ARTICLE

Rapid Vascular Responses to Muscle Contraction

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CLIFFORD, P.S. and M.E. TSCHAKOVSKY. Rapid vascular responses to muscle contraction. *Exerc. Sport Sci. Rev.*, Vol. 36, No. 1, pp. 25–29, 2008. *Continuous measurements reveal that muscle blood flow increases within the first second after contraction. The increase in blood flow is attributable to rapid vasodilation as confirmed by direct observations of arterioles within contracting muscles. New evidence suggests that mechanical deformation of the vascular wall during contraction may be a causative factor.*
Key Words: contracting muscle, exercise hyperemia, functional hyperemia, muscle blood flow, vasodilation

INTRODUCTION

The mechanisms of exercise hyperemia (*i.e.*, the increase in skeletal muscle blood flow during exercise) have been under investigation since the 19th century. From the beginning, researchers postulated that a substance or substances released from contracting muscle resulted in vascular relaxation and an increase in blood flow. Although it became clear as early as the 1930s (1) that exercise hyperemia was initiated immediately with the onset of contractions, research on this topic throughout most of the 20th century focused primarily on determinants of the magnitude of steady-state exercise hyperemia, based on the conceptual framework of the metabolic hypothesis. Although some progress has been made in characterizing the relationship between metabolism and blood flow, we do not currently have a satisfactory understanding of the nature of vascular control mechanisms that can account for the magnitude of steady-state exercise hyperemia.

In the 1990s, attention began to focus on understanding determinants of the dynamic adaptation of muscle blood flow to exercise. This was in part due to the advancement of Doppler ultrasound techniques for continuous measurement of exercising limb blood flow in humans (21,22), investigations of the muscle pump hypothesis to explain the initial few seconds of exercise hyperemia (20), and renewed interest in potential neural influences on muscle blood flow (3,25). The progress of research in this area over the last 15–20 yr has shed new light on our understanding of the nature of vasoregulation in exercising muscle and has highlighted the need to revisit some of the traditional concepts of exercise hyperemia. Of note is the realization that the factors initiating exercise hyperemia may differ from those that maintain it. This article examines recent advances in our understanding of rapid vascular responses to skeletal muscle contraction including the response to a single contraction and to changes in intensity during repeated contractions. New evidence supports the hypothesis proposed independently by our laboratories (8,23) that vascular deformation during contraction may contribute to rapid vascular responses.

Blood Flow After a Single Contraction

Careful analysis of the blood flow response to a single contraction allows assessment of the speed of the response unhindered by the confounding effects of subsequent contractions. Results of *in vivo* experiments in the human forearm or canine hind limb have revealed that skeletal muscle blood flow is elevated "immediately" (within 1 s) after the release of a brief contraction (5,15,22,23). See the example in Figure 1 in which blood velocity in the brachial artery increased in the first heart beat after contractions at 15% or 50% of maximal voluntary contraction. For both intensities, blood flow continued to increase until it peaked 3–4 cardiac cycles postcontraction.

Whether the immediate increase is a consequence of vasodilation or the muscle pump has been a difficult question to resolve. The pattern of continued increase in blood flow observed *in vivo* (15,22) and shown in Figure 1B argues against the muscle pump effect and in favor of rapid vasodilation. If the muscle pump was the primary determinant of the initial blood flow response to contraction, one would expect the peak blood flow to be observed immediately postcontraction when the arterial to venous

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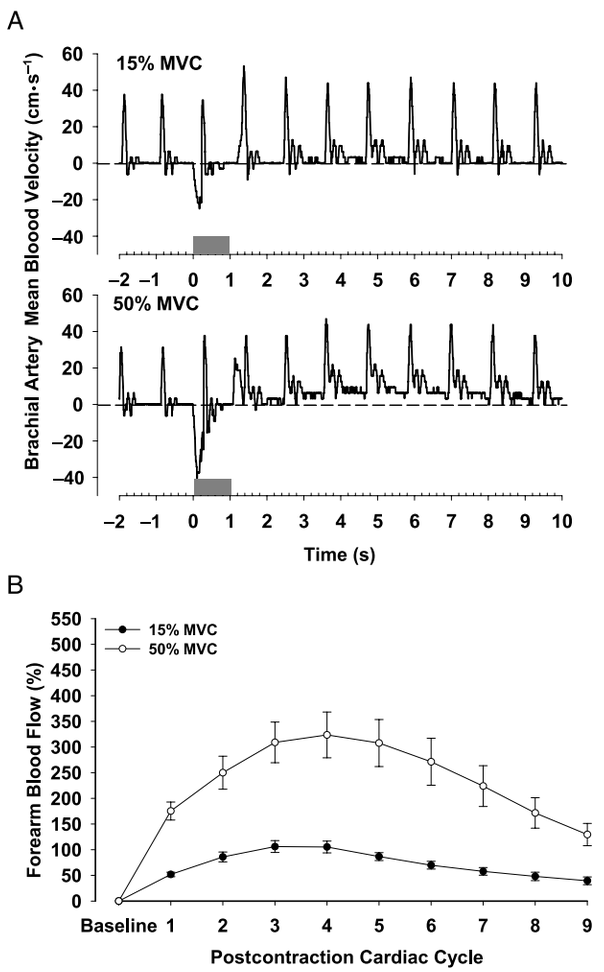

Figure 1. Rapid alterations in forearm blood flow (FBF) in response to single 1-s isometric forearm contractions. A. Brachial artery mean blood velocity waveforms in response to a single 1-s forearm contraction at 15% and 50% maximal voluntary contraction (MVC). Contraction period is indicated by *gray bars*. Brachial artery diameter remains constant within and between MVC conditions, so that mean blood velocity is directly proportional to FBF. B. Percent change in FBF after single 1-s isometric forearm contractions at 15% and 50% MVC intensities. [Adapted from Tschakovsky, M.E., A.M. Rogers, K.E. Pyke, N.R. Saunders, N. Glenn, S.J. Lee, T. Weissgerber, and E.M. Dwyer. Immediate exercise hyperemia in humans is contraction intensity dependent: evidence for rapid vasodilation. *J. Appl. Physiol.* 96:639–644, 2004. Copyright © 2004 American Physiological Society. Used with permission.]

pressure gradient would be maximized. This temporal dissociation of the peak blood flow effect from the presumed contraction-related changes in intravascular pressure provided indirect evidence of vasodilation and set the stage for renewed interest in microvascular investigations using intravital videomicroscopy.

In Situ Visualization of the Microvasculature

Early observations of vessel diameter *in situ* presented a confusing picture with latencies for vasodilation after contraction ranging from 2 s (10) to 20 s (7). Recent *in situ* studies of intramuscular arterioles in the cremaster and spinotrapezius now provide definitive evidence of increased arteriolar diameter within the first second after contraction. For hamster cremaster muscle stimulated at various frequencies and durations, Mihok and Murrant (12) and Murrant (14) reported a significant dilation of transverse arterioles within 1 s after contraction (Fig. 2). VanTeeffelen and Segal (24) observed an immediate increase in red blood cell velocity at the level of the feed arteries after a single brief contraction of hamster retractor muscle. Furthermore, they observed rapid dilation of arterioles at all levels of the microcirculation, with the incidence of rapid dilation being greatest at the terminal arterioles (7 of 8 responders). It is particularly striking that the timing of the increase and decrease of diameter in these studies mirrors that of the blood flow response to a single contraction.

Blood Flow Response to Transitions in Exercise Intensity

Rapid adjustments in muscle blood flow to changes in exercise intensity have been demonstrated in humans. In the human forearm, muscle blood flow increases immediately when contraction intensity is increased from mild to moderate (17,18) during rhythmic dynamic forearm handgripping. The time course and magnitude of this change are identical to an increase in contraction intensity from rest to mild contractions. Thus, rapid vasodilatory mechanisms are not restricted to initiating exercise hyperemia from rest but are capable of responding in muscle that is already exercising. Additionally, this rapid vasodilation is resistant to desensitization during repeated transitions from mild to moderate exercise intensity (16).

Our understanding of rapid vascular control has now expanded to include responsiveness to reductions in exercise intensity. Rogers *et al.* (16) repeatedly changed contraction intensity between mild and moderate during rhythmic dynamic forearm exercise every 1, 2, or 7 contractions and observed immediate changes in blood flow for the 2 and 7 contraction conditions regardless of the direction of change in contraction intensity (Fig. 3). These changes were symmetrical, meaning that the magnitude and time course

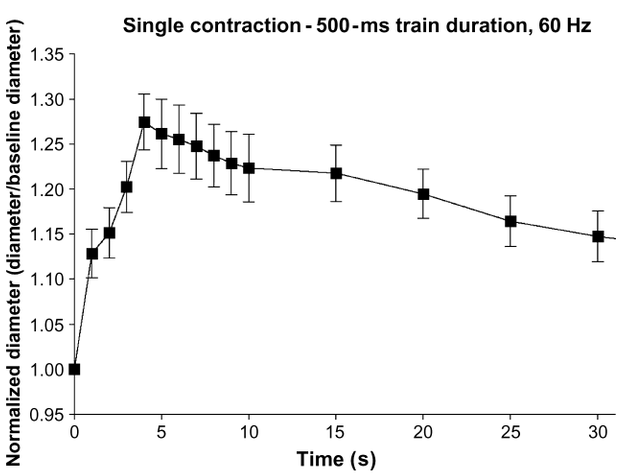

Figure 2. Time course of the change in transverse arteriolar diameter after a single contraction of 500-millisecond duration at a stimulus frequency of 60 Hz. Courtesy of Murrant (14); not previously published.

of increase and decrease in blood flow were the same. Furthermore, they did not diminish with repeated changes in contraction intensity.

Nature of Rapid Vascular Control Mechanisms in Contracting Muscle

The temporal profile of muscle blood flow responses to single contractions and transitions in exercise intensity during rhythmic exercise has provided some important clues as to the nature of rapid vasodilatory mechanisms. First, these mechanisms can initiate dilation of resistance vessels within 1 s of a brief contraction (15,22). Second, the magnitude of muscle vasodilation initiated by these mechanisms is proportional to contraction intensity (23). Third, they are capable of responding in muscle that is already exercising (16–18). Fourth, they are resistant to desensitization with repetitive changes in exercise intensity (16). Fifth, they are rapidly and repeatedly reversible (16).

Vasoregulatory control in exercising muscle has historically involved the search for a vasoactive substance or substances released from contracting myocytes. It is reasonable to assume that the nature of this type of vasoregulatory control is capable of explaining the magnitude of steady-state exercising blood flow. However, for a vasoactive substance to account for the above observations of rapid blood flow adjustments, its interstitial concentrations would have to rapidly and repeatedly fluctuate with contraction intensity. That this could occur seems highly unlikely, given the time required for production of a vasoactive substance from the skeletal muscle myocyte and its diffusion to the

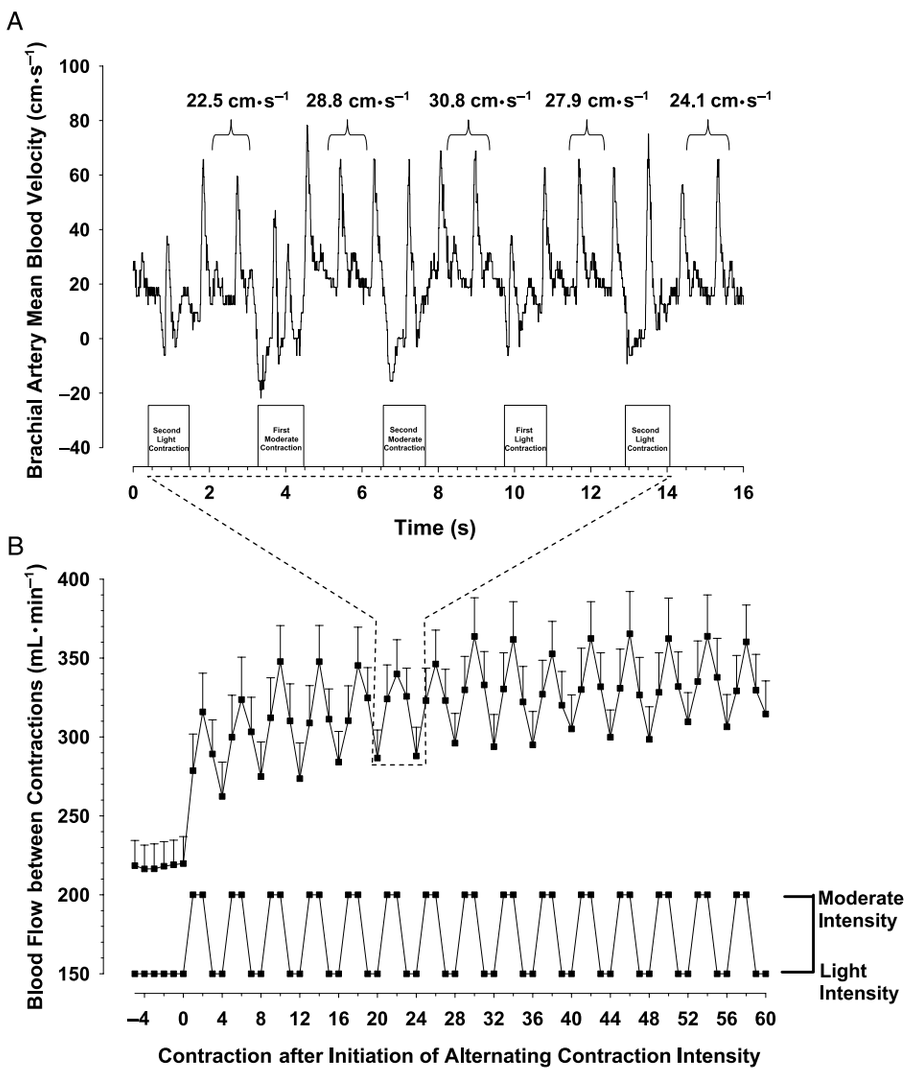

Figure 3. Rapid alterations in forearm blood flow (FBF) in response to repeated step changes in contraction intensity. A. Brachial artery mean blood velocity waveforms during transitions from light to moderate and back to light intensity. Values above *brackets* are mean values over the relaxation period. Brachial artery diameter remains constant across transitions, so that mean blood velocity is directly proportional to FBF. Note that changes in contraction intensity (both increasing and decreasing) have immediate effects on blood velocity. B. Forearm blood flow response averaged across all subjects with repeated changes in contraction intensity (two contractions per intensity for each cycle). Peak blood flow varies according to the intensity of contraction. [Adapted from Rogers, A.M., N.R. Saunders, K.E. Pyke, and M.E. Tschakovsky. Rapid vasoregulatory mechanisms in exercising human skeletal muscle: dynamic response to repeated changes in contraction intensity. *Am. J. Physiol. Heart Circ. Physiol.* 291:H1065–H1073, 2006. Copyright © 2006 American Physiological Society. Used with permission.]

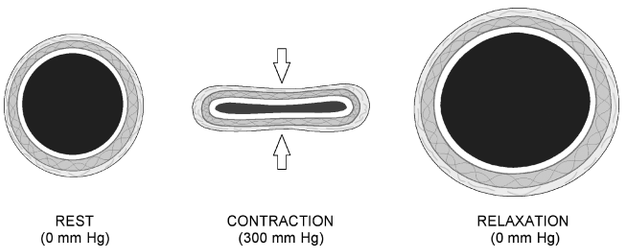

Figure 4. Schematic diagram showing cross-section of a single arteriole within skeletal muscle, compression due to muscle contraction, and subsequent vasodilation. Values in parentheses represent typical intramuscular pressures in human soleus muscle during running (2). The mechanisms responsible for dilation have not yet been identified but could involve activation of mechanosensitive ion channels or integrins.

interstitial space where it can act on adjacent vascular smooth muscle.

Understanding rapid vasoregulation in exercising muscle therefore requires that we consider mechanisms of an alternative nature, which do not rely on release and reuptake of a substance related to metabolic activity. Vascular deformation as a result of elevated extravascular pressure within the contracting muscle may activate an intrinsic mechanosensitive mechanism that causes dilation (Fig. 4). Such a mechanism was originally posited by Mohrman and Sparks (13) and recently put forward by Hamann *et al.* (8) and Tschakovsky *et al.* (23) based on the *in vivo* blood flow response to contraction in humans.

Both smooth muscle and endothelial cells are known to be mechanosensitive. Smooth muscle cells alter myogenic tone in response to changes in transmural pressure, and endothelial cells cause dilation in response to changes in intraluminal shear stress. Arterioles within the muscle are exposed to elevated extravascular pressure during muscle contractions. In fact, intramuscular pressures of 270 mm Hg have been recorded at moderate running speeds in humans (2) and can reach 570 mm Hg during maximal contraction (19).

The postulate that mechanical deformation of the skeletal muscle vasculature during contraction can elicit vasodilation was directly tested in recent studies (4). Rat soleus feed arteries were mounted on micropipettes in a chamber with luminal diameter measured using an inverted microscope. The design of the chamber allowed it to be sealed, so that the extravascular pressure could be varied to mimic the compression because of muscle contraction. Pressure pulses of 600 mm Hg were delivered for 1 and 5 s and as a series of 5 repeated 1-s pulses with 1 s between each pulse. During application of external pressure, the lumen of the artery was completely closed, but immediately after release of pressure, diameter was significantly increased. A typical example is shown in Figure 5. As seen in this figure, the time course is remarkably similar to that for the change in blood flow after a brief muscle contraction. The magnitude of dilation was not affected by increasing the duration of compression but was enhanced by increasing the number of compressions. This response was partially reduced by removal of the endothelium, indicating the involvement of both endothelium-dependent and independent signaling pathways.

The mechanisms responsible for dilation to extravascular compression have not yet been identified. The smooth muscle component may involve activation of mechanosensitive ion channels that would hyperpolarize the cell and initiate a cascade of events culminating in decreased calcium concentration within the cell. Integrins, which provide a direct physical link between the extracellular matrix and the cytoskeletal microfilaments, could also be engaged. Because integrins are capable of modulating membrane ion conductances, this mechanism would provide another means for a very rapid mechanotransduction system that does not require diffusion of a soluble mediator. It is noteworthy that both mechanosensitive ion channels (6) and integrins (11) have been implicated in myogenic tone development that is a function of intravascular pressure. The endothelial component most likely acts via nitric oxide, prostaglandin, and/or endothelium-derived

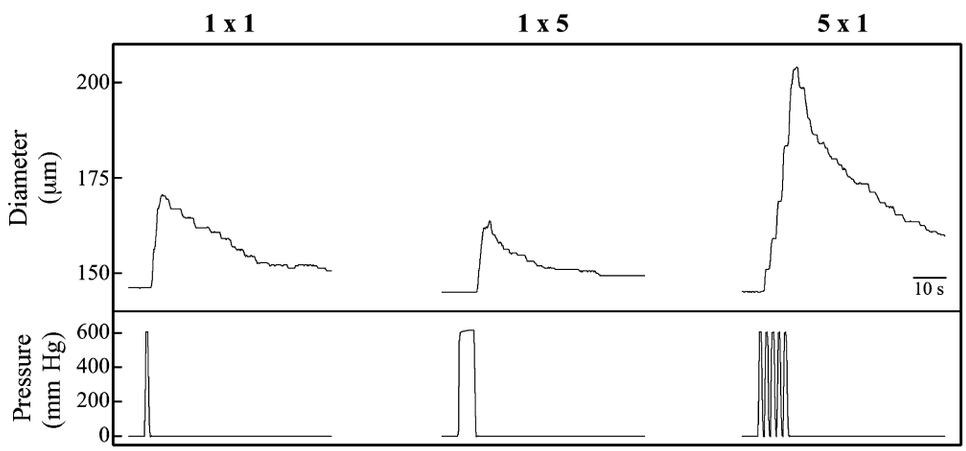

Figure 5. Response of a single soleus feed artery to external pressure. *1 × 1* indicates one pressure pulse of 1-s duration. *1 × 5* indicates one pressure pulse of 5-s duration. *5 × 1* indicates 5 separate 1-s pulses with 1 s between each pulse. Diameters were tracked manually by moving a cursor on the videoscreen. (Reprinted from Clifford, P.S., H.A. Kluess, J.J. Hamann, J.B. Buckwalter, and J.L. Jasperse. Mechanical compression elicits vasodilatation in rat skeletal muscle feed arteries. *J. Physiol. (London).* 572:561–567, 2006. Copyright © 2006 Blackwell Publishing. Used with permission.)

hyperpolarizing factors that are also involved in flow-mediated vasodilation. Future research clearly needs to delineate the specific mechanisms responsible for compression-induced vasodilation.

Recently, Kirby *et al.* (9) showed that brief compression can elicit vasodilation in the human forearm. They observed a dose-response relationship over a range of cuff pressures between 25 and 100 mm Hg. However, one important caveat to this study was that mechanical compression via external cuff could account for only a part of the immediate response to a single contraction. This indicates either that there are additional mechanisms involved or that external compression does not adequately mimic the vascular distortion occurring with contraction, or both. Nevertheless, the data from both animals and humans provide intriguing evidence that vascular deformation during contraction can elicit dilation of intramuscular arteries and arterioles.

SUMMARY/CONCLUSIONS

Mechanical deformation of the vascular wall could represent a feed-forward mechanism for skeletal muscle vasodilation at the onset of exercise. These findings provide further impetus for studying how vascular compression elicits skeletal muscle vasodilation. Furthermore, there is a need to understand the time course of involvement of mechanical compression, elevated potassium, and metabolic factors in producing the early adaptations of skeletal muscle blood flow to dynamic exercise.

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