Point: The muscle pump raises muscle blood flow during locomotion

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A long-standing gap in our understanding of muscle perfusion during muscular activity has been the huge (2×) discrepancy between the levels of blood flow achieved by "maximal" chemical vasodilation or electrically evoked contractions and those achieved during locomotory-type exercise. The classical prevailing thought has been that there must be some unidentified or "missing" vasodilator substance. In 1987, Laughlin (5) proposed that for locomotory-type exercise the muscle pump, via a number of potential mechanisms, could in fact be the missing factor. Perplexingly, studies continue to emerge using electrically evoked contractions to allegedly probe muscle pump function, often providing predictable evidence that the muscle pump does not contribute to active hyperemia in a setting where the pump is proposed not to exist.

There are nearly as many models of exercise as there are investigators examining response to muscular activity, ranging from isometric contractions elicited by electrical stimulation of isolated muscles to voluntary, rhythmic, whole body exercises involving all the major muscle groups in the body (2). The contribution of the muscle pump to muscle perfusion is likely to differ among all of these models, ranging from no contribution (indeed an impediment) during an isometric contraction to a presumed peak contribution during upright locomotory exercise (5). The aim here is to identify exercise modes where the muscle pump provides effective support of muscle perfusion.

The lumped functions of what is collectively referred to as the "muscle pump" include multiple local and central circulatory effects (12). For example, the expulsion and central mobilization of peripheral venous blood volume raises cardiac filling pressure, stroke volume, and thus cardiac output. In this way the muscle pump makes more blood flow available to be directed to active muscle and thereby indirectly promotes muscle hyperemia. The focus here is on mechanisms by which the muscle pump can directly contribute to muscle hyperemia by acting locally within muscle.

A body of circumstantial evidence exists supporting the notion the skeletal muscle circulation processes the proper physiological and anatomical substrate to endow it with the capability for self-perfusion. Muscle blood vessels are well tethered to the surrounding muscle, ensuring that muscle mechanical factors are transmitted to the vasculature (12). Passive changes in muscle length elicit venular length and diameter changes expected for a pump chamber. Application of negative pressure outside muscle (which mimics the proposed sucking action of the muscle pump) rapidly increases arterial inflow (7). The speed with which veins refill from the arterial circulation after muscle relaxation indicates that the muscle pump works like a "bellows pump" (1). Manipulation of stride frequency leads to immediate and proportional changes in muscle blood flow in a setting where vasodilator drive is presumably clamped (13). Finally, when muscle arteries and veins are "short-circuited" and isolated from the remainder of the circulation, rhythmically active muscle readily perfuses itself (16).

Direct evidence of muscle pump function has proven harder to come by; indeed, it has been proposed that instrumentation required to probe for muscle pump function may in fact obliterate that very function (6). The weight placed on any evidence for or against the muscle pump hypothesis provided by any particular experimental model should be in strict accordance with how well the model has been explicitly documented to not in anyway impede circulation. In addition, of course, positive results should be favored over negative results.

The speed, magnitude, and dependence on venous pressure of the hyperemic response to locomotory-type exercise point to the muscle pump as its cause. In response to very mild locomotion (15), the muscle pump may be the exclusive cause. For example, if the evidence that vasodilation is delayed by 10 s in such settings (14, 15, 17) is correct, the vasoconstriction seen at this time (15) would signify that arteriolar diameters are reduced in response to this type of exercise, i.e., completely opposite of the presumed response.

Via its venous pressure-lowering function (9, 18), the muscle pump accounts for nearly all of the increase in blood flow to dependent limbs of upright humans (and likely other relatively tall animals) during mild to moderate rhythmic exercise (10, 18) and provides further assistance to active hyperemia in smaller animals during tilting (3).

The onset of exercise hyperemia is typically reported to be less than 1 s (2a), and brief, steady levels of heightened flow can be attained within a few seconds (14, 15). Can relaxation of vascular smooth muscle account for such rapid dynamics?

Gorczynski et al. (4) examined the coupling between skeletal muscle activity and arteriolar vasodilation by direct inspection. They measured arteriolar diameters using videomicroscopy when adjacent muscle fibers were made to contract by electrical stimulation of muscles. Although a wide range of activation patterns were examined, none were specifically designed to mimic the recruitment patterns generated during locomotory exercise. In response to twitch contractions (which probably best mimics muscle activation during locomotion), arterioles demonstrated a delay to the onset of dilation that ranged from 20 to 5 s for twitch frequencies of 1–8 per second. These results indicate that for twitch contractions, vascular smooth muscle responses are probably too slow to account for the rapid rise in conductance that accompanies locomotion.

Wunsch et al. (19) studied the time course of vasodilation of isolated arterioles to directly applied vasodilator substances. This approach faithfully mimics the release of vasodilator substance from muscle but eliminates a portion of the normal diffusion distance and is therefore expected to speed responses. No vasodilation was detectable until 4 s after direct application of a number of putative functional hyperemic vasodilators. Presumably, for exercise, additional delays must be added to this 4-s lag to account for the time required for the production, release, diffusion, and accumulation of such substances that occur in vivo in response to the onset of muscle activity. More rapid initiation of vasodilation has been observed, but the ensuing dilation takes 10 s or longer to reach a peak or steady level (4, 11). This relatively sluggish dynamic characteristic does not provide a likely explanation for the observation that vascular conductance can achieve an initial, brief steady level within a few steps (14).

Lutjemeier et al. (8) employed a clever design in which the period after cessation of knee extensor exercise equal to period

of a single contraction/relaxation cycle during the preceding exercise was used as a measure of the perfusion provided during exercise by the arterial-venous pressure gradient and level of vasodilation in isolation (i.e., no muscle pump). They found that light exercise provided a net benefit to perfusion. That is, the muscle pump indeed promoted muscle perfusion in a manner independent of its effects on venous hydrostatic pressure, i.e., venous pressure likely remained depressed during the immediate postexercise period used for comparison. Moderate intensities of exercise provided no net gain or impedance to hyperemia, whereas heavy exercise provided a net impediment to hyperemia; importantly, blood flow during relaxation from a contraction under all conditions was consistently higher than flow during the immediate postexercise period. Several features of this study weigh importantly on the role of the muscle pump during locomotion. First, the mode of muscle contraction employed likely caused a much greater impediment to flow during the contraction than is expected during locomotion. Their subjects performed relatively long (~1 s) and relatively forceful contractions (up to 40% maximal voluntary contraction force). The briefer, milder contractions employed during locomotion are expected to provide far less impediment to flow. Second, the mode of muscle relaxation and passive muscle relengthening (where they consistently observed blood flow augmentation) faithfully mimics the patterns seen during locomotion. Thus muscle contraction during locomotion is expected to provide far less impediment to flow, and muscle relaxation during locomotion is expected to provide an equal (greater?) tendency to improve flow. In view of these considerations, the results of Lutjemeier (8) shed considerable light on muscle pump function during locomotory exercise.

GRANTS

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Counterpoint: The muscle pump is not an important determinant of muscle blood flow during exercise

It is well known that muscle contractions evoke an immediate increase in blood flow to active skeletal muscle (1, 2, 4, 5, 8, 9, 11–15). In fact, studies employing both human and animal models have shown that skeletal muscle blood flow is significantly elevated within 1 s after the release of a brief contraction (2, 11, 13, 14). A potential mechanistic explanation invokes the concept of the muscle pump, which is hypothesized to elevate skeletal muscle blood flow by mechanical rather than metabolic factors (6). As the muscle contracts, the veins within the muscle are compressed and the venous contents are expelled. On relaxation, it is thought that the muscle fibers (which are tethered to the walls of the veins) open the lumen of the compliant vessels and create low pressure (6, 7). The reduction in venous pressure increases the pressure gradient across the muscle vascular bed and enhances muscle perfusion. Ideally, to support this hypothesis one need only measure the fluctuations in venous pressure within the muscle during contractions. Unfortunately, it has been technically impossible to measure

pressure in the venules of skeletal muscle. This technical limitation has created a situation in which the muscle pump theory has persisted despite the lack of direct confirmation. On the basis of the available data, we contend that the muscle pump is not an important determinant of muscle blood flow during exercise.

Our position is based on three lines of evidence. First, the magnitude of contraction-elicited changes in blood flow is far greater than can be accounted for by putative changes in intravascular pressure. Second, the time course of changes in blood flow does not correlate with that predicted from the muscle pump. Third, in the absence of vasodilation, muscle contractions do not evoke an increase in muscle blood flow.

By definition, the muscle pump can only influence blood flow for as long as venous pressure is reduced. Once arterial inflow replaces the volume of blood expelled during contraction, venous pressure is restored and there can be no further effect of the muscle pump on blood flow. Therefore, the proportion of skeletal muscle hyperemia attributable to the muscle pump should be directly related to the volume of blood needed to replace that expelled from the veins. Evaluation of this idea is facilitated under experimental conditions where the refilling of the veins is not interrupted by a subsequent contraction, i.e., a single brief contraction. In anesthetized dogs positioned in an upright position to maintain a normal hydrostatic gradient, we obtained continuous measurements of arterial and venous blood flow before, during, and after maximal tetanic contractions of 1-s duration evoked by electrical stimulation of the sciatic nerve (15). The volume of blood expelled from the veins during muscle contraction and the volume of blood flowing into the arterial circulation were calculated by integrating the pulsatile blood flow tracings. In the horizontal upright position, muscle contraction ejected a volume of 1.6 $\pm$ 0.2 ml from the venous circulation. The cumulative arterial blood volume amounted to 32.9 $\pm$ 4.4 ml. Because the venous circulation should have been refilled by the first 1.6 ml of blood, the additional 30+ ml of blood must be explained by some other mechanism. Thus under these conditions, the muscle pump can be responsible for only a small percentage of the total arterial inflow after contraction.

If the muscle pump is the primary determinant of the initial blood flow response to contraction, then one would expect the peak blood flow to be observed in the first few cardiac cycles after a single contraction. That time course is not what is observed in the human forearm or canine hindlimb. Studies using continuous Doppler ultrasound measurements in humans show an immediate contraction-induced elevation in arterial blood flow with a peak occurring 4–5 s after release of contraction (1, 9, 13, 14). With the use of the same canine model described above, arterial blood flow was elevated within the first second after contraction and then increased progressively until reaching a peak at 4–7 s (11, 15). Furthermore, at the prevailing blood flows in the dog, it can be calculated that the venous volume expelled would have been refilled in $<$1 s, eliminating the basis for any muscle pump effect after this time. Thus careful analysis of the time course of the blood flow response to a single contraction reveals a progressive increase in blood flow and temporal dissociation of the peak blood flow effect from the presumed contraction-related changes in intravascular pressure. This time course is incompatible with the postulate of the muscle pump playing the primary role in the observed hyperemia.

One of the challenges for investigators interested in this topic is that the muscle pump and vasodilator mechanisms may be activated simultaneously (13, 16). It would be desirable to study the muscle pump in isolation without any dilation of the skeletal muscle vasculature. A novel experimental approach to accomplish this objective in vivo is to infuse K^+ intra-arterially to raise the external potassium concentration, which clamps the membrane potential in a depolarized state, rendering the vascular smooth muscle unable to relax. In anesthetized dogs, the increase in hindlimb blood flow after tetanic contraction was prevented by intra-arterial infusion of K^+ (4). That is to say, in the absence of vasodilation, there was virtually no change in blood flow. The K^+ infusion protocol did not alter the force produced by contraction, indicating that this experimental manipulation should have had no discernible effect on muscle pump function. Another method of impairing the dilator ability of the skeletal muscle vasculature is to infuse a potent vasodilator to elicit maximal vasodilation before initiating contractions. When this approach was employed in anesthetized animals, muscle contractions did not further increase blood flow (3, 10), except in the case of spontaneous contractions of the diaphragm (10). One drawback of in situ exercise models is that electrical stimulation simultaneously activates all the fibers within the muscle (synchronous contractions). The fact that spontaneous diaphragmatic contractions increased diaphragm blood flow (10) prompted the suggestion that the muscle pump may be more effective in dynamic exercise when the muscles are contracting asynchronously (6). Experiments in our laboratory (5) used a similar approach of minimizing changes in local vascular tone by infusing high doses of adenosine before the commencement of treadmill exercise in conscious dogs. Under these conditions, voluntary contractions failed to increase blood flow to the exercising muscles. A straightforward interpretation of our data is that the magnitude of any change in venous pressure elicited by the muscle pump was inadequate to elevate blood flow at the onset of exercise. Taken as a whole, data isolating the influence of the muscle pump (3–5, 10) do not support the ability of the muscle pump to increase blood flow when the muscle vascular bed is unable to dilate.

In summary, examination of the blood flow response to a single contraction reveals that the muscle pump cannot adequately account for the magnitude of the hyperemia nor the time course of the response. Furthermore, there is no increase in muscle blood flow to electrically stimulated or spontaneous contractions when vasodilation is prevented. That the muscle pump aids venous return to the heart cannot be refuted, but the preponderance of the evidence suggests that it is not an important determinant of muscle blood flow during exercise.

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REBUTTAL FROM DR. SHERIFF

The studies employing electrically evoked, isometric muscle contractions (4, 6, 9) elegantly demonstrate the absence of a muscle pump in this setting, which prompted the proposal of a locomotory muscle pump in the first place. Given that voluntary muscle recruitment normally ejects 23 ml blood/kg muscle (8), the 2 ml of blood ejected by electrical activation (9) is only ~5% of the expected 35 ml (assuming 1.5 kg of muscle in the dog hindlimb), suggesting that electrically evoked isometric muscle contraction trapped blood within muscle, rather than expelling it. The small (50–100%) rise in blood flow induced "sans" muscle pump (4, 6, 9) is far smaller than the twofold rise seen during mild locomotion (5) despite electrical activation of all muscle fibers (10× motor threshold sciatic nerve stimulation) vs. recruitment of a small fraction of motor units during walking, again signifying that there is indeed "something missing" in these "reduced" preparations. Also, comparing the time course of responses to a so-called "brief" 1-s duration contraction (4, 6, 9) to locomotion is problematic because in locomotion it takes 8 strides (>4 s) for a muscle to accumulate 1 s of activity due to the briefer rhythmic contractions employed during locomotion. Finally, in contrast to the lack of influence of tilting (6), Folkow et al. (3) found a considerable muscle pump effect in dependent cat limbs.

Patterson and Shepherd (7) assessed the influence of exercise on blood flow in a vasodilated limb and found a positive result, i.e., a rise in blood flow, due to the muscle pump and/or further vasodilation. Why didn't either or both of these mechanisms raise iliac artery flow in the study by Hamann et al. (5)? Clearly the limbs were not near their maximal flow capacity; flow in these 20-kg dogs was raised to 1 l/min (5), and in 13-kg dogs this artery can accommodate at least 1.6 l/min mean flow (2). The use of a flow probe with a 2 l/min maximal flow limit (5) would impose a constraint were systolic flow to exceed 2 l/min, and, again, in 20-kg dogs this artery should be able to accommodate close to 2.5 l/min mean flow (1, 2). Absent documentation that downstream arterial pressure was unaffected by probe implantation, the possibility exists that surgical instrumentation imposed a flow limitation (perhaps even preventing systolic flow from exceeding the capability of the probe).

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REBUTTAL FROM DRS. CLIFFORD, HAMANN, VALIC, AND BUCKWALTER

Our esteemed colleague maintains that the muscle pump does not exist in electrically evoked contractions and that "vasodilation is delayed by 10 s" after contraction. What is it then that produces the rapid increase in muscle blood flow after a brief

contraction elicited by electrical stimulation? If there is neither a muscle pump nor vasodilation, how can blood flow increase in the first second and peak within 4–7 s? (6, 10)

Results using electrically evoked contractions are too readily dismissed by claiming that the muscle pump does not exist in this setting. There is no justification given nor reference cited for this claim. This is certainly not Laughlin's position. He suggests that the pump "may be more effective in locomotory exercise," but never implies that it is nonexistent in electrical stimulation (2).

The potential for rapid vasodilation is demonstrated by direct evidence from monitoring arteriolar diameter in the spinotrapezius (4) and cremaster (5) preparations. That the rapid increase in hindlimb blood flow represents vasodilation was shown by the fact that blocking the smooth muscle's ability to relax abolished the increase in flow (1). In response to Sheriff's question "can relaxation of vascular smooth muscle account for such rapid dynamics?" our answer is an emphatic yes.

As admitted in his opening argument, there is only "a body of circumstantial evidence" supporting the muscle pump theory. Alternative explanations for results are not entertained. Manipulations of stride frequency (7) and grade (8) do not adequately control other variables. Lutjemeir et al. (3) assumed that vasodilator influences would remain constant after cessation of exercise with no consideration given to the notion that vasodilation may ebb rapidly. Because vasodilation can occur in the first cardiac beat after contraction (9), it may be reversed just as quickly.

From the initial evidence that translocation of blood from the venous circulation aids cardiac filling, elaborate explanations have evolved regarding how the muscle pump might influence muscle blood flow. This situation is reminiscent of the well-known children's story, "The Emperor's New Clothes," in which an elaborate hoax was played by men who pretended to weave beautiful cloth on an empty loom. The townspeople profusely complimented the emperor's new clothes, which in reality did not exist. The time has come for us to acknowledge the scientific equivalent of "the emperor has no clothes"—the muscle pump is not an important determinant of muscle blood flow during exercise.

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POINT-COUNTERPOINT CALL FOR COMMENTS

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