cause exercise hyperemia continue to remain poorly understood, that the puzzle is incomplete, and that the shift away from integration to reductionism over the last 20 or 30 years has not moved us much closer to clear-cut answers about muscle blood flow and exercise. Mostly, we have learned more about what is not causing exercise hyperemia. Additionally, many of the most fundamental observations on this topic have been made in conscious humans and animals, and studies like that of Rogers and colleagues (5) continue to answer important questions and raise even more provocative ones. So, those of us interested in integration will continue to wait for the reductionists.

REFERENCES