MINIREVIEW

Regulation of Skeletal Muscle Blood Flow During Contractions (43965)

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Abstract. **Skeletal muscle blood flow increases nearly 20-fold during exercise. Despite experimental work in this area for more than a century, the physiological mechanisms responsible for the regulation of skeletal muscle blood flow during contractions remain relatively unknown. Historically, experiments have focused on identifying chemical factors associated with increased tissue metabolism that also act as vasodilators. However, functional vasodilation cannot be attributed to changes in the local concentration of any single metabolic factor. The rapid increase in muscle blood flow during the initial moments of exercise led others to consider a role for neural mechanisms in the development of functional hyperemia. However, a specific neural pathway has not been identified. Mechanical factors, such as vascular compression and increases in perfusion pressure, also affect vascular resistance and skeletal muscle blood flow. Yet the specific manner in which these mechanical factors interact during muscle contractions is not well understood. The recent determination that arterial feed vessels, upstream from the active tissue and microcirculation, also dilate during muscle contractions has led to the consideration that these vessels are primarily responsible for the regulation of bulk flow to the tissue. Since these vessels are anatomically separated from the active tissue, more complex, indirect regulatory mechanisms must be explored. It is also likely that the specific factors responsible for functional vasodilation and increased muscle blood flow during exercise differ between muscle fiber types and relative contraction intensities. Consideration of these factors may lead to a better understanding of the regulation of muscle blood flow.** [P.S.E.B.M. 1996, Vol 211]

It has been recognized for well over a century that skeletal muscle blood flow increases dramatically during muscle contractions (1, 2). Muscle blood flow generally increases in proportion to the metabolic demands of the tissue, a relationship reflected by positive correlations between muscle blood flow and running speed (3, 4), contraction frequency (5, 6), and muscle oxygen consumption (7–9). The increase in blood flow during exercise is limited to actively contracting muscles (4) and, in fact, is specifically directed to the recruited fibers within a given muscle group (6). Peak muscle blood flow during exercise is estimated to be 300–400 ml/min/100 g, a 20-fold increase relative to that at rest (10).

Because of the apparent relationship between metabolic activity and muscle blood flow, it has been hypothesized that the local metabolic state of the tissue directly affects flow by altering arteriolar tone and vascular resistance; the dilation of arterial vessels during muscle contraction has been termed "functional vasodilation." The vasoactive properties of oxygen, as well as a variety of metabolic by-products, have been well documented (5, 8, 11–14). Skeletal muscle blood flow is also regulated by neural influences and resting

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vascular tone is largely determined by tonic sympathetic constrictor activity; sympathetic denervation results in a 2-fold increase in resting muscle blood flow (15, 16). Vasodilator fibers have also been identified in the skeletal muscles of some species (17–20) and potential mediators include β-adrenergic, cholinergic, and purinergic transmission. Metabolic and neural vasoregulatory mechanisms are interdependent, as metabolic by-products can off-set the vascular response to sympathetic neural stimulation (11, 21, 22).

While hormonal control is generally considered a long-term regulatory process, it cannot be ignored in the determination of steady-state vascular diameters during muscle contractions. Of particular importance during exercise are the increased circulating concentrations of epinephrine and norepinephrine resulting from the increases in adrenal and neural sympathetic activity (23–25). Locally released humoral agents, such as prostaglandins and other endothelial-derived relaxing factors (EDRFs), also significantly and selectively influence skeletal muscle vascular tone (26). In addition, the local concentration of vasoactive chemicals in venular blood has been shown to influence arteriolar diameters through yet undetermined mechanisms (27, 28).

Mechanical or pressure-dependent factors also contribute to the regulation of skeletal muscle blood flow. These factors include the increase in systemic mean arterial pressure that generally accompanies exercise (29), the increase in tissue hydrostatic pressure and mechanical torquing of arterial vessels that occur during isometric and dynamic muscle contractions (30–32), and the pumping action of phasic muscle contractions on venous outflow (33–35). In addition, pressure-dependent myogenic vascular responses contribute to blood flow regulation in skeletal muscle. Myogenic responses are intrinsic to vascular smooth muscle cells and result in active vasodilation and vasoconstriction in response to decreases and increases in distending pressure, respectively (36, 37).

Historically, most studies of functional vasodilation have focused on regulation of the microvascular arterioles within the active tissue. However, the importance of dilation of the feed arteries has become increasingly evident. Without dilation of these upstream vessels, it would not be possible to accommodate the large (20-fold) increases in muscle blood flow that occur during exercise at physiological arterial pressures (38, 39). The manner in which the resistance of the upstream vasculature is regulated during muscle contractions is not well understood.

The various stimuli that can alter vascular diameters and skeletal muscle blood flow are illustrated in Figure 1. The resulting skeletal muscle blood flow is presumably determined by an integration of dilator and constrictor stimuli. The apparent role of each regulatory system in the regulation of skeletal muscle blood flow during contractions is the focus of this review.

Metabolic Regulation

The apparent relationship between skeletal muscle blood flow and the rate of aerobic metabolism suggests that a factor related to muscle metabolism may regulate functional hyperemia. The possibility that specific chemical changes in the vascular environment could elicit vasodilation was supported by the early observation that infusion of venous blood from a contracting

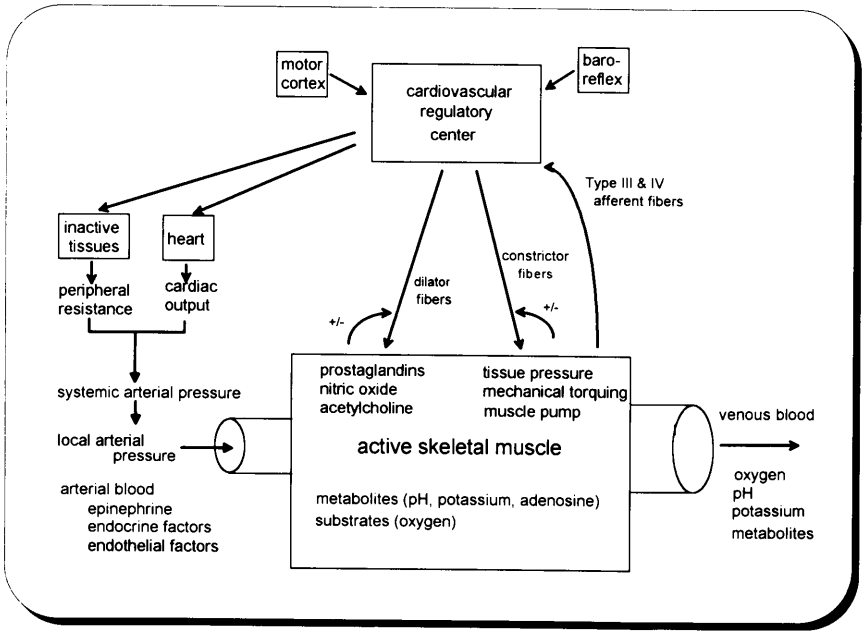

Figure 1. A schematic representation of the metabolic, humoral, neural, and mechanical factors contributing to the regulation of skeletal muscle blood flow.

muscle causes vasodilation in a resting recipient muscle, while blood from a resting muscle has no vascular effects (40, 41). The vasoactive properties of a variety of biochemical compounds related to muscle metabolism or contraction have been studied in the pursuit of finding the "magic bullet" that causes functional vasodilation.

Oxygen. Probably the most widely studied potential chemical mediator of skeletal muscle functional vasodilation is oxygen. Increases and decreases in local oxygen tension (PO_2) result in constriction and dilation of arteriolar vessels, respectively (14, 42–46). Theoretically, the increase in tissue metabolism and oxygen consumption that accompanies muscle contractions results in a decrease in local oxygen tension, which, in turn, either directly or indirectly through metabolic by-products, inhibits vascular smooth muscle force production and favors vasodilation. The role of oxygen in the regulation of functional hyperemia is supported by experimental evidence that muscle blood flow increases to maintain oxygen delivery to active muscle when arterial oxygen content is experimentally reduced (8). In addition, the venous blood PO_2 is roughly proportional to the decrease in vascular resistance during muscle contractions (47), suggesting a possible dose-response relationship. Although several studies demonstrate that venous blood PO_2 decreases with exercise (11, 13, 47, 48), direct measurements indicate that tissue PO_2 is restored to resting values during 2–3 min of phasic muscle contractions, while functional vasodilation is maintained throughout the contraction period (49–51); these results are illustrated in Figure 2, Panels 1 and 3. In addition, Gorczinsky and Duling (52) found the time courses for the onset and recovery of functional vasodilation in the hamster cremaster muscle to be significantly shorter than those for tissue PO_2; that is, functional vasodilation occurred prior to any detectable decrease in tissue PO_2. However, Lash and Bohlen (50), and Boegehold and Bohlen (51) have found an immediate decrease in tissue PO_2 with the onset of muscle contraction in the rat spinotrapezius muscle, followed by a recovery of tissue PO_2 to resting levels as functional hyperemia develops (Fig. 2, Panel 3). In addition, measurements of PO_2 in the area immediately adjacent to an arteriolar vessel, depicted in the second panel of Figure 2, indicate that the oxygen tension at the vessel wall remains constant, or may actually increase, during sustained functional hyperemia (50, 52). These combined results suggest the time course and spatial location of decreases in tissue PO_2 are not consistent with a direct oxygen stimulus for functional vasodilation. However, it should be noted that tissue PO_2 (52), peri-venular PO_2 (50) (illustrated in Fig. 2, Panel 4), and the oxygen content of venous blood (11, 13, 47, 48) have been shown to decrease during muscle contractions. Therefore, the possibility remains that oxygen plays a role in functional vasodilation through an indirect pathway; a decrease in PO_2 at some location in the tissue may elicit arteriolar vasodilation through neural or chemical mediation.

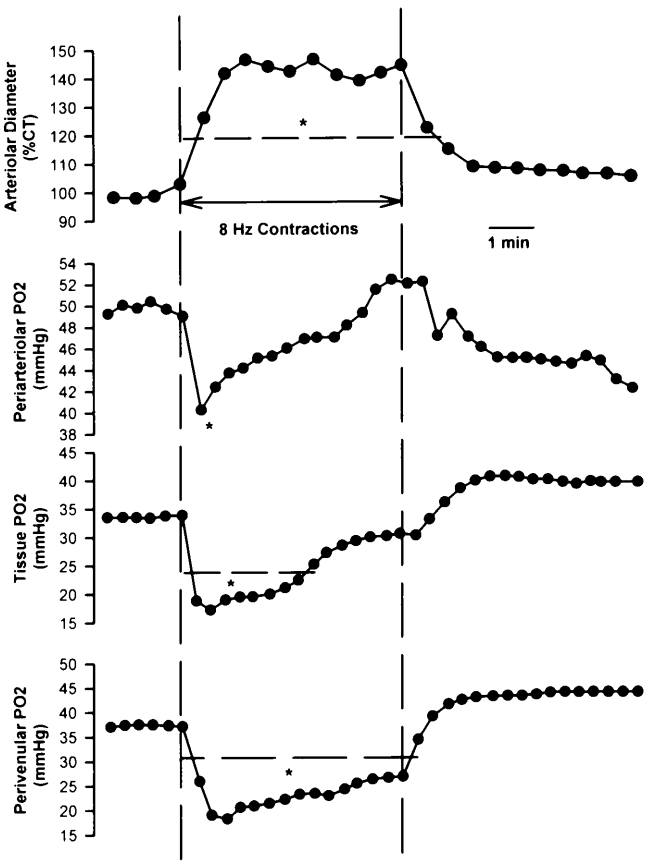

Figure 2. Arteriolar diameter and periarteriolar, tissue, and perivenular oxygen tensions in the resting and contracting rat spinotrapezius muscle. Arteriolar diameter increases with the initial contractions and reaches a steady-state level within the first 90 sec of contractions. Periarteriolar and tissue oxygen tensions decrease with the onset of muscle contractions, but recover to near resting levels after 2–3 min of phasic muscle contractions. Therefore, functional vasodilation is maintained despite relatively normal periarteriolar and tissue oxygen tensions. Perivenular oxygen tension decreases with the onset of contractions, and recovers only slightly with prolonged contractions, such that it remains significantly below resting levels throughout the contraction period; these results parallel measurements of venous blood oxygen tension. Therefore, reductions in local oxygen tension in the vicinity of the arteriolar vascular smooth muscle are not necessary for the expression of functional hyperemia. However, decreases in venular or perivenular oxygen tension may contribute to vasodilation during muscle contractions. Horizontal dashed line and asterisk delineate time during which variable is significantly different from pre-contraction resting values. Based on data presented by Lash and Bohlen (50).

Adenosine. Adenosine is a potent vasodilator of the skeletal muscle vasculature and a potential by-product of increased tissue metabolism and ATP hydrolysis. The extent to which the interstitial adenosine concentration increases during skeletal muscle contractions has been found to be variable among species,

muscle fiber types, and contraction conditions. The apparent role of adenosine in functional or exercise hyperemia has also varied between studies. Local application of adenosine deaminase, which promotes the degradation of vasoactive adenosine, has been shown to decrease functional vasodilation in the hamster cremaster muscle (14, 53); in contrast, systemic administration of adenosine deaminase had no effect on hindlimb blood flows during treadmill running in the rat (54). Similarly, theophylline, used to block receptors for adenosine, reduced functional vasodilation in the hamster cremaster muscle (53), but aminophylline, a theophylline salt, was shown to have no effect in the rat cremaster (55) or dog calf muscles (56). In addition, although blockade of adenosine formation has been shown to reduce postcontraction hyperemia in the highly oxidative dog gracilis muscle (57), measurements of the actual tissue concentration during contractions of this muscle do not demonstrate accumulation of interstitial adenosine (58). However, the 5′-nucleotidase in skeletal muscle appears to be localized in the vicinity of blood vessels, such that tissue samples may substantially underestimate the concentration of adenosine at the vessel wall (59–61). Interestingly enough, Kille (57) has found that inhibition of either adenosine uptake or degradation enhances postcontraction hyperemia. These results, in general, support the assumption that adenosine formation occurs during muscle contractions, but whether or not a hemodynamic effect is manifested during exercise remains in question.

It is likely that these variable results can be at least partially reconciled by differences in skeletal muscle fiber types and stimulation parameters between the studies (62). A study by Schwartz and McKenzie (63) illustrates that adenosine deaminase reduced muscle blood flow by ~40% during high intensity contractions of the highly oxidative slow-twitch cat soleus muscle, secondarily reducing oxygen consumption and force production. However, adenosine deaminase failed to affect blood flow, oxygen consumption, or muscle performance during low-intensity contractions of the soleus muscle, or during low- or high-intensity contractions of the fast-twitch cat gracilis muscle. These authors (63) concluded that vascular responses to intrinsic adenosine release are most evident during high-intensity contractions of oxidative muscle fibers. They also note that the activity of the 5′-nucleotidase responsible for the formation of adenosine from AMP is proportional to the oxidative capacity of the tissue, and, therefore, adenosine production is more likely to occur in slow-twitch oxidative fibers than in fast-twitch glycolytic fibers. Adenosine release from skeletal muscle cells is also modulated by the local pH (61, 62, 64). During high-intensity contractions, anaerobic metabolism contributes significantly to local energy production and the resulting lactic acidosis may facilitate adenosine release and the subsequent increase in blood flow. Therefore, it appears that, in the presence of high metabolic activity and the enzymatic ability to break down AMP, adenosine plays a major role in the expression of functional hyperemia. The intermediate breakdown products of ATP, ADP, and AMP are also vasoactive. However, measurements of venous blood concentrations during muscle contractions found concentrations approximately one-fifth of the threshold concentration for vasodilation (65, 66), suggesting minimal contributions to functional hyperemia.

Vasoactive Ions. Since the early studies of functional vasodilation identified the vasodilator effects of venous blood from contracting muscle (40, 41), subsequent studies focused on identification of vasodilator chemicals in the venous effluent. Significant correlations between the venous concentration of a substance and the magnitude of functional hyperemia were assumed to support a potential cause-and-effect or dose-response relationship, and arterial infusions were used to assess the range of concentrations that produced vascular responses. Potassium ion (11, 13, 41, 47), hydrogen ion (13, 41, 47), magnesium ion (13, 41) concentrations, and overall osmolarity (11, 13, 41, 47) were among the vasoactive substances found to be increased in the venous blood of active skeletal muscle, and each has been considered to play a role in functional vasodilation.

Venous blood potassium concentration increases during muscle contractions (11, 13, 41, 47), presumably due to potassium efflux from skeletal muscle cells during depolarization and excitation. The concentration of potassium in venous blood has been found to be proportional to the change in vascular resistance in active skeletal muscle (5, 47), and the vasodilator effects of local potassium infusion (41) and application (5) have been demonstrated. While these studies implicate the possibility of a cause-and-effect relationship between tissue potassium and functional vasodilation, other studies have found both the increase in venous potassium (67) and the dilator response to infused potassium (41) to be transient in nature, suggesting a role in the initiation, but not maintenance, of functional vasodilation. In addition, infusion of potassium into the arterial circulation to produce venous concentrations comparable to those observed in exercise had no effect on resting muscle blood flow or on the relationship between oxygen consumption and tissue blood flow during contractions of the dog gastrocnemius muscle (7). Further, microelectrode measurements next to the arteriolar wall found no significant changes in local potassium ion concentration during various frequencies of contraction in the rat spinotrapezius muscle (50). Therefore, local potassium release has been virtually dismissed as a primary mediator of

functional hyperemia. However, a recent study suggests that increases in systemic blood potassium concentration during exercise of a large muscle mass, such as cycling in humans, may be sufficient to induce vasodilation in other vascular beds, including resting skeletal muscle (68).

Hydrogen ion efflux also increases during muscle contractions (13, 41, 47), presumably as a result of increases in anaerobic metabolism. While there is no apparent correlation between venous blood hydrogen ion concentration and vascular resistance (47), a decrease in venous blood pH appears to be sustained throughout the contraction period (41). However, periarteriolar measurements of hydrogen ion activity failed to find significant changes in the concentration during muscle contractions with sustained functional vasodilation in the rat spinotrapezius muscle (50). In addition, increasing the periarteriolar hydrogen ion concentration by 30–40 n*M* (pH 7.4–7.1) by superfusion with an acidic fluid resulted in less than a 10% dilation in arteriolar vessels in the resting muscle (50). Therefore, the physiological changes in local pH are likely too small to elicit a substantial amount of vasodilation during muscle contractions.

The osmolarity of venous blood also increases during muscle contractions (11, 13, 41, 47), presumably the result of increased concentrations of various ions and metabolic by-products. Generalized increases in osmolarity can result in 20%–30% dilation of skeletal muscle arterioles (69). However, the increase in venous blood osmolarity during muscle contractions was found to be unrelated to the magnitude of the decrease in vascular resistance (5, 47), and the duration of hyperosmotic conditions was found to be transient (13, 41, 67). In addition, infusion of hyperosmotic solutions to produce venous osmolarities comparable to those seen during exercise does not produce comparable vasodilation (13), nor does it alter the relationship between blood flow and tissue oxygen consumption (7). Therefore, increases in local osmolarity are not likely responsible for a substantial portion of functional vasodilation.

It is important to point out that although evaluation of the relationships between vascular resistance and venous blood or arterial infusion concentrations of vasoactive chemicals may provide circumstantial evidence for a role in functional vasodilation, no cause-and-effect conclusions can be drawn. As can be seen from the data presented for oxygen in Figure 2, venous blood concentrations may not accurately reflect changes in tissue or periarteriolar concentrations of various substances. In addition, arterial infusion likely does not mimic the spatial distribution of chemical concentrations produced during muscle contractions. However, absence of a change in periarteriolar concentration does not eliminate a given substance from having a role in functional vasodilation, as indirect effects related to venous blood concentrations may be present.

Additive and Synergistic Effects. Arteriolar vasodilation during skeletal muscle contractions cannot be attributed to changes in the local concentration of any single chemical related to increased tissue metabolism. However, simultaneous alteration of multiple chemical factors has a synergistic effect on vascular resistance. For example, Skinner and Costin (11) found that simultaneous manipulations of the oxygen content, potassium concentration, and osmolarity of arterial blood could produce vasodilation comparable to that seen during contraction of the dog gracilis muscle, while manipulation of any single factor resulted in only modest dilation. Stowe *et al.* (67) found that correction of the PO_2 and pH completely abolished the vasodilator properties of venous blood from the contracting dog gracilis muscle. In addition, Mohrman and Regal (9) evaluated the relationships between venous blood PO_2, PCO_2, and skeletal muscle blood flow under resting and exercise conditions, and concluded that the combined influences of oxygen and carbon dioxide "could account for nearly all of the hyperemia response to steady-state muscle exercise." It is possible that a variety of chemical combinations can result in profound increases in skeletal muscle blood flow, and the specific combination responsible for functional dilation may differ between skeletal muscle fiber types, contraction frequencies, stimulation parameters, and species.

Prostaglandins. Prostaglandin production increases in skeletal muscle during muscle contractions as evidenced by an increase in the efflux of the stable breakdown products of arachadonic acid metabolism (prostacyclin [$PGF1\alpha$] and prostaglandin E_2 [PGE_2]) (48, 70, 71). Both prostacyclin and PGE_2 are potent vasodilators of the skeletal muscle microcirculation and likely play a role in the regulation of basal vascular tone (72). Prostaglandins are released in response to local hypoxia (43, 45, 73), a condition that may exist in some tissue locations during muscle contractions. Prostaglandins are also released from the vascular endothelium in response to an increase in flow velocity (26, 73–75), a mechanism that may be involved in the dilation of the feed arteries during contractions (76).

The role of prostaglandins in the expression of exercise hyperemia has primarily been studied by blocking prostaglandin production through inhibition of cyclo-oxygenase with indomethacin or aspirin. As early as 1976, Kilbom and Wennmalm (73) found that systemic administration of indomethacin did not alter resting blood flow to the human forearm, but significantly reduced both reactive (~50%) and functional (~25%) hyperemia. Blood flows were measured both during and after isometric contractions and after com-

pletion of dynamic contractions. A 1985 study by Cowley *et al.* (77) found similar results for the human leg using treadmill walking: administration of either indomethacin or aspirin did not alter resting flow, but significantly reduced both peak and total recovery blood flows by ~50%. Recovery time to resting blood flow was also hastened in the presence of both cyclo-oxygenase inhibitors. While these two studies suggest a major role for prostaglandins in the expression of functional hyperemia, the results are limited by the fact that, at least for dynamic exercise conditions, blood flow measurements were obtained after the cessation of muscle contractions. A 1979 study by Nowak and Wennmalm (78) used the indicator dilution method for blood flow measurements and found that systemic administration of indomethacin had no effect on leg blood flow during treadmill walking. Therefore, although these results seem to indicate a role for prostaglandins in reactive and postexercise hyperemia, they do not conclusively demonstrate a role for prostaglandin-mediated dilation during dynamic muscle contractions.

The role of prostaglandins in functional hyperemia has also been challenged by results obtained in experimental animals, where blood flow measurements during exercise were possible. Specifically, administration of indomethacin (i) reduced reactive hyperemia, but not the hyperemia during dynamic contractions in the isolated dog hindlimb (79); (ii) did not alter the relationship between oxygen consumption and blood flow during free flow conditions in the dynamically contracting dog hindlimb (48); and (iii) did not alter blood flow during static contractions of the cat hindlimb (80). One study also reported that indomethacin actually increased functional hyperemia after 10-sec contractions in the isolated dog hindlimb (81). Administration of meclofenamate, another cyclo-oxygenase inhibitor, was found to have no effect on the vascular responses during hypoxia, reactive hyperemia, or muscle stimulation in the isolated dog hindlimb (82), further suggesting a minor role, at most, for prostaglandins in the mediation of functional hyperemia.

A more recent study of the effects of indomethacin in the human forearm found a 10%–20% reduction in blood flow measured during transient pauses (4–5 sec) in muscle contractions (70), presumably providing more direct evidence that prostaglandins are involved in blood flow regulation during human exercise. However, in this study indomethacin also reduced resting muscle blood flow by ~25%, and, it is possible that the reduction in flow observed during exercise was secondary to the increase in basal vascular tone (83, 84).

In summary, the experimental evidence indicates that prostaglandins play a role in reactive and postexercise hyperemia in humans, and suggests, but does not conclusively prove, a role in functional vasodilation during exercise. In a related issue, the local release of kinins also increases immediately after the cessation of muscle contractions (85); these chemicals may have direct dilator effects on the local vasculature as well as secondary effects mediated through the stimulation of prostaglandin production.

Neural Regulation

The rapid response of arteriolar vessels to skeletal muscle contraction suggests that neural mechanisms may be involved in at least the initial phase of functional vasodilation (86). Honig and Frierson (86) documented vasodilation after a single twitch of the dog gracilis muscle and Gorzinsky, Klitzman, and Duling (30, 52) observed local dilation of arteriolar vessels after one twitch of a single muscle fiber or small group of fibers in the hamster cremaster muscle; similar results have been reported for the rat spinotrapezius muscle (87). In these cases, the local vascular responses were essentially instantaneous and were presumed to occur in the absence of significant increases in metabolism or accumulation of metabolic by-products. However, the conclusion that neural mechanisms play a major role in functional vasodilation was traditionally challenged by the fact that exercise hyperemia is expressed in extrinsically denervated muscles (88). Yet, Honig (86, 89) has demonstrated that local application of an anesthetic partially blocks the vasodilation observed during sustained muscle contractions in chronically and acutely denervated tissues. These results led him to conclude that "intrinsic" neurons are involved in the vascular response to muscle contractions (86); the presence of neural ganglion cells in the walls of arterioles in chronically denervated skeletal muscle had previously been demonstrated in his laboratory (90).

Neural vasodilation could result from the activation of vasodilator fibers or the withdrawal of constrictor influences. In the intact tissue, the skeletal muscle vasculature is under tonic sympathetic tone, and acute denervation results in more than a 2-fold increase in resting muscle blood flow (15, 16). However, there is a generalized increase in sympathetic neural activity during exercise which favors peripheral vasoconstriction, rather than vasodilation (24, 25, 29). In an attempt to reconcile the increase in active skeletal muscle blood flow and vascular conductance in the face of increased sympathetic activity, Remensnyder (91) theorized that a "functional sympatholysis" occurs in active skeletal muscle. He proposed that the metabolic conditions associated with muscle contractions decrease the vasoconstrictor effects of sympathetic activation, either through modulating the release of norepinephrine or by interfering with receptor-binding and postreceptor events. Subsequently, a variety of local chemical conditions (i.e., increased potassium,

hydrogen ion, adenosine, and osmolarity; decreased oxygen) were found to inhibit the skeletal muscle vascular responses to sympathetic stimulation (11, 21, 22, 92, 93), primarily by reducing the release of norepinephrine. It was concluded that the vasculature of active skeletal muscle tissue was protected from sympathetic vasoconstriction during exercise.

However, more recent evidence suggests that functional sympatholysis is not a consistent phenomenon. Rowell (10, 29) has presented the argument that maximal dilation of a large mass of exercising muscle would result in a precipitous decline in arterial pressure in humans due to the functional limitations of maximal cardiac output. He concludes that, at least under some conditions, the vascular bed of active skeletal muscle is not maximally dilated, but rather is constricted in response to sympathetic activation in an attempt to preserve mean arterial blood pressure. Supporting evidence is found in the fact that the carotid baroreflex is fully maintained during total body exercise, a condition that requires sympathetic constriction in active muscle tissues to accomplish homeostatic reflex changes in arterial pressure (94, 95). Subsequent studies have demonstrated that direct sympathetic stimulation during muscle contractions does produce vasoconstriction relative to the functionally dilated state (96), and this constriction can be of sufficient magnitude to limit muscle oxygen consumption (16, 96). In addition, while the data presented in Figure 3 from Dodd and Johnson (97) demonstrate that functional vasodilation does occur in the presence of sympathetic stimulation, the vasculature obviously remains constricted relative to that observed in the absence of sympathetic stimulation. Recent studies have further demonstrated the physiological presence of sympathetic constriction during both light and moderate intensity exercise of a small muscle mass (human forearm) (16, 98). These results from Joyner *et al.* (98) are presented in Figure 4 and illustrate higher blood flows to the active forearm during supine exercise when compared with upright exercise. Presumably, general sympathetic activity is higher in the upright position due to the hydrostatic effects on baroreceptor activity, and this sympathetic activity is expressed as vasoconstriction and a decrease in blood flow to the active muscle. Likewise, calf blood flow during low-intensity exercise has been shown to be greatly reduced by the addition of exhaustive hand grip exercise, concurrent with an increase in sympathetic activity to both muscle groups (99). These experiments (16, 98, 99) demonstrate sympathetic modulation of active skeletal muscle blood flow during conditions in which cardiac output could easily maintain arterial pressure during maximal functional vasodilation. However, sympathetic neural constriction is not evident in the initial moments of exercise (98); therefore, sympathetic withdrawal may very well play a role in the initial vascular responses during muscle contractions. A recent study by Thomas, Hansen, and Victor (93) suggests that the efficacy of sympathetic activation during muscle contractions is fiber type and intensity dependent. They found α_2-mediated constriction to be inhibited during high- but not low-intensity contractions of glycolytic muscles; adrenergic vasoconstriction was not inhibited during high- or low-intensity contractions of oxidative muscles. These results may explain the opposing conclusions of other studies evaluating functional sympatholysis during muscle contractions. In any event, the recent data clearly demonstrate that sympathetic vasoconstriction continues to modulate skeletal muscle blood flow during most forms of human exercise.

Sympathetic vasodilator fibers have been identified in skeletal muscle tissues of various species. The presence of arteriolar β-adrenergic receptors is illustrated by the vasodilation elicited during low dose (10^{-10}–10^{-8} g/ml) topical application of adrenaline and noradrenaline (100). Physiologically, sympathetic

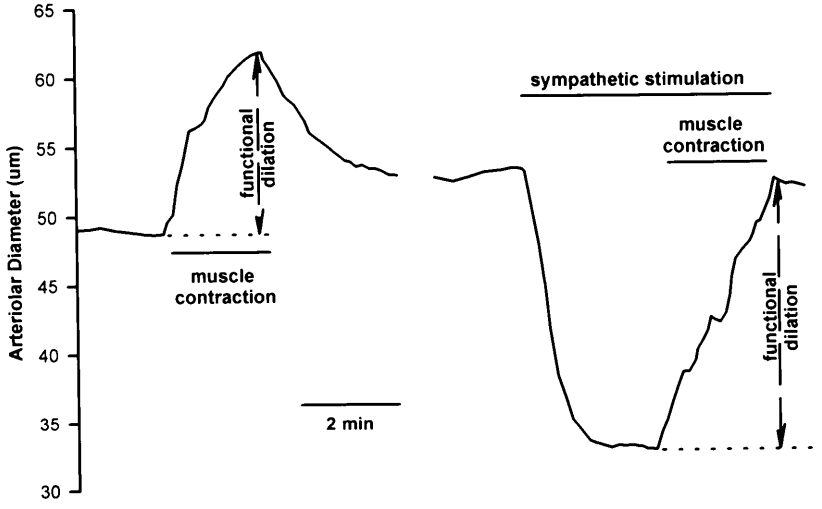

Figure 3. The left tracing illustrates the arteriolar dilation in response to 4-Hz contractions of the cat sartorius muscle. The right tracing illustrates the effects of 8-Hz sympathetic stimulation in the resting and contracting muscle. Sympathetic stimulation results in profound vasoconstriction in the resting muscle. Simultaneous sympathetic stimulation and muscle contraction results in functional dilation, but the arteriole remains constricted relative to the diameter observed in the absence of sympathetic stimulation. Figure based on personal communication from L. Dodd and P. C. Johnson. Completed study presented by Dodd and Johnson (97).

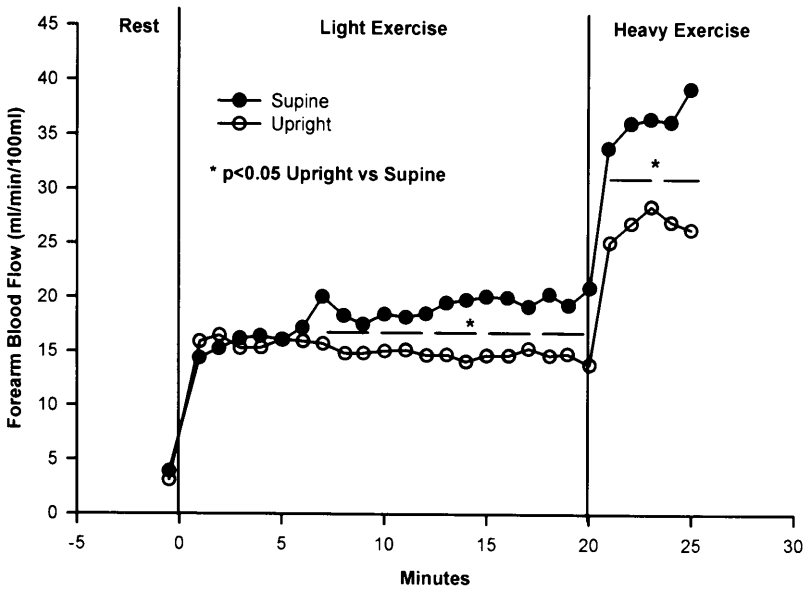

Figure 4. Forearm blood flow response to light and heavy exercise, performed in the supine and upright positions. During upright conditions, it is expected that sympathetic neural activity is increased due to the gravitational effects on carotid baroreceptor activation. Blood flow to the exercising forearm is lower in the upright than supine position during steady state light intensity exercise and throughout the heavy exercise period. These data suggest that sympathetic vasoconstriction reduces blood flow to active skeletal muscle. Horizontal dashed lines and asterisks delineate time during which significant group differences were evident. Based on data presented by Joyner *et al.* (98).

stimulation can produce a 35% decrease in hindlimb vascular resistance in the presence of α-receptor blockade, and this response is abolished by the β-antagonist propranolol (17, 101). Lundvall and Jarholt (102) further demonstrated that β-mediated dilation partially offsets α-mediated constriction during general sympathetic activation, as α- and β-receptors are simultaneously stimulated by the release of norepinephrine. The β-dilation effects seem to be most prevalent in the smaller arterioles, and may play a role in facilitating homogeneous capillary perfusion during a low-flow state (17). It seems reasonable to conclude that β_2-adrenergic dilation may contribute to increased capillary perfusion during low-intensity exercise associated with low levels of sympathetic activation. Circulating norepinephrine and epinephrine likely have effects parallel to sympathetic activation, although differences in receptor specificity will determine the net change in vascular resistance.

Sympathetic cholinergic fibers have also been identified in the skeletal muscle of several species (18–20, 103). In humans, atropine was found to block the vasodilation in the contralateral forearm muscle during isometric handgrip contractions, suggesting this dilation was mediated by sympathetic cholinergic activity (104). In contrast, Armstrong and Laughlin (105) found that atropine did not alter skeletal muscle blood flow during treadmill exercise in rats. Although the ganglia cells of denervated skeletal muscle described by Honig (90) stained positive for cholinesterase, functional studies led him to conclude that the final neurovascular smooth muscle mediator was something other than acetylcholine. Other punitive neurotransmitters for functional vasodilation include ATP, vasoactive intestinal polypeptide (VIP), Substance P, and dopamine (106). These substances are either co-released during sympathetic stimulation or located in separate neurons. The continued study of nontraditional neurotransmitters may increase our understanding of the role of neural vasodilation in skeletal muscle functional hyperemia.

Mechanical Factors

Figure 5 schematically illustrates the various mechanical factors that may affect muscle blood flow during contractions. From a purely hemodynamic perspective, the increase in systemic mean arterial pressure that generally accompanies exercise (29) increases skeletal muscle blood flow by simply providing an increase in perfusion pressure. This pressor response is primarily accomplished by an increase in cardiac output, but is also accompanied by a necessary increase in the vascular resistance of nonexercising tissues, such as visceral organs and inactive skeletal muscle tissues (24, 29). Several regulatory systems seem to be involved in this response. There is some evidence that feed-forward sympathetic activation, originating in the cortex, plays a role in the pressor response during volitional exercise (25, 107). In addition, for unknown reasons, the regulatory range of the carotid baroreflex is shifted upward during exercise such that sympathetic activation is reflexly elicited to increase arterial pressure to this higher range (29, 94).

The pressor response to muscle contraction is also mediated by the metabolic conditions of the active muscle tissue (108). Type III and IV afferent neurons located in skeletal muscle tissue respond to various chemical, metabolic, and mechanical stimuli, and activation of these neurons leads to a reflex pressor response (29, 109). Current data indicate that this reflex response is not related to venous blood oxygen content (110), absolute or relative concentrations of cre-

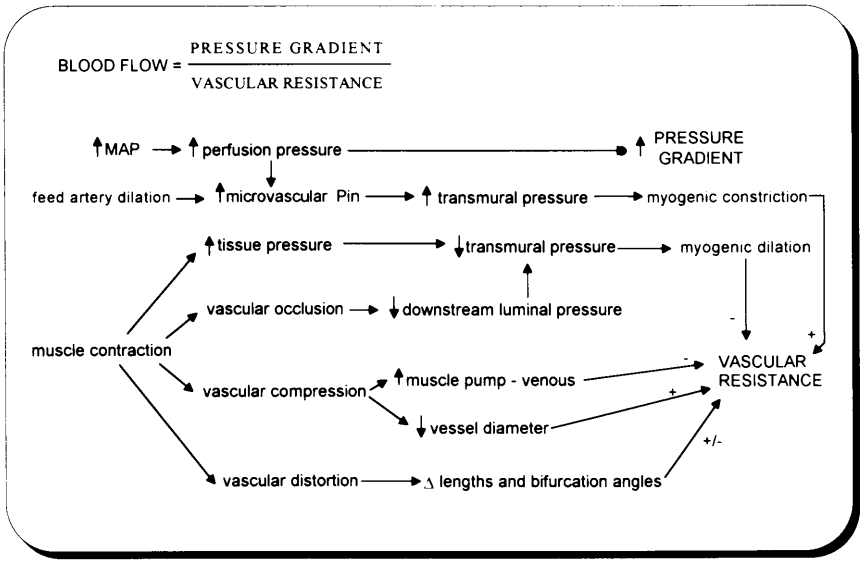

Figure 5. Schematic representation of the various mechanical factors which may affect skeletal muscle blood flow during exercise.

atine phosphate or inorganic phosphate (111, 112), or steady-state changes in interstitial potassium concentrations (110, 113). The primary metabolic mediator of the reflex appears to be local pH. Sheriff *et al.* (110) found a proportional relationship between muscle pH and systemic arterial pressure in the dog. Subsequently, others (111, 112) found significant relationships between the degree of acidosis in contracting skeletal muscle and the sympathetic nerve activity to inactive muscles in humans. Rotto, Stebbins, and Kaufman (114) have also demonstrated that lactic acid is more effective in eliciting reflex sympathetic heart rate and pressor responses than equimolar concentrations of hydrochloric acid, suggesting that lactate may provide some facilitatory effects under physiological conditions. In addition, administration of either cyclooxygenase inhibitors (80) or captopril (80, 115) diminishes the reflex pressor response to muscle contraction, suggesting that local production of prostaglandins and kinins plays a role in the response. Recent results from Sinoway *et al.* (116) have further demonstrated that physical conditioning of a skeletal muscle suppresses the reflex sympathetic activation in response to contractions and alters the relationship between muscle pH and sympathetic activation. These results suggest that the effects of local pH are modulated by other factors. Many of the local chemical conditions which potentially contribute to functional vasodilation also appear to elicit or facilitate reflex increases in perfusion pressure during muscle contractions, which further enhances muscle blood flow.

Pressure-dependent or myogenic vascular responses also contribute to blood flow regulation in skeletal muscle. The myogenic response is intrinsic to the vessel wall and is expressed as constriction in response to an increase in distending pressure, and dilation in response to a decrease in distending pressure (36, 37). As illustrated in Figure 5, an increase in blood pressure and dilation of upstream arterial vessels during exercise would contribute to an increase in distending pressure in the skeletal muscle microcirculation, and hence, a stimulus for myogenic vasoconstriction. However, tissue pressure also increases during muscle contractions (31, 32) and a mechanical torquing and occlusion of vessels likely occurs (117, 118) during even low-intensity contractions (15%–30% of maximal force production) such that luminal pressures are decreased downstream from the site of obstruction. Under these conditions, the pressure gradient across the vessel wall (transmural pressure; P[internal] – P[external]) decreases in the distal vasculature of contracting muscle, and, hence, a stimulus for myogenic dilation exists.

A study by Mohrman and Sparks (31) reported that the increases in tissue pressure during muscle contractions, which they measured to be greater than 100 mm Hg, could account for ~50% of the dilation observed following brief (1 sec) tetanic contractions of the dog gastrocnemius muscle. In contrast, Bacchus *et al.* (32) found no flow response to 25– to 50–mm Hg pulsatile changes in extravascular pressure in the isolated dog gracilis muscle, and concluded that myogenic dilation does not contribute to functional hyperemia. The opposing results in these two studies could be related to the magnitude and duration of the applied pressure stimulus. Bacchus *et al.* (32) used square wave pressure pulses (2 or 5 pulses/sec) of 15–50 mm Hg in magnitude to correspond to the pressure changes measured (10–30 mm Hg) during phasic contractions at 2–5 Hz. In contrast, Morhman and Sparks (31) used 50– to 125–mm Hg pressures applied continuously for 1 sec to correspond to the pressures they measured during tetanic contractions. To date, no subsequent studies have attempted to reconcile these opposing results.

Despite this controversy, the myogenic reactivity

of the skeletal muscle vasculature has been further evaluated. Early reports suggested that the vasoconstrictor response to a rapid increase in intravascular pressure was significantly suppressed during muscle contractions (119). However, more recent studies indicate that myogenic constriction can override metabolic dilation in both resting (120) and contracting (121) muscle tissue. Meininger *et al.* (120) have clearly shown that myogenic constriction is maintained in the presence of extremely low tissue PO_2s (<10 mm Hg) in resting skeletal muscle. In addition, Lash and Shoukas (121) partitioned the vasoconstrictor response to baroreflex activation into neural and pressure-dependent components, and their results for intermediate sized (2A) arterioles of the rat spinotrapezius muscle are illustrated in Figure 6. As expected, arterial pressure increased 20–25 mm Hg during bilateral occlusion of the carotid arteries, and arterioles constricted in both the resting and contracting muscle (normal occlusion). However, when arterial blood pressure was maintained constant during carotid artery occlusion (isobaric occlusion), arteriolar diameter remained relatively constant, indicating that the constriction observed during normal occlusion conditions was secondary to the increase in arterial pressure.

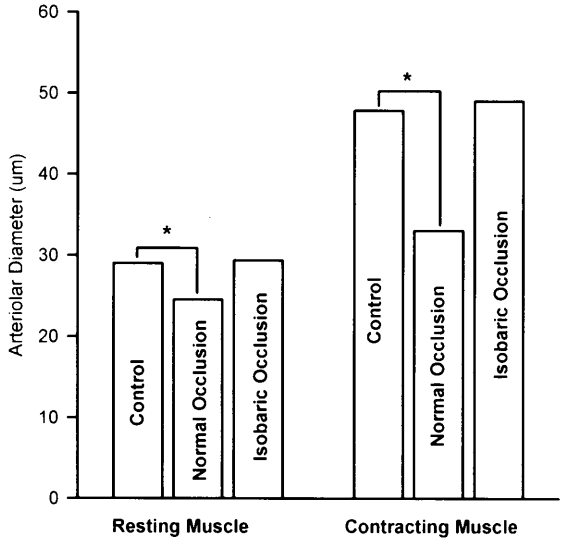

Figure 6. Response of rat spinotrapezius muscle arterioles to bilateral occlusion of the common carotid arteries. Carotid occlusion results in a decrease in the pressure sensed by the carotid baroreceptors, which subsequently elicits a reflex pressor response. During normal occlusion conditions, mean arterial pressure increased ~25 mm Hg. During isobaric occlusion conditions, arterial pressure was maintained constant by volume displacement. In both the resting and contracting muscle, intermediate sized arterioles constricted significantly (*) during normal but not isobaric occlusion conditions. These data indicate that the constriction observed during normal conditions was secondary to the increase in perfusion pressure, and was possibly myogenic in origin. Further, functional vasodilation was reduced by 60%–70% during normal occlusion conditions, suggesting that myogenic factors can significantly reduce functional hyperemia. Based on data presented by Lash and Shoukas (121).

This pressure-dependent constriction may be attributed to either autoregulatory attempts to maintain a constant blood flow or myogenic attempts to maintain a constant wall tension or stress. The estimated change in blood flow (based on changes in vessel diameter and perfusion pressure) suggests that flows during normal occlusion conditions were reduced ~50% in both resting and contracting muscle, which is not consistent with the concept of blood flow autoregulation. Therefore, it is likely that myogenic constriction is at least partially responsible for the constriction observed during carotid artery occlusion. With respect to exercise, the results from contracting muscle indicate that pressure-dependent constriction can suppress functional vasodilation of intermediate and small sized arterioles by 60%–70% in this preparation. The potential for myogenic vascular regulation during muscle contractions is apparent, but the degree to which myogenic dilation and/or constriction modulates functional hyperemia remains unknown.

Vascular compression during muscle contractions may also directly inhibit blood flow through the active tissue. Gray and Staub (117) found that the calculated vascular resistance of skeletal muscle actually increased during tetanic isometric contractions of the dog calf muscle at greater than 40% of maximal tension. In an attempt to determine the anatomical origin of this increase in vascular resistance, they evaluated the possibilities of vessel compression and vessel occlusion. In their particular model, tissue pressure, as reflected by wedge pressure in the isolated circulation, increased 10–65 mm Hg during contractions, depending on the state of the vascular bed (empty or full). Since their estimates of tissue pressure did not exceed mean arterial pressure, they concluded that backflow could not occur and that vascular compression was not responsible for the increase in resistance. However, they did not seem to consider the fact that the hydrostatic pressure in the small arteries and arterioles within the tissue are likely less than 60% of aortic pressure (38), and that compression of these vessels would increase the effective resistance, independent of actual flow reversal. In addition, they further dismissed the role of vascular compression by citing their data indicating that passive stretch of the muscle, which produced increases in longitudinal tension and tissue pressure comparable to those seen during contraction, resulted in a significantly smaller increase in vascular resistance. However, closer examination of the data suggests that more than 50% of the increase in vascular resistance observed in the actively contracting muscle could be explained by passive mechanical factors related to the increase in tissue pressure. In a concurrent study, Gray, Carlsson, and Staub (118) used angiography to visualize vessel morphometry during muscle contractions, and found significant

"twisting or nipping" of vessels entering the muscle tissue or transversing independent fasciculi. They concluded that such distortion of the larger vessels was the primary cause of the increase in vascular resistance during contractions.

While these studies may not clearly distinguish between vascular compression and occlusion during muscle contractions, they do illustrate an important point: skeletal muscle blood flow is mechanically restricted during force production at intensities greater than 40% maximal tension. This effect is sustained during tetanic contractions, and is intermittent during phasic contractions. As a corollary, the contraction duty cycle (contraction-relaxation) may significantly alter total muscle blood flow at comparable work loads. In addition, the structural characteristics of the muscle may alter the degree to which mechanical factors can restrict flow. For example, one skeletal muscle preparation frequently used to evaluate the microvasculature, the rat spinotrapezius muscle, can be described as pennate in structure (i.e., flat and fan shaped), and only the smaller microvessels (third and fourth order) penetrate the muscle surface. The anatomical characteristics of this muscle likely minimize any increases in tissue pressure, and the arrangement of the vasculature likely minimizes the occurrence of vascular compression. In addition, the concurrent contraction of all fibers, as elicited by electrical stimulation during experimental conditions, also likely minimizes the torquing of vessels which would occur with asynchronous contraction of adjacent fasciculi. Therefore, it is not surprising that vascular compression and/or occlusion are not apparent during experimental observations (personal observations). Similar conditions are likely also present in the cremaster muscle preparation, which is generally composed of four muscle cell layers arranged in an alternating perpendicular fashion. It is likely that neither of these preparations accurately reflect the mechanical conditions of the vasculature during volitional recruitment of a more "typical" skeletal muscle. Nakao and Segal (122) have also recently described the effects of changes in muscle length on microvascular diameters, bifurcation angles, and interbranch lengths. Such alterations in vessel morphology could significantly increase or decrease the hemodynamic resistance of the muscle vasculature.

While the previous discussion indicates that mechanical factors may restrict blood flow, others (33–35, 123) have suggested that skeletal muscle contractions actually facilitate flow, especially the rapid increase in skeletal muscle blood flow at the onset of exercise. Theoretically, the contraction of surrounding skeletal muscle forces blood out through the venous circulation, effectively producing a "muscle pump." Reversal of flow during muscle relaxation is prohibited by the venous valves. Sheriff *et al.* (33) have determined that the muscle pump is responsible for 30%–50% of the increase in muscle blood flow during low intensity contractions, and is responsible for the bulk of the immediate increase in flow during all conditions. They (33) also hypothesize that, in upright humans and animals, the compression of the venous system during muscle contractions and the presence of venous valves allows for a transient separation of the muscle vasculature from the hydrostatic fluid column, thereby reducing venous pressure and increasing the perfusion pressure gradient across the muscle tissue; such an effect has also been implied by data collected in humans (34, 35). In addition, Laughlin (124) has proposed that, with muscle relaxation, the release of compressive forces allows the parenchymal tissue to recoil, pulling open the encompassed veins and creating a negative pressure, which also effectively increases the arteriovenous pressure gradient. The net effect of these various potential mechanical factors would be to increase the "virtual conductance" of the muscle circulation (33), as calculated from measurements of pressure and flow. These effects are independent of changes in arterial diameter, or traditional "functional vasodilation."

Upstream Arterial Vasodilation

Approximately 40%–50% of total vascular resistance is located upstream from the microcirculation of skeletal muscle tissue (i.e., in the feed arteries) (38). Based on this data, for a constant perfusion pressure, total elimination of the microvascular resistance would result in only a 2.5-fold increase in muscle blood flow. In both humans and animals, skeletal muscle blood flow increases more than can be accounted for by complete elimination of the microvascular resistance and any physiological increase in mean arterial pressure or perfusion pressure (3, 4, 125). In 1986, Segal and Duling (39) noted this discrepancy and hypothesized that vessels upstream from the tissue must also dilate during skeletal muscle contractions; they subsequently published observations of a 25% increase in feed artery diameter during contraction of the cremasteric and gracilis muscles of the hamster (126, 127). Data from Bjornberg, Maspers, and Mellander (128) also suggested that large arterioles (>25 μm in diameter) and small arteries play a major role in skeletal muscle functional hyperemia. A coordination of upstream functional dilation was also described by Saito, Eraslan, and Hester (129), who found that an increase in metabolism of the distal hamster cremaster muscle (2,4-dinitrophenol [DNP]) resulted in dilation of the large arterioles (1A) in the anatomically isolated proximal tissue. Lash (38) subsequently quantified the degree of upstream dilation by modeling the vasculature as three series resistance elements and calculating the

changes in segmental resistance from measurements of pressure and flow. Those results, presented in Figure 7, indicate that the resistance of the vasculature upstream from the muscle tissue decreases by 80%–90%, to 10%–20% of control, during moderate- and high-intensity muscle contractions. Based on a *radius*^{4} relationship to segmental resistance, these data reflect an average dilation of 80% in the primary resistance vessels of the proximal vasculature. Further calculations indicate that dilation of the proximal vessels accounts for 30%–40% of the total increase in skeletal muscle blood flow observed under these experimental conditions. Williams and Segal (130) have determined that the dilatory capacity of feed vessels varies with the fiber type of the dependent muscle; greater dilatory reserve is present in vessels supplying the most oxidative tissues. The dilatory responses of feed vessels during muscle contractions are also fiber type dependent, with less dilation required by the most oxidative tissues at like relative contraction intensities.

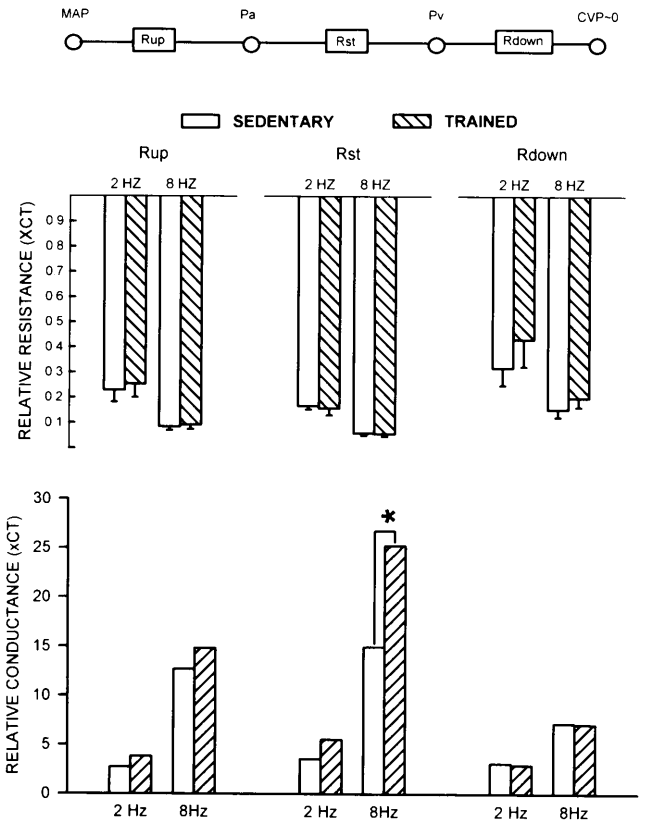

Figure 7. The effects of 2- and 8-Hz contractions of the rat spinotrapezius muscle on segmental vascular resistances (upper panel) and conductances (lower panel). Vascular resistances were calculated from measurements of pressure and flow for the upstream (feed arteries), microvascular (spinotrapezius [st]), and downstream (venous) segments. The decrease in resistance of the upstream segment reflects dilation of the feed arteries which are anatomically separated from the active muscle tissue. The magnitude of the decrease in upstream resistance is consistent with an 80% dilation of the resistance vessels during 8-Hz contractions. When expressed as vascular conductance (1/R), differences are apparent between sedentary and treadmill trained groups. The greater increase in conductance in trained animals reflects enhanced functional dilation of the arterioles (see Fig. 10). This vascular adaptation occurs despite the absence of an increase in oxidative enzyme activity in this muscle tissue. Based on data presented by Lash (38).

The dilation of upstream vessels has raised several questions related to the regulation of muscle blood flow, primarily because these vessels are not directly exposed to the mechanically and metabolically active tissue. Alterations in neural output may contribute to upstream arterial dilation. Feed-forward neural dilation may play a role in upstream arterial dilation during volitional exercise (25), and mechanical and/or chemical reflexes likely remain intact in experiments in anesthetized animals. Alternatively, Segal and Duling (127) have proposed that cell-to-cell communication along vascular structures contributes to upstream dilation. They have described propagated dilatory responses which span across branch orders (131) and from micro- to macro-vascular arterial vessels (126) during distal application of vasoactive drugs. The cellular mechanisms responsible for this communication are not completely understood, but recent work by these investigators suggest that gap junctions between either vascular endothelial or smooth muscle cells play a role in the transmission of this response (132–134).

A second possible mechanism for upstream arterial dilation is flow-mediated dilation through endothelial-derived relaxing factors (EDRFs; e.g., nitric oxide or prostaglandins). Presumably, metabolic dilation of the small arteriolar vessels results in an increase in flow through the proximal vessels, which, in turn, results in a release of EDRF from the endothelium and subsequent dilation of those proximal vessels (76). The role of prostaglandins in exercise hyperemia has been previously discussed in this review. It should be noted that, in the majority of studies cited, indomethacin was administered systemically such that prostaglandin production in the endothelium of upstream vessels, as well as the microvessels, would be attenuated. Therefore, the observed effects of indomethacin on skeletal muscle blood flow were likely a combination of the effects on upstream arterial and microvascular functional dilation.

The EDRF nitric oxide, or a related nitrosothiol compound, has been shown to play a role in determining basal vascular tone and reactivity to other vasoactive stimuli in skeletal muscle tissue (135). Sagach, Kindybalyuk, and Kovalenko (136) have reported that blockade of nitric oxide formation (gossipol) or action (through cGMP with methylene blue) significantly reduces functional hyperemia (by ~80%) in the isolated dog gastrocnemius muscle; conversely, administration of L-arginine, which enhances nitric oxide formation, results in nearly a 2-fold increase in the hyperemic response. A microvascular study by Hester, Eraslan, and Saito (137) demonstrates that blockade of EDRF

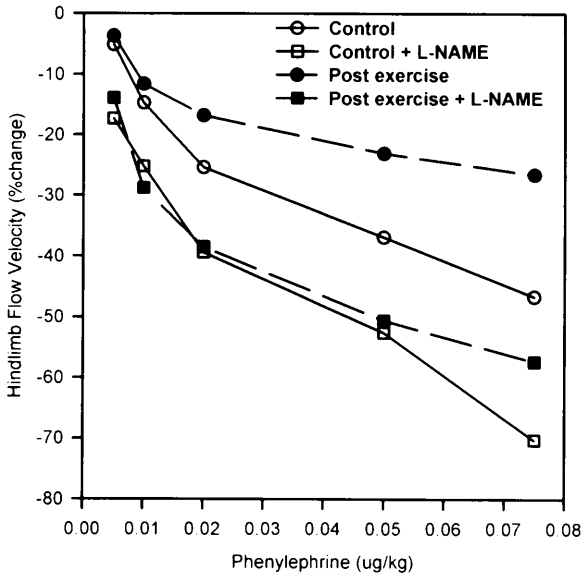

Figure 8. Decreases in rat hindlimb blood flows, reflecting vasoconstriction, during local infusion of phenylephrine (PE). An acute bout of treadmill running significantly decreases the vascular response to PE. Local administration of L-NAME, an inhibitor of nitric oxide production, results in a significant enhancement of the vascular response to all concentrations of phenylephrine tested, during both control and postexercise conditions. These data suggest that the suppression of vascular reactivity immediately following acute exercise is due to nitric oxide release during and immediately following treadmill running, and provide circumstantial evidence that nitric oxide release plays a role in functional vasodilation. Based on data presented by Patil, DiCarlo, and Collins (140).

formation (with Nω-nitro-L-arginine methyl ester; L-NAME) results in a ~25% suppression of functional dilation in the largest and intermediate-sized arterioles of the rat cremaster muscle, leading them to conclude that EDRF plays a major role in the response. Likewise, Hirai *et al.* (138) found that systemic administration of L-NAME reduced blood flow to hindlimb skeletal muscles of the conscious rat, both at rest and during treadmill running; the inhibition of the flow response was largest in the most oxidative muscles. Shen *et al.* (139) found a similar reduction of flow to the dog digitorum longus during treadmill running with the inhibition of EDRF production, but flows to four other active muscles were not significantly affected. There are at least two potential complicating factors in these studies, namely the effects of EDRF blockade on (i) resting vascular tone and (ii) systemic arterial blood pressure. Preconstriction of vessels tends to inhibit vasodilatory responses (83, 84), and the L-NAME suppression of basal EDRF release results in constriction of the largest arterioles and increases in the vascular resistance of the resting muscle. However, in the study by Hester *et al.*, the authors (137) point out that the dilation of intermediate sized arterioles is also inhibited by EDRF blockade in the absence of any effect on resting diameter. Yet, when initial diameters of the largest arterioles were regulated during EDRF blockade by addition of sodium nitroprusside, the same laboratory concluded that neither nitric oxide nor prostaglandins are involved in proximal arteriolar dilation during metabolic stimulation with DNP (129); these different results may simply reflect alterations in the initial vascular tone. Secondly, the systemic blockade of EDRF results in a 25– to 50–mm Hg increase in systemic arterial pressure (129, 138, 139). Therefore, inhibition of EDRF is likely accompanied by a substantial increase in the stimulus for myogenic constriction, which can inhibit functional vasodilation independent of effects on local EDRF action (121). However, the results of Sagach (136) were determined in the presence of relatively constant perfusion pressures.

Patile, DiCarlo, and Collins (140) have presented further circumstantial evidence that nitric oxide modulates vascular responses during exercise, and these

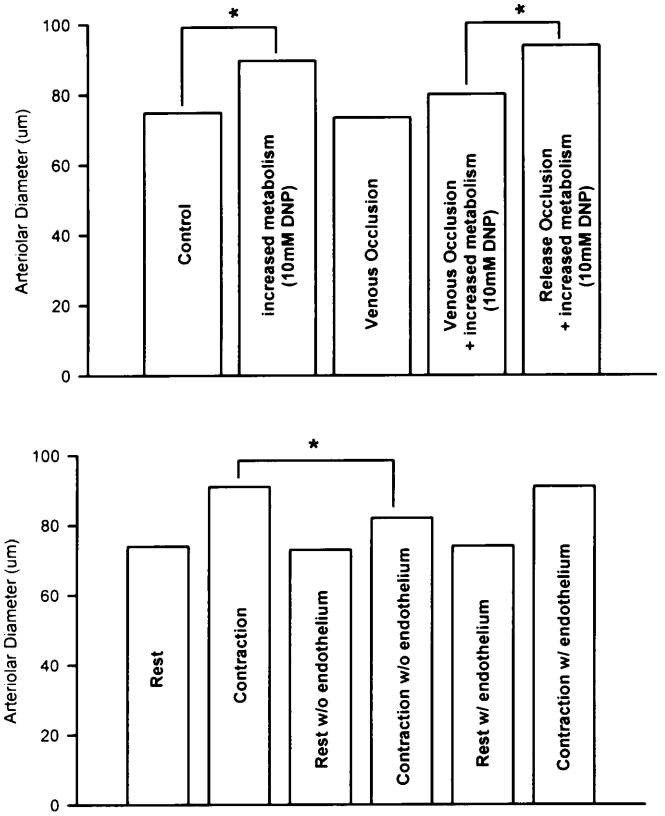

Figure 9. The effects of venular manipulation on arteriolar dilation in the rat cremaster muscle. As shown in the upper panel, large arterioles in the proximal tissue dilate when metabolism of the distal tissue is increased by application of 2,4-dinitrophenol (increased metabolism). However, this dilation does not occur when flow in the adjacent venule is occluded (Venous Occlusion + increased metabolism). The lower panel demonstrates that disruption of the venular endothelium (air bubble) suppresses the functional dilation of the adjacent arteriolar segment during muscle contractions (Contraction w/o endothelium). Functional dilation in arteriolar segments adjacent to venules with intact endothelium were unchanged (Contraction w/ endothelium). Together, these two studies suggest that biochemical or flow-related mechanisms stimulate the venular endothelium to release a vasodilator substance which enhances functional dilation of the adjacent arteriole during muscle contractions. Based on data presented by Saito, Eraslan, and Hester (137, 142).

results are presented in Figure 8. By measuring blood flow to the rat hindlimb, they determined that the vascular response to phenylephrine is suppressed immediately following acute exercise (Fig. 8, Control versus Post Exercise). However, local administration of L-NAME completely reverses this postexercise suppression (Fig. 8, squares), with no effect on systemic arterial pressure. These results suggest that the initial suppression of the vascular response to phenylephrine (Fig. 8, Post Exercise) is due to the release of nitric oxide during the exercise and recovery periods. Together, the majority of the current results seem to support a role for nitric oxide and other EDRFs in the coordinated response of larger arterial and arteriolar vessels during muscle contractions.

The anatomical proximity of the larger arterial and venous vessels (largest arterioles and all arteries) creates another potential mechanism for upstream arterial dilation, namely venous-arterial communication. Falcone and Bohlen (141) have demonstrated that venular release of EDRF can cause dilation of the nearby arteriole, and Hester (27) has reported that addition of adenosine to venular blood results in dilation of the paired arteriole. Saito, Eraslan, and Hester (28) have also determined that dilation of the feed vessels during distal application of DNP is dependent on flow in the adjacent venule, and these results are presented in the upper panel of Figure 9. The lower panel of Figure 9 illustrates results from another study by Saito *et al.* (142), in which they demonstrate that local disruption of the venular endothelium reduces functional dilation of the adjacent arteriole by ~50% (Fig. 9, Contraction w/o Endothelium versus Contraction). In the same preparation, functional dilation is maintained in arteriolar segments adjacent to venules with intact endothelium (Fig. 9, Contractions w/ Endothelium). If this response is mediated by the release of a vasoactive chemical, it is likely that the venular endothelium that remained intact produced enough chemical to influence arteriolar diameters adjacent to denuded venules. Therefore, these data suggest that the venular endothelium mediates more than 50% of the arteriolar dilation observed during muscle contractions. Together, these results suggest that a chemical or mechanical factor in venular blood, possibly EDRF, contributes significantly to the functional vasodilation of large arteriolar vessels. Presumably, such venous-arterial communication can also occur at the macrovascular level. Such a control system is teleologically relevant, as the content of the venous blood, which reflects substrate removal and metabolite production, would contribute to the regulation of arterial flow to the tissue.

Summary and Future Directions

Despite the persistent work in this area, the primary mechanisms responsible for the dilation of arterial vessels during skeletal muscle contractions remain relatively unknown. It seems apparent that metabolic, neural, humoral, and mechanical factors contribute to the coordinated cardiovascular response to exercise. The fact that no specific mediators have been identified may indicate that some yet to be discovered chemical or neurotransmitter regulates functional vasodilation. However, it may also indicate that the response is well preserved and protected by a redundancy of systems. Therefore, when any single regulatory mech-

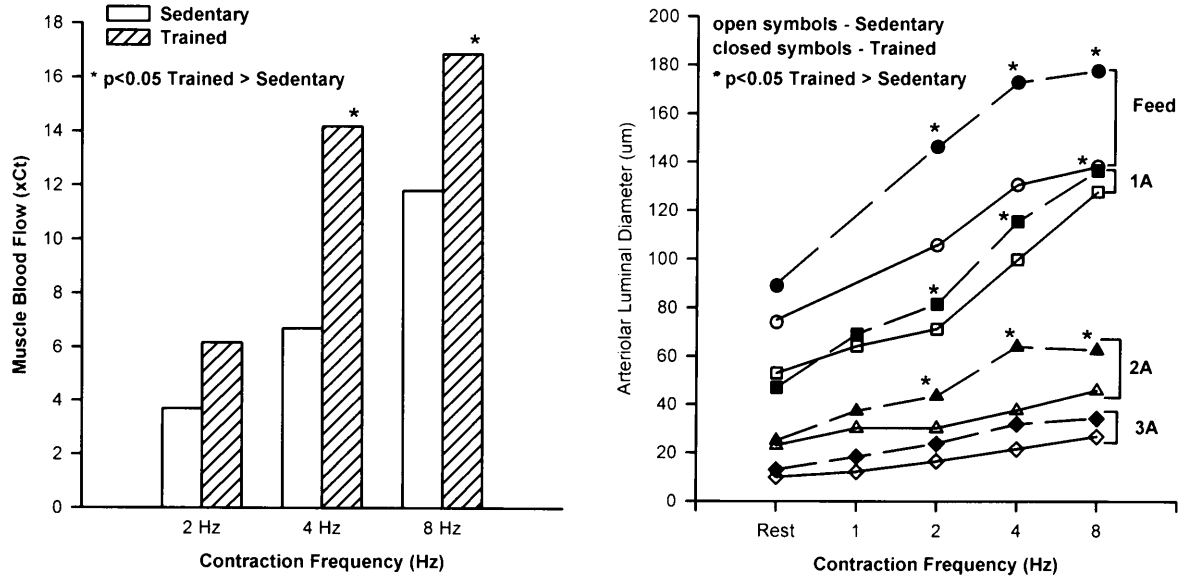

Figure 10. Functional hyperemia (left panel) and arteriolar vasodilation (right panel) in the rat spinotrapezius muscle of sedentary and treadmill trained rats. Blood flow in response to muscle contractions is significantly greater in trained than sedentary rats, as is the dilation of the terminal feed arteries and large (1A) and intermediate (2A) sized arterioles. These vascular adaptations occur despite the absence of an increase in oxidative enzyme activity in this muscle tissue. Based on data presented by Lash and Bohlen (148), and Lash (38).

anisms is removed experimentally, the other regulatory factors are adequate to elicit a relatively "normal" response. Similarly, the synergistic effects of concurrent stimuli present during muscle contractions may limit the interpretation of the results of experiments in which a single factor (i.e., tissue pH) is altered in isolation. In addition, the primary mediators of functional dilation may differ greatly between muscle fiber types and various contraction conditions (i.e., isometric versus phasic contractions, relative intensity, etc.). These factors have not been consistently considered in many of the past studies.

As is apparent by this review, many questions remain to be resolved regarding the role of nearly every known dilator mechanism in the expression of functional hyperemia. The close relationship between tissue metabolism and tissue blood flow (7–9) strongly suggests some common regulatory factor. However, under some conditions, this relationship is less apparent, and the active muscle tissue may be under- or over-perfused relative to the metabolic demands (143, 144). The roles of both constrictor and dilator neural factors are not completely understood, and few studies have evaluated the involvement of neural control outside of traditional adrenergic and cholinergic transmission. The various contributions of mechanical factors to the regulation of muscle blood flow are only beginning to be appreciated, and further evaluations of the role of myogenic factors and the physiological impact of the venous pump are warranted. And finally, the recognition that feed arteries contribute significantly to functional hyperemia, despite the anatomical separation from the contracting tissue, has led to investigations of mechanisms previously overlooked, such as cell-to-cell communication, flow-mediated dilation, and venous-arterial communication.

One approach that may be helpful in identifying the factors regulating functional vasodilation is to evaluate vascular reactivity in muscles in which the functional dilation is enhanced or suppressed relative to the "normal" condition. There are several models appropriate for this type of study. For example, aerobic exercise training has been shown to enhance the blood flow to hindlimb muscles during electrical stimulation (145) and treadmill running in rats (146). Similarly, an increased maximal flow capacity to skeletal muscle has been found in aerobically trained humans (147). In addition, as illustrated in Figure 10, the blood flow response and dilation of arteriolar vessels during muscle contractions are greater in the spinotrapezius muscle of treadmill-trained rats than in their sedentary counterparts; this vascular adaptation is evident despite the fact that this muscle showed no increase in oxidative enzyme activity (38, 148). The effects of exercise training on spinotrapezius muscle vascular resistance and conductance are also presented in Figure 7; the increase microvascular functional vasodilation is reflected in the greater relative increase in vascular conductance in trained animals. Likewise, Spontaneously Hypertensive (143, 149) and Dahl Salt-Sensitive (150) rats show enhanced dilation of skeletal muscle arterioles during contractions, when compared with their normotensive counterparts. In contrast, hindlimb suspension has been shown to reduce the hyperemia associated with muscle contractions (151). In order to increase our understanding of the regulation of skeletal muscle blood flow during contractions, it will be helpful to evaluate not only the "normal" vasculature, but also various models of enhanced or suppressed functional dilation.

The author would like to acknowledge Dr. H. Glenn Bohlen, without whose support and encouragement this review and the related work would not have been possible.

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