HIGHLIGHTED TOPIC | Skeletal and Cardiac Muscle Blood Flow

Immediate exercise hyperemia: contributions of the muscle pump vs. rapid vasodilation

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Tschakovsky, Michael E., and Don D. Sheriff. Immediate exercise hyperemia: contributions of the muscle pump vs. rapid vasodilation. J Appl Physiol 97: 739–747, 2004; 10.1152/japplphysiol.00185.2004.—A striking characteristic of the blood flow adaptation at exercise onset is the immediate and substantial increase in the first few (0–5 s) seconds of exercise. The purpose of this mini-review is to put into context the present evidence regarding mechanisms responsible for this phase of exercise hyperemia. One potential mechanism that has received much attention is the mechanical effect of muscle contraction (the muscle pump). The rapid vasodilatory mechanism(s) is another possible mechanism that has recently been shown to exist. This review will provide the reader with 1) an understanding of the basic physics of blood flow and the theories of muscle pump function, 2) a critical examination of evidence both for and against the contribution of the muscle pump or rapid vasodilatory mechanisms, and 3) an awareness of the limitations and impact of experimental models and exercise modes on the contribution of each of these mechanisms to the immediate exercise hyperemia. The inability to measure microvenular pressure continues to limit investigators to indirect assessments of the muscle pump vs. vasodilatory mechanism contributions to immediate exercise hyperemia in vivo. Future research directions should include examination of muscle-contraction-induced resistance vessel distortion as a trigger for rapid smooth muscle relaxation and further investigation into the exercise mode dependency of muscle pump vs. rapid vasodilatory contributions to immediate exercise hyperemia.

muscle blood flow

IN A REST-TO-EXERCISE TRANSITION, muscle blood flow typically increases to a steady-state level tightly regulated to metabolic demand for oxygen (7, 41). Figure 1 illustrates the dynamic characteristics of the exercise hyperemia response. A typical observation in human forearm or knee extension/flexion exercise is a biphasic response characterized by an immediate and substantial increase in muscle blood flow that plateaus by 5–7 s, with a second, slower adaptation to steady state initiated by ∼15–20 s (27, 37, 61–63) In contrast, the onset of locomotion in conscious animals (dogs, rats) typically results in a monophasic response that rapidly (within 10 s) reaches peak flow (11, 54, 55). Thereafter, at moderate work rates, blood flow actually decreases somewhat over time to steady state. The focus of this review is on the immediate (0–5 s) increase in blood flow at exercise onset.

Because blood flow through a vascular bed is thought to be proportional to 1) the arteriovenous pressure difference across that bed and 2) the vascular conductance of that bed, both the mechanical activity of muscle contraction and relaxation affecting this pressure gradient and imparting energy on blood flow (the muscle pump), as well as vasodilatory signals determining vascular conductance, must be considered as possible mechanisms. Presently, controversy exists regarding the contribution of the muscle pump vs. rapid vasodilation. We approach this controversy by putting into context the evidence both for and against contributions by either mechanism. In addition, we draw the reader’s attention to the potential impact of experimental model selection and exercise mode on the relative contribution of each mechanism.

THE PHYSICS OF BLOOD FLOW

Vascular anatomy. The architectural aspects of the vasculature within skeletal muscle are well characterized and generally conform to the characteristics seen in other organs. In resting muscle, the majority of the total resistance is provided by the arterioles. Resistance here can be modified by a host of chemical, neural, and hormonal signals that alter the level of tone in the vascular smooth muscle cells. There is a well-developed capillary bed that promotes the exchange of substances within the muscle. The veins are well endowed with valves. Importantly, with respect to muscle pump function, the vessels located within muscles are well tethered to the surrounding tissue (6), meaning that mechanical forces developed by the skeletal muscle are likely transmitted to the vasculature as well.
to the height of the column of fluid, the density of the fluid, and the gravitational constant. The hydrostatic pressure will develop immediately with the change in posture in the arteries because they contain no structures (e.g., valves) that could interrupt the formation of a continuous column of blood along the length of the arterial system. The same is not true on the venous side due to the venous valves, which are expected to close and thereby interrupt the formation of a continuous column of blood along the large veins. Thus a transient increase in the pressure gradient is expected across tissues in dependent regions owing to the greater local arterial pressure. This will work to augment the flow of blood through these tissues, a factor that will persist until the veins are filled enough to open the venous valves. Once a continuous column of blood is established on the venous side of the circulation, the hydrostatic pressures on the arterial and venous side will cancel each other such that the pressure-flow relationship across dependent tissues is largely unaffected by gravity. The same is not true for the pressure-volume status of the dependent tissues. The hydrostatic component of luminal pressure will increase the transmural pressure gradient (luminal pressure minus tissue pressure) such that additional blood volume will accumulate in the dependent regions, particularly in veins because they are relatively more compliant than the arteries. The increase in local capillary luminal pressure attributable to the hydrostatic effects of gravity will also lead to increased filtration.

THEORIES OF MUSCLE PUMP FUNCTION

During static muscle contractions and during the contraction period of dynamic exercise, the flow of blood through the muscle is impeded because of mechanical compression and possible kinking of vessels within the muscle. Some other factor(s) that promotes blood flow in association with muscle activity must first overcome the contraction-induced impediment to flow for the muscle pump to be effective (see Fig. 2).

Multiple mechanisms by which the mechanical activity of muscle contraction and relaxation may cause or contribute to muscle hyperemia have been proposed. Most stem from Laughlin’s seminal review (31). One mechanism is the venous emptying produced by muscle contraction. Any reduction in venous pressure produced by venous emptying would be expected to promote the flow of blood from arteries into those venous segments whose volume and pressure have been reduced. This mechanism should be particularly potent in relatively tall animals in which venous pressure is elevated by the hydrostatic effects of gravity. A second possible mechanism is that the mechanical activity of contraction propels blood through muscle via a “milking” action. Laughlin (31) also proposed that mechanical restoring forces imposed during muscle relaxation may create a negative luminal pressure within veins, thereby widening the pressure gradient driving flow across the muscle. This effect may depend on the nature of the relaxation (active relengthening of muscle by antagonist muscle action vs. load-mediated eccentric contraction relengthening). Importantly, red blood cells appear to be able to withstand large negative pressures without rupturing. Reported threshold pressures for rupture range from −120 mmHg (44) to over −720 mmHg (13).

Finally, muscle contraction has been suggested to impart kinetic energy to blood flow (31). However, there are a number
of critical considerations regarding this hypothesis. First, kinetic energy is imparted on venous flow during contraction when arterial inflow is actually impeded (see Fig. 2). Second, on relaxation, the closing of venous valves to prevent backflow would mechanically separate venous blood from arterial blood. Thus arterial inflow would be temporarily and mechanically uncoupled from the kinetic energy imparted to venous outflow during contraction.

To the potential mechanisms proposed by Laughlin (31), we submit the following additional ideas. One possibility is that the mechanical deformation of vascular smooth muscle cells during contraction could disrupt cross bridges, thereby initiating a rapid, mechanically induced vasodilation. A second possibility is that, when a muscle contraction blocks the flow of blood through muscle, the pressure drop associated with the flow of blood must be eliminated as well. This means that the pressure along the vessel from the arteries to site of the blockade should rise to aortic pressure. Because the site of blockage is presumed to be in the veins, this means that the arterioles may in essence get “charged up” to a pressure that is much higher than normal (e.g., 100 vs. 50 mmHg) during the contraction phase. On relaxation of the muscle, the discharge of this pressure would provide a larger than normal transient pressure driving flow across into the veins, operating like a microwindkessel. However, it must be acknowledged that the duration of this particular effect of the muscle pump might be extremely brief given the very low compliance of the arterial circulation.

**EVIDENCE FOR THE MUSCLE PUMP**

*Contribution of venous hydrostatic pressure.* The idea that the muscle pump can improve muscle perfusion by reducing the venous hydrostatic pressure in dependent limbs is relatively well supported by experimental studies. Pollack and Wood (50) were among the early investigators to document that walking greatly lowered venous pressure at the ankle, although the impact this would have on local muscle perfusion was not addressed. Folkow and coworkers evaluated muscle perfusion in both animals (18) and humans (19) while the hydrostatic component was experimentally manipulated and found that perfusion was augmented in dependent limbs. These findings have also been substantiated by more recent studies (36, 51, 58). An isolated muscle pump preparation developed by Scharff and Van Bibber (36) also provides evidence of the ability of the mechanical forces produced during rhythmic muscle contraction and relaxation to act on muscle vasculature in a manner sufficient to initiate and sustain a flow of blood. Finally, an in vivo simulation of the mechanical influence of muscle contraction in the absence of the actual metabolic consequences of muscle contraction has also been employed to test for muscle pumping. Tschakovsky et al. (66) showed that rhythmic forearm muscle compression via 1-s/2-s forearm cuff inflation/deflations induced increases in flow but only under conditions in which a venous hydrostatic column existed.

*Can the muscle pump “suck” blood?* The evidence supporting the idea that the muscle pump contributes directly to muscle perfusion in a manner other than a simple reduction of the hydrostatic component of pressure is largely indirect. The angiographic evidence provided by Almen and Nylander (1) provides perhaps the most compelling evidence. These investigators had subjects perform calf contractions while contrast medium was infused into superficial cutaneous veins. On muscle relaxation, contrast medium was rapidly convected into deep veins. On the basis of the speed of the transport (i.e., too fast to be explained by passive drainage through the high-resistance perforator veins that connect the superficial and deep veins), Almen and Nylander proposed that the muscle pump operated like a “bellows-pump,” sucking blood into the deep
veins from the superficial veins and presumably from arteries as well. Others have observed a similar phenomenon (15). To our knowledge, no attempt has been made to establish whether this apparent “sucking action” is modulated by contraction mode, contraction force, duty cycle, or posture. Consistent with this, Fig. 2 (arterial inflow panel) demonstrates that on relaxation of forearm contractions there is often a brief augmented pulse of arterial inflow immediately on relaxation of forearm contractions.

Contributions of contraction frequency and intensity. A number of studies have provided indirect evidence of muscle pumping based on altering contraction frequency [e.g., treadmill speed (stride frequency) or pedaling cadence] and/or contraction force (e.g., treadmill grade) both in the rest-work transition and during ongoing exercise. A common assumption is that contraction frequency constitutes a major determinant of muscle pump efficacy (18, 22, 55, 63) just as cardiac frequency can constitute a major determinant of cardiac pump efficacy.

Several studies have altered treadmill speed and grade at the onset of locomotion to investigate their influence on blood flow (see Fig. 3). When the potentially confounding influence of autonomic nerve activation at exercise onset is blocked in dogs, blood flow initially rises in proportion to treadmill speed (contraction frequency) (Fig. 1C), a finding consistent with the muscle pump hypothesis (54, 55). When the autonomic nerves and nitric oxide synthase are both inhibited, an increase in treadmill grade does not induce an augmentation of blood flow in dogs until ~10 s after the onset of locomotion (54). When locomotion is initiated across a wide range of speeds and grades in rats with normal autonomic and nitric oxide synthase function, speed begins to exert a significant effect on blood flow soon (3 s) after the start of locomotion, whereas the eventual influence of grade takes much longer to be expressed (>10 s) (54). The authors of these studies have interpreted these findings as follows. The muscle pump at least initially raises blood flow in proportion to contraction (stride) frequency (treadmill speed), and this effect has been shown to lead to a tripling of blood flow at best. The conclusion that frequency is important has also been reached from studies in humans. Gotshall et al. (22) examined the importance of cycling cadence at a fixed total workload and found that total vascular conductance was higher at higher cadences, a finding they attributed to more effective muscle pumping.

This conclusion is partly justified by other studies that indicate that the onset of vasodilation is delayed at the onset of exercise (21, 38, 69) or after an increase in work rate (57); however, this finding is far from universal (see below). Second, increased muscle force production, at least as modified by treadmill grade, does not augment muscle pump function nor does it appear to induce a rapid vasodilation in these animal models. If it accomplished either, blood flow would have differed across treadmill grades much sooner than 10 s into locomotion. If the muscle pump did not increase blood flow at exercise onset (see below), a key question arises. Why would locomotion at different speeds but not grades induce varying degrees of vasodilation soon (3 s) after exercise onset when contraction rates vs. intensities are not expected to induce different vasodilatory mechanisms?

Treadmill speed and grade have also been altered systematically during ongoing exercise in an effort to tease out the possible roles of the muscle pump and of vasodilation in altering blood flow (57). Sheriff and Zidon (57) imposed competing alterations in treadmill speed and grade in rats performing voluntary locomotion, i.e., treadmill speed was reduced when treadmill grade was increased and vice versa. The rationale was that the alterations in chemical vasodilator drive from each factor would cancel each other, thereby revealing whether there were any residual changes in flow attributable to contraction frequency-induced alterations in muscle pump function. These investigators found that under these conditions alterations in muscle blood flow corresponded directly to changes in contraction frequency, suggesting that there is a direct mechanical coupling between contraction frequency (muscle pump frequency) and blood flow.
EVIDENCE AGAINST THE MUSCLE PUMP

Exercise onset. Shoemaker et al. (63) examined the effect of contraction intensity vs. frequency in a human forearm dynamic handgripping model with contraction/relaxation duty cycles of 1 s/1 s vs. 1 s/2 s. In contrast to observations from Sheriff’s laboratory in rat and dog treadmill locomotion (54, 55, 57), these investigators observed that the early increase in blood flow was explained by contraction intensity and not by frequency. In addition, Hamann et al. (23) recently demonstrated that increases in blood flow after 1 s of stimulation of isolated canine muscle can only be explained by vasodilation. These differences may be due to the effectiveness of the muscle pump being dependent on the type of muscle contractions (31).

High blood flow conditions. Several studies employing electrical stimulation of isolated muscle have provided evidence against the muscle pump enhancing peak muscle blood flow (16, 46). As noted earlier, the unphysiological recruitment patterns of electrically activated muscle may not engage the muscle pump effectively. Also, any negative results, such as these, are open to Laughlin’s proposal that instrumentation needed to evaluate the muscle pump may impede its function (35).

However, a recent study by Hamann et al. (25) in which voluntary locomotion was used also provides evidence against the idea that the muscle pump enhances peak muscle blood flow. In this study, locomotion onset failed to further elevate blood flow above that occurring during maximal adenosine hindlimb vasodilation, a finding clearly at odds with the earlier findings of Laughlin (31) in which a substantially higher hindlimb vasodilation, a blood flow above that occurring during maximal adenosine infusion, was demonstrated during locomotion in rats compared with “peak” vasodilator infusion.

It is not presently known whether muscle pump effectiveness is diminished at high (intense exercise) vs. low (rest) muscle arterial inflow rates. Flow may not rise in a high flow state with the onset of contractions because refilling of the veins is so rapid that the gain in pressure gradient is too brief to offset the increased impedance to inflow during contractions (see Fig. 3). However, the observation that flow remained constant in the Hamann et al. study indicates that some factor (muscle pumping?) offset the tendency of muscle contractions to impede flow such that blood flow was maintained.

EVIDENCE FOR AND AGAINST RAPID VASODILATION

Approaches to the examination of the onset of vasodilation in contracting muscle have typically employed 1) in situ rodent cremaster or spinotrapezius muscle (21, 38) or in vitro isolated vessel models (69), which allow direct measurement of resistance vessel diameter in response to muscle fiber stimulation or topical application of putative exercise vasodilator substances, and 2) measurement of arterial inflow during voluntary contractions in humans (10, 24, 65, 66) or stimulated contractions in dog muscle (40, 42, 47). Each approach has its own set of advantages and limitations.

Direct observation of resistance vessels. Evidence from direct measurement of resistance vessel diameter in response to muscle fiber recruitment suggests that the onset of vasodilation varies with twitch stimulation frequency. Marshall and Tandon (38) reported that terminal arteriolar vasodilation began ~10 s after a single twitch contraction, with primary arterioles dilating within 20 s. As twitch frequency increased to 8 Hz, dilation was initiated within 1 s of the onset of the twitch for all arteriole levels, whereas with titanic contractions 30% terminal arteriolar dilation had occurred within 2 s of a 1-s tetanus. Other investigators have commonly observed a longer delay (anywhere from 5 to 20 s, depending on vessel and muscle stimulation) in vasodilation in response to rodent muscle stimulation (14, 21, 68). For example, Cohen et al. (14) examined the response of upstream vessels after stimulation of muscle fibers isolated under a single capillary module. This preparation eliminated any of the muscle pump effect of contraction. However, it also limited the mechanisms of vasodilation to a capillary endothelium-mediated ascending vasodilation. In this study, there was a >10-s delay in the onset of dilation of the arteriole directly supplying the capillary module, indicating this mechanism has a sluggish response.

Recently, Wunsch et al. (69) employed topical application of the vasodilators K+, sodium nitroprusside, and adenosine at varying concentrations on isolated rat secondary resistance vessels and observed that, although the magnitude of vasodilation induced was proportional to the concentration of vasodilator applied, the onset of dilation was consistently delayed by 4–6 s regardless of concentration. Observations of a delay in vasodilation in response to muscle stimulation or direct application of known vasodilators have commonly been cited to indicate that vasodilator mechanisms are simply too slow to explain the immediate exercise hyperemia.

“Whole-muscle” muscle blood flow observations. In contrast, observations from in situ stimulated dog muscle and voluntary human forearm muscle contraction models consistently indicate a rapid vasodilatory response. Anrep and von Saalfeld (2) originally demonstrated a proportionality between peak muscle blood flow and contraction intensity after a single 1-s contraction. Blood draining a muscle after a single contraction resulted in vasodilation when infused into a resting muscle vascular bed, indicating the existence of a stable vasodilating substance. Corcondilas et al. (15), using strain gauge plethysmography, also observed a contraction intensity-dependent early blood flow increase after 0.3-s isometric forearm contractions.

The recent application of Doppler ultrasound to obtain beat-by-beat blood flow measurements in humans has provided further evidence for rapid vasodilation. First, Tschakovsky et al. (66) [see also Fig. 2 in Hughson and Tschakovsky (27)] demonstrated that blood flow was immediately elevated and then progressively decayed to baseline in response to a single forearm cuff inflation/deflation, whereas, in response to a single forearm contraction, blood flow continued to increase over three subsequent cardiac cycles. This latter observation is inconsistent with an exclusive muscle pump effect of a single contraction and has also been observed with 1-s stimulation of isolated dog muscle (40, 42, 47).

More recently, Tschakovsky et al. (65) demonstrated that the immediate (first cardiac cycle after contraction release) hyperemia in response to single brief forearm contractions performed above heart level is proportional to contraction intensity. The authors minimized muscle pump contribution via 1) arm above heart position to eliminate the venous hydrostatic column (33, 58), 2) use of isometric contractions (31), and 3) assessment of the response across contraction intensities in which venous emptying was not different (i.e., muscle pump
effect on arteriovenous pressure gradient was similar). In addition, Saunders and Tschakovsky (52) recently demonstrated an immediate increase in forearm blood flow during a transition from 10% to 20% maximal voluntary contraction rhythm dynamic forearm handgripping that was of the same magnitude as the immediate hyperemia in the rest to 10% maximal voluntary contraction transition. Again, forearm position above heart level eliminated the venous hydrostatic column before exercise onset. Because muscle pump effectiveness as assessed by venous emptying was not enhanced with increasing contraction intensity, these data are consistent with a rapid vasodilatory response at the onset of both a rest-exercise and exercise-exercise transition. A sucking action of the muscle pump can also be ruled out to explain the effects observed in these studies. This is because the authors examined the first full cardiac cycle of the relaxation phase that was unaffected by any potential immediate sucking action of muscle relaxation (see Fig. 2, arterial inflow panel).

Finally, a recent study by Hamann et al. (23) demonstrated that the immediate hyperemia in response to a brief muscle contraction in an isolated dog muscle preparation is virtually eliminated when smooth muscle membrane potential is “clamped” via substantial arterial K+ infusion. This intervention had no effect on muscle force production, thus clearly demonstrating that vasodilation is obligatory for the immediate hyperemia in this model. Furthermore, the rapid vasodilatory mechanism(s) acts via smooth muscle membrane hyperpolarization and not via protein kinase A-initiated myosin light chain phosphatase activity or sarcoplasmic reticulum uptake of intracellular Ca2+ (34).

Data demonstrating a rapid vasodilation do not argue against the existence of a muscle pump. Rather, they merely indicate that, when the venous emptying effect of the muscle pump contribution has been removed (arm above heart level, exercise-exercise transition) or when it cannot contribute to further increases in flow (2 cardiac cycles following single contraction release), a rapid vasodilation is apparent.

**POTENTIAL MECHANISMS OF RAPID VASODILATION**

Although considerable effort has been directed at determining vasoregulatory mechanisms contributing to the steady-state exercise hyperemia, much less attention has been paid to the immediate exercise hyperemia. Van Teeffelen and Segal (67) have demonstrated that steady-state vasodilation increases in proportion to the tension developed by a given number of active motor units and in proportion to the number of active motor units at a given tension. This is consistent with the spatial distribution of microvascular units relative to motor unit fibers (20). Thus increases in both motor unit recruitment and tension per motor unit may contribute to the contraction intensity-dependent immediate vasodilatory response observed in human forearm studies. This is supported by recent in vivo evidence from Hamann et al. (24) in which the peak blood flow response to a single forearm contraction increased with both the strength and duration of muscle contraction. It therefore appears reasonable to hypothesize that the rapid vasodilatory mechanism(s) responsible for immediate vasodilation is related to muscle activation.

“Muscle activation” vasodilator candidates. Candidates to explain this immediate contraction intensity-dependent vasodilation would have to appear and exert their effects very rapidly. Temporal resolution in the measurement of interstitial concentrations of vasodilators has limited the ability to directly measure such changes. However, the interstitial concentrations of two known vasodilators that are involved in neuromuscular activation, K+ (26, 43) and acetylcholine (68), could increase immediately and in proportion to muscle contraction intensity.

The present evidence regarding K+ is mixed. K+ was originally thought to exert its effect by increasing smooth muscle Na+-K+-ATPase pump activity (45). More recent evidence points to a predominant K+ inward-rectifying channel mechanism (28). Mohrman and Sparks (43) were the first to confirm that the magnitude and time course of K+ appearance was consistent with a role in the immediate hyperemic response to a single contraction. However, although Burger et al. (12) observed an ~20% dilation already present by 4 s (the first measurement taken) in coronary vasculature, Wunsch et al. (69) observed a 4- to 6-s delay in vasodilation onset after direct application of K+ to secondary resistance vessels. With regard to acetylcholine, although it has been observed that a motor nerve source of acetylcholine evokes vasodilation in hamster cremaster muscle (68), blockade of muscarinic receptors with atropine does not alter the immediate exercise hyperemia in exercising human (10, 11, 59) or rat (4) skeletal muscle. Furthermore, in dog and human skeletal muscles, acetylcholine spillover from motor nerves does not appear to reach muscarinic receptors, as no vasodilation is observed during motor nerve stimulation of paralyzed skeletal muscle (2, 17, 47).

**Mechanical compression/distortion of resistance vessels.** Another intriguing possibility is that of a mechanical compression/distortion effect on resistance vessel tone due to muscle contraction. The contraction intensity-dependent magnitude of rapid vasodilation (15, 65, 66) would suggest a graded response to mechanical compression/distortion. This is consistent with the observation that interstitial pressure increases in proportion to muscle contraction intensity (51, 64). Such changes would lower vascular transmural pressure and potentially evoke a myogenic vasodilation. Although Mohrman and Sparks (42) observed a rapid increase in blood flow in response to external muscle compression and attributed this to a myogenic mechanism, others have observed no effect of mechanical muscle compression without the presence of an initial venous hydrostatic column (5, 66). However, simple muscle compression may not represent the true mechanical distortion of muscle contraction.

Hamann et al. (24) recently proposed that this mechanical distortion affects the endothelial cells lining the vasculature much like pressure and shear stress do (29, 30), whereas Tschakovsky et al. (65) proposed direct effects on smooth muscle. Nitric oxide, prostaglandins, and endothelial-derived hyperpolarizing factor are known mediators of endothelial-dependent vasodilation (8, 49). To date, experiments that employed prostaglandin or nitric oxide blockade in isolation have not affected the change in blood flow in the first 0–5 s of exercise in humans (10, 59) or dogs (54). Recently, combined nitric oxide and prostaglandin blockade has been demonstrated to substantially reduce steady-state blood flow (9). In contrast, the first investigation of combined blockade on the rapid vasodilation in an exercise-exercise transition by Saunders et al. (51a) found no effect on the immediate percent increase in blood flow with increased contraction intensity. Endothelial-
derived hyperpolarizing factor has yet to be investigated in this context.

Recent evidence from Hamann et al. (23) demonstrated that clamping smooth muscle membrane potential virtually eliminates immediate vasodilation. This was evidenced by elimination of a blood flow response to single 1-s stimulation of isolated dog muscle under these conditions. These data indicate that, if muscle compression/distortion can rapidly reduce arteriolar tone in isometric contractions, it must do so by evoking changes in smooth muscle membrane potential. It is also possible that shortening/lengthening contractions are required to disrupt latched smooth muscle cross bridges. Clearly, this area warrants further investigation through the application of different in vivo, in situ, and in vitro experimental approaches.

ADVANTAGES AND LIMITATIONS OF EXPERIMENTAL MODELS

Isolated vessel and rodent muscle preparations. Isolated vessel and rodent muscle preparations allow for direct measurement of resistance vessel changes and provide the clearest indication of vasodilatory onset. However, these preparations do not simulate potentially critical aspects of the in vivo muscle environment. First, the rodent muscles used to allow microscopy measurements are very thin and therefore may not replicate the actual compression/distortion forces of muscle contraction on resistance vessels that would be found in vivo. Thus, if muscle contraction-induced compression/distortion plays a role in the rapid vasodilatory response, these models would be unable to assess such a contribution. Second, given that muscle stimulation did result in very rapid vasodilation in the experiment of Marshall and Tandon (38) but not in that of Wunsch et al. (69), the selective topical application of individual vasodilators may not represent the true initial vasodilatory stimulus experienced by resistance vessels in contracting muscle. An intriguing distinction between Wunsch et al. and Marshall and Tandon is the lack of a mechanical distortion in the study of Wunsch et al., in which the vasodilatation was delayed.

In situ and in vivo whole muscle models. In contrast, measurements of whole limb blood flow and arterial blood pressure in vivo and in stimulated isolated dog muscle preparations, although representative of the true in vivo environment, provide indirect assessment of resistance vessel dilation. Because it remains impossible to measure microvenular pressure in vivo, continuous assessment of the true pressure gradient for flow cannot be determined and factored in to the calculation of muscle vascular conductance. Instead, indirect approaches must be used to minimize muscle pump effectiveness (limb position above heart level to eliminate venous hydrostatic column, exercise-exercise transitions with increasing contractions, isometric contractions) to isolate a vasodilatory influence on calculated vascular conductance.

Experimental model influences on observed mechanisms. Observations in animal locomotion models are fairly consistent in demonstrating that treadmill speed (contraction frequency) rather than grade (contraction intensity) determines the magnitude of the immediate exercise hyperemia (3, 32, 53–55). Recent observations of substantially (~5 s) delayed exercise-to-exercise transition vasodilation in rodent treadmill exercise (53, 57) and delayed (10 s) effect of contraction intensity on the early exercise hyperemia suggest that immediate flow increases are exclusively due to a muscle pumping effect. However, in the human forearm, the biphasic adaptation in which the immediate increase in forearm blood flow reaches a plateau by 5 s of exercise is inconsistent with the delayed onset of vasodilation at ~5 s of exercise (60). Whether the bases of differences in human forearm vs. rodent treadmill locomotion are species dependent and/or muscle activation dependent is not clear. It has been proposed that muscle activation in the 1-s forearm contraction model is the equivalent of accumulated muscle activation in the rodent or dog over a period of 5 s of treadmill locomotion (54). However, brief (0.3 s) forearm contractions (15) also demonstrate a contraction intensity-dependent immediate exercise hyperemia.

Regardless, both intensity and duration of contraction may well influence vasodilatory delay and explain differences between experimental models cited. Species size and gait differences, as well as exercise modality, have the potential for influencing muscle activation magnitude and duration. For example, activities such as stair climbing, rowing, or downhill skiing can involve contractions of intensity and duration similar to the forearm contraction models employed.

SUMMARY AND FUTURE DIRECTIONS

The preponderance of evidence indicates the existence of a mechanical effect of muscle contraction on muscle blood flow. This effect is rapid enough to contribute to the immediate exercise hyperemia and appears sensitive to contraction frequency but not intensity. Although venous emptying-mediated increases in the local arteriovenous pressure gradient can clearly increase muscle blood flow, the hypothesis that venous tethering-facilitated negative pressure in the microvenules also occurs remains unconfirmed. Animal locomotion models emphasize a contraction frequency dependence of muscle pump function and generally indicate a delay in vasodilatation. These data suggest that the muscle pump is the sole contributor to immediate exercise hyperemia. In contrast, single contraction models in human forearm and in isolated dog muscle consistently demonstrate the existence of rapid vasodilatory mechanisms. We conclude that both the muscle pump and rapid vasodilation can contribute to the immediate exercise hyperemia. The relative role and contribution of each may be a function of contraction intensity and duration and may vary between species.

The inability to measure venous pressure in muscle microvenules continues to hamper efforts to directly assess the relative contribution of the muscle pump vs. rapid vasodilatory mechanisms. Furthermore, investigations into vasodilatory mechanisms have failed to clarify specific mechanisms. A possible unexplored mechanism is that of muscle contraction-induced compression/distortion of resistance vessels leading to rapid reductions in smooth muscle tone. Development of suitable experimental models is required.

ACKNOWLEDGMENTS

We thank Eric Harlan for the suggestion of the “microwindkessel.”

GRANTS

Work from D. D. Sheriff’s laboratory was supported by National Heart, Lung, and Blood Institute Grant HL-46314. Work from M. E. Tschakovsky’s laboratory was supported by a grant from the Natural Sciences and Engineer-
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