Local control of skeletal muscle blood flow during exercise: influence of available oxygen

Darren P. Casey1,2 and Michael J. Joyner1
Departments of 1Anesthesiology and 2Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota
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Casey DP, Joyner MJ. Local control of skeletal muscle blood flow during exercise: influence of available oxygen. J Appl Physiol 111: 1527–1538, 2011. First published September 1, 2011; doi:10.1152/japplphysiol.00895.2011.—Reductions in oxygen availability (O2) by either reduced arterial O2 content or reduced perfusion pressure can have profound influences on the circulation, including vasodilation in skeletal muscle vascular beds. The purpose of this review is to put into context the present evidence regarding mechanisms responsible for the local control of blood flow during acute systemic hypoxia and/or local hypoperfusion in contracting muscle. The combination of submaximal exercise and hypoxia produces a “compensatory” vasodilation and augmented blood flow in contracting muscles relative to the same level of exercise under normoxic conditions. A similar compensatory vasodilation is observed in response to local reductions in oxygen availability (i.e., hypoperfusion) during normoxic exercise. Available evidence suggests that nitric oxide (NO) contributes to the compensatory dilator response under each of these conditions, whereas adenosine appears to only play a role during hypoperfusion. During systemic hypoxia the NO-mediated component of the compensatory vasodilation is regulated through a β-adrenergic receptor mechanism at low-intensity exercise, while an additional (not yet identified) source of NO is likely to be engaged as exercise intensity increases during hypoxia. Potential candidates for stimulating and/or interacting with NO at higher exercise intensities include prostaglandins and/or ATP. Conversely, prostaglandins do not appear to play a role in the compensatory vasodilation during exercise with hypoperfusion. Taken together, the data for both hypoxia and hypoperfusion suggest NO is important in the compensatory vasodilation seen when oxygen availability is limited. This is important from a basic biological perspective and also has pathophysiological implications for diseases associated with either hypoxia or hypoperfusion.

hypoxia; hypoperfusion; vasodilation

DURING DYNAMIC MUSCLE CONTRACTIONS there is an increased metabolic demand that is matched closely by increases in skeletal muscle blood flow (exercise hyperemia) and oxygen delivery. Blood flow increases rapidly at the onset of contractions and can increase up to 100-fold over resting values during intense exercise (2). The mechanisms responsible for increasing blood flow at the onset of exercise as well as maintaining it over time involve a complex interaction between mechanical factors and various local metabolic and endothelial derived substances that influence vascular tone (132). Over the last several decades exercise hyperemia in general and the potential mechanisms responsible for the regulation of flow to contracting skeletal muscles have been reviewed extensively (13, 33, 35, 68, 75, 80, 81, 131, 152). These reviews have focused primarily on blood flow responses during exercise under normoxic conditions. However, reductions in oxygen (O2) availability (i.e., hypoxia) bring about several cardiovascular adjustments and can have profound influences on the circulation. Along these lines, the mechanisms responsible for the local regulation of skeletal muscle blood flow during exercise are likely enhanced and possibly different than those during normoxic exercise.

Therefore, the purpose of this review is to discuss how O2 availability can impact blood flow and vasodilation in contracting skeletal muscles. Although cardiac pumping capacity (especially during large muscle mass and/or high intensity exercise) can be important in the hyperemic response to exercise, the emphasis in this review is on the local mechanisms regulating active muscle blood flow under conditions of reduced O2 availability during submaximal exercise. Specifically, this review will focus on 1) how acute hypoxia and hypoperfusion interact with exercise to govern the hyperemic responses in contracting muscles of humans and 2) the local vasodilator signals involved in the regulation of muscle blood flow during acute systemic (hypoxia) and local (hypoperfusion) reductions in O2 availability. We will also discuss the potential role of any systemic pressor response under these conditions.

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**SYSTEMIC HYPOXIA**

**Effect on Blood Flow to Resting Muscle**

At rest acute exposure to moderate hypoxia elicits vasodilation and an augmented blood flow in skeletal muscle vascular beds of young apparently healthy humans (9–11, 25, 26, 37, 84, 124, 158, 160, 161). This vasodilation occurs despite the resting muscle being relatively overperfused, as evidenced by limited \( O_2 \) extraction (25, 26, 59). The augmented skeletal muscle vasodilation in response to hypoxia also occurs despite an enhanced sympathetic vasoconstrictor activity (52, 83, 130, 143). Evidence suggests that a reduced \( \alpha \)-adrenergic responsiveness associated with hypoxia is not responsible for this dilation (37, 161). Local blockade of \( \alpha \)-adrenergic receptors in the forearm reveals a substantially greater vasodilator response during systemic hypoxia (158, 160). Thus activation of sympathetic vasoconstrictor nerves during hypoxia likely masks the degree of vasodilation. It should be noted that other studies have reported that hypoxia-mediated forearm vascular conductance was unaffected by local blockade of sympathetic nerves (9) and \( \alpha \)-adrenergic blockade (118). Taken together, vasodilation prevails over the vasoconstrictor response in determining vasomotor tone during acute hypoxia in resting skeletal muscle.

A number of vasodilator substances or systems, including but not limited to \( \beta \)-adrenergic receptor activation, nitric oxide (NO), prostaglandins, and adenosine, have been implicated to be involved in hypoxic vasodilation at rest and have been previously reviewed in detail (51). Briefly, we and others (10, 158, 160) have demonstrated that \( \beta \)-adrenergic receptor activation is responsible for a substantial portion of the hypoxic vasodilation at rest. Moreover, a large portion of the \( \beta \)-adrenergic receptor-mediated hypoxic vasodilation at rest occurs through a NO pathway (158). This is consistent with the NO-dependent nature of at least some of the vasodilator responses to \( \beta_2 \)-mediated vasodilation (31, 45). Along these lines, NO synthase (NOS) inhibition attenuates the hypoxic vasodilator response in the human forearm in some studies (11, 25) but not others (90). In the latter study, the investigators locally blocked \( \beta \)-adrenergic receptors via intra-arterial infusions of propranolol prior to the experimental trials with NOS inhibition and therefore potentially masked the NO-mediated vasodilator response that is observed in other studies without concurrent \( \beta \)-adrenergic blockade. Under similar conditions, single inhibition of prostaglandin synthesis also did not attenuate the vasodilator response to systemic hypoxia (90). However, the combined inhibition of NO and prostaglandins abolished the vasodilator response to hypoxia at rest, thus indicating a synergistic role between these two pathways in regulating peripheral vascular tone and ultimately blood flow (90). Recent evidence suggests both interstitial and plasma adenosine stimulates NO and prostacyclin formation in the human leg under normoxic conditions (103). Moreover, there is strong evidence in animals that adenosine plays a major role in hypoxia-induced skeletal muscle vasodilation (15, 100, 114, 115, 141). However, available data related to the contribution of adenosine in the hypoxic vasodilator response in human studies are conflicting (25, 26, 84).

**Hypoxic Exercise**

The combination of submaximal dynamic exercise and hypoxia produces a “compensatory” vasodilation and augmented blood flow in contracting muscles (both quadriceps and forearm) relative to the same level of exercise under normoxic conditions (16, 26, 32, 122, 126, 160, 161). This augmented vasodilation exceeds that predicted by a simple sum of the individual dilator responses to hypoxia alone and normoxic exercise. Additionally, this enhanced hypoxic exercise hyperemia is proportional to the hypoxia-induced fall in arterial \( O_2 \) content, thus preserving muscle \( O_2 \) delivery and ensuring it is matched to demand (32, 49, 122, 126). Compensatory vasodilation is also observed when \( O_2 \) availability is reduced by carbon monoxide administration and/or experimentally induced anemia (48, 49, 121, 122). In this context, \( O_2 \) delivery, rather than blood flow, appears to be the regulated variable producing the augmented hyperemia during hypoxic exercise (47).

**Potential Causes of Compensatory Vasodilation**

Acute exposure to systemic hypoxia results in substantial reductions in arterial \( O_2 \) content (\( CaO_2 \)) as well as arterial \( O_2 \) tension (\( PaO_2 \)). Theoretically, reductions in each of these variables could serve as a signal for the compensatory vasodilation observed during hypoxic exercise (77, 78, 122). Roach and colleagues (122) reported that blood flow and \( O_2 \) delivery to the lower limbs during rhythmic two-legged knee extension exercise with normoxia, anemia, hypoxia, and anemia + hypoxia were dependent on \( CaO_2 \) not \( PaO_2 \). Evidence that a low \( PaO_2 \) alone does not cause vasodilation was based on the observation of similar limb blood flows in the two conditions (hypoxia and anemia) with nearly identical \( CaO_2 \) but widely different \( PaO_2 \) (47–538 mmHg) (49). Taken together, these results strongly suggest that factors sensitive to \( CaO_2 \) serve as the signal for the compensatory increases in skeletal muscle blood flow and vasodilation during hypoxic exercise.

**Regulation of the Vascular Tone During Hypoxic Exercise**

**Vasodilator line-up: usual suspects?** Several vasodilator pathways have been proposed and examined as likely regulators of skeletal muscle blood flow in response to changes in \( CaO_2 \). Increases in arterial epinephrine are evident with acute exposure to systemic hypoxia and are increased further during submaximal cycling exercise (92). Additionally, an intensity-dependent rise in arterial epinephrine occurs during incremental forearm exercise, suggesting that \( \beta \)-adrenergic receptor-mediated vasodilation might contribute to the augmented hypoxic exercise hyperemia (161). Wolfel and colleagues (163) originally demonstrated that \( \beta \)-adrenergic blockade reduced \( O_2 \) delivery to the contracting muscles during submaximal exercise at altitude, but was compensated for by an enhanced tissue \( O_2 \) extraction. However, the use of systemic \( \beta \)-blockade reduced cardiac output and likely engaged vasconstricting cardiovascular reflexes, therefore making it difficult to determine whether alterations in \( \beta \)-adrenergic receptor-mediated vasodi-
lation within skeletal muscle vasculature contributed to the reduced O\textsubscript{2} delivery. Along these lines, local inhibition of \(\beta\)-adrenergic receptors (via intra-arterial infusion of propranolol) has demonstrated that in the absence of overlying sympathetic vasoconstriction, \(\beta\)-adrenergic receptor activation contributes to the hypoxic compensatory vasodilation during mild (10% maximum voluntary contraction; MVC) forearm exercise (160). However, the \(\beta\)-adrenergic component decreases with increased exercise intensity (20% MVC). Taken together, this suggests that other local vasodilating factors are likely responsible for the compensatory vasodilation during hypoxic exercise, especially at higher exercise intensities.

NO release from an endothelial source and/or desaturation of hemoglobin in erythrocytes (85, 109, 140, 147) has been proposed during hypoxia. Along these lines, there is a significant blunting of the compensatory vasodilation in the forearm during mild to moderate (10–20% MVC) hypoxic exercise after NOS inhibition (25). Although NO-mediated mechanisms contribute to the compensatory vasodilation during hypoxic exercise, it appears that it is regulated through different pathways with increasing exercise intensity. At lower-intensity forearm exercise (10% MVC) NO contributes to the compensatory vasodilation via \(\beta\)-adrenergic receptor activation. At higher intensity exercise the contribution of NO becomes independent of the \(\beta\)-adrenergic receptors (19). Therefore, an alternative and currently unknown stimulus for NO-mediated vasodilation occurs during higher intensity hypoxic exercise.

Increases in plasma but not skeletal muscle interstitial NO during hypoxia in humans suggest an endovascular or endothelial NO source (85). Therefore, it is possible that the augmented vasodilation during hypoxic exercise is a result of the direct release of NO from endothelial cells and/or erythrocytes. In this context, luminal hypoxia can elicit the direct release of NO from the endothelium (109) and from erythrocytes in the form S-nitrosohemoglobin (147). However, based on the location for intraluminal N\textsuperscript{\textdagger}-monomethyl-L-arginine (NOS inhibitor) administration and the fact that NOS inhibition is effective in reducing forearm blood flow during hypoxic exercise (25), it is reasonable to suspect that the NO responsible for the compensatory vasodilation is from endothelial sources vs. an erythrocyte source. Furthermore, the effectiveness of NOS inhibition in reducing the compensatory vasodilatation during hypoxic exercise also argues against the idea that nitrite and/or formation of erythrocyte nitroso species is a key vasodilator in this response (39, 46). Along these lines, if nitrite were responsible, either directly or indirectly (via reduction to NO), the compensatory vasodilation would have been maintained despite NOS inhibition.

In animals adenosine is thought to be a key mediator of skeletal muscle blood flow during normoxic exercise (95, 107, 110, 111). However, adenosine receptor blockade appears to only modestly attenuate the exercise-induced skeletal muscle vasodilation in human limbs, but these findings are not consistent (26, 91, 98, 112). The classic adenosine hypothesis proposes that adenosine mediates vasodilation and helps to ensure adequate blood flow to metabolically active tissue during periods of reduced O\textsubscript{2} availability (i.e., hypoxia and/or ischemia) (7). This concept would therefore suggest that adenosine may contribute to the compensatory vasodilation during hypoxic exercise. However, our group demonstrated that adenosine is not obligatory for the compensatory vasodilation during hypoxic exercise in humans (26). This was observed with and without overlying sympathetic \(\alpha\)-adrenergic vasoconstriction, suggesting that the enhanced sympathetic outflow associated with systemic hypoxia did not mask any underlying adenosine-mediated vasodilation. Moreover, adenosine does not contribute to the compensatory vasodilation after NOS inhibition, thus indicating that adenosine does not act through an NO-independent pathway in this response (25). Using positron emission tomography (PET) imaging, Heinonen and colleagues (59) recently demonstrated that adenosine receptor antagonism (via aminophylline) did not affect blood flow in exercising human quadriceps femoris muscle, suggesting no contribution of adenosine to capillary blood flow during hypoxic exercise. Additionally, adenosine receptor blockade did not change blood flow heterogeneity within the active and inactive muscles during hypoxic exercise.

Deoxygenation (i.e., hypoxia) and mechanical deformation (i.e., exercise) of red blood cells can lead to ATP release from erythrocytes (6, 64, 144, 145). Moreover, venous plasma levels of ATP are elevated during hypoxia at rest and during exercise compared with normoxic conditions (48, 99). Both in vitro and in vivo studies suggest that ATP-induced vasodilation is mediated through a NO pathway (28, 94, 96), thus an ATP/NO-mediated component to the compensatory vasodilation during hypoxic exercise is an attractive hypothesis. It is believed that the vasodilator actions of ATP are mediated through the purinergic P\textsubscript{2} receptors located on vascular endothelial cells (113). Unfortunately, specific pharmacological antagonists for P\textsubscript{2} receptors to address the role of ATP in the hypoxia-induced compensatory vasodilation are currently unavailable for human use. However, it is important to note that experimentally increasing limb vasodilation during hypoxic exercise (via intra-arterial ATP infusion) does not improve leg and systemic O\textsubscript{2} consumption due to a reduction in O\textsubscript{2} extraction across the exercising leg (17). Another potential candidate for stimulating and/or interacting with NO in the compensatory vasodilator response might be prostaglandins. There is strong evidence that suggests an interaction between prostaglandins and NO in the regulation of skeletal muscle blood flow at rest and during normoxic exercise (97, 101, 133, 134). As indicated earlier, there is also evidence to suggest a synergistic role between these two pathways in the compensatory vasodilation during hypoxia at rest (90). Recent evidence suggests that combined NO/PG inhibition substantially reduces forearm blood flow and vasodilation during hypoxic exercise in young healthy adults (29). It is important to note that the aforementioned study did not include single inhibition trials of each vasodilator pathway of interest (NO and prostaglandins). Therefore, it is difficult to discern the relative contribution of PGs and its interaction with NO in the compensatory vasodilation during hypoxic exercise.

**Sympathetic Restraint of Hypoxia-Induced Compensatory Vasodilation**

In young healthy humans the sympathetic response to exercise is greater in hypoxia than it is in normoxia (54, 69, 136). The increased sympathetic vasoconstrictor activity has been postulated to be needed to match O\textsubscript{2} delivery with O\textsubscript{2} demand (88) and maintain arterial blood pressure during the hypoxic stress and in turn limit the degree of compensatory vasodilation (148). Along these lines, \(\alpha\)-adrenergic receptor blockade in the
human forearm (160) and in the hindlimbs of dogs (148) reveals a greater vasodilation during hypoxic exercise compared with control hypoxic exercise conditions (i.e., during saline infusion). Despite the augmented sympathetic vasoconstrictor activity a substantial compensatory vasodilatation persists during hypoxic exercise. It is well documented that sympathetic vasoconstrictor responses are blunted in the vascular beds of contracting skeletal muscle of animals (150, 151) and humans (36, 56, 57, 117, 153), a phenomenon referred to as "functional sympatholysis." Moreover, there is evidence to suggest that hypoxia can attenuate vasoconstrictor responses to sympathetic nerve activation and exogenous norepinephrine in resting skeletal muscle of animals and humans (12, 60, 61). Therefore, it is possible that an augmented functional sympatholysis might partially explain the compensatory vasodilation during hypoxic exercise. In this context, Hansen et al. (55) demonstrated a reduced forearm vasoconstrictor responsiveness to lower body negative pressure during moderate hypoxic exercise compared with normoxic exercise. However, our laboratory (161) has demonstrated that the greater vasodilation observed during hypoxic forearm exercise was not due to a reduced postjunctional vasoconstrictor responsiveness (augmented functional sympatholysis) to endogenous norepinephrine (via intra-arterial infusion of tyramine).

Compensatory Vasodilation: Is it Always Present?

It is clear that compensatory vasodilation occurs in response to acute hypoxia during submaximal forearm (19, 25, 26, 29, 160, 161) and single and/or two-legged knee extension (16, 32, 77, 122, 126) exercise. That is, during submaximal exercise, alterations in oxygen availability are compensated for by an augmented muscle blood flow to help maintain O2 delivery to the active muscles. However, this compensatory vasodilation appears to be absent during maximal exercise, especially when performed with a large muscle mass (74, 77, 78, 120). The muscle blood flow and vasoconstrictor response to maximal exercise during moderate and severe hypoxia are likely limited to a certain degree by a reduction in maximal cardiac output (16) and not fully capable of compensating when the maximal pumping capacity of the heart is taxed. Under these circumstances it seems likely baroreflex-mediated vasoconstrictor responses are engaged. However, it is important to note that even in well trained cyclists who have a high cardiovascular reserve, leg blood flow and leg O2 consumption is reduced at peak exercise using the one-legged knee extension model (119). The lack of a compensatory vasodilation is also observed during submaximal exercise after acclimatization (long-term exposure to hypoxia), which may be due to an increase in CaO2.

In summary, the studies discussed here clearly demonstrate that reductions in available O2 via systemic hypoxia promote compensatory vasodilation and an augmented blood flow in skeletal muscle vascular beds at rest and during submaximal exercise. The compensatory vasodilation during hypoxic exercise is essential to ensure the maintenance of oxygen delivery to the active muscles. It appears that factors sensitive to CaO2 serve as the signal for the compensatory increases in skeletal muscle blood flow and vasodilation during hypoxic exercise. In humans, NO-mediated vasodilation plays an obligatory role in the augmented blood flow during incremental hypoxic exercise. However, the NO-mediated component of the compensatory vasodilation during hypoxic exercise is regulated through different pathways with increasing exercise intensity. That is, a β-adrenergic receptor-stimulated NO component exists during low-intensity hypoxic exercise, whereas the source of NO contributing to compensatory dilation is less dependent on β-adrenergic mechanisms as exercise intensity increases. It is currently unclear what the stimulus of NO release is with increasing intensity of muscle contraction but does not appear to be adenosine. ATP released from erythrocytes and/or endothelial-derived prostaglandins remain attractive candidates for stimulating NO during higher intensity hypoxic exercise.

The vasodilator response to acute hypoxia detailed above in young healthy humans has been demonstrated to be attenuated in older adults at rest and during exercise (27, 79). Additionally, limited reports suggest that compensatory vasodilation is impaired in some populations with cardiovascular risk factors (5), whereas it is preserved in others (86, 157). From a clinical perspective, if an attenuated vasodilator response occurs in other vascular beds (i.e., coronary circulation) with aging and cardiovascular risk factors, certain individuals may be at risk of reduced perfusion of the myocardium and consequently myocardial injury during exercise with hypoxia.

HYPEROXIA: THE OPPOSITE SIDE OF THE COIN

It is apparent that compromises in O2 availability (i.e., hypoxia) elicit a compensatory vasodilator response in skeletal muscle vascular beds to ensure adequate O2 delivery. Conversely, increased O2 availability (i.e., hyperoxia) reduces resting muscle blood flow in humans (8, 58, 116, 165). Additionally, muscle blood flow is reduced during and after hyperoxic exercise compared with normoxic conditions (24, 48, 116, 159). The challenge of increasing O2 availability by increasing the fraction of inspired O2 (i.e., FiO2 = 100% O2) under normobaric environments is that Cao2 can only be elevated 5–10%. Additional approaches using hyperoxia (FiO2 = 100% O2) superimposed on experimentally induced polycythemia have also been employed to study the effects of increased O2 availability on muscle blood flow during knee-extensor exercise (47). However, this approach only resulted in an ~11% increase in CaO2. These relatively small increases in CaO2 are near the signal-to-noise ratio for muscle blood flow measurements. To address this potential limitation, studies on the blood flow response in the exercising forearm to larger increases in estimated Cao2 via hyperbaric hyperoxia have recently been performed (24). Large increases in estimated O2 content (~25–30%) resulted in a substantial reduction in exercising forearm blood flow despite significantly higher perfusion pressures, thus indicating a greater increase in vascular resistance compared with normoxic conditions (24). The blunted forearm vascular conductance during hyperoxic exercise (~25% lower) mirrored the estimated increase in arterial O2 content (~25–30%). These findings during hyperbaric hyperoxic exercise parallel previous findings in which hypoxic-mediated increases in forearm vascular conductance during exercise mirrors the fall in O2 content (25, 26).

The mechanisms responsible for the increased vascular resistance and reduced blood flow during hyperoxic exercise are currently unclear. In general, the potential mechanisms include but are not limited to 1) greater sympathetic restraint and/or
2) decreased release of or responsiveness to local vasodilators within the contracting muscle. Although hyperoxia reduces muscle sympathetic nerve activity at rest (62, 135, 165), it is unclear whether this holds true during exercise and contributes to the reduced muscle blood flow and vasodilation. Limited evidence suggests that hyperoxia does not appear to enhance the magnitude of change in sympathetic nerve activity to non-active skeletal muscle during dynamic exercise (135). Additionally, it is possible that increased oxygen levels may attenuate functional sympatholysis and therefore enhance vasoconstriction in the contracting muscles (55). Finally, some evidence suggests that the vascular response (i.e., constriction) to hyperoxia in the hindlimbs of dogs is not mediated by the autonomic nervous system but is rather attributed to a direct action of high arterial O₂ tension (4). Therefore, it is possible that the increase in vascular resistance under hyperoxic exercise conditions may be a direct vasoconstrictor action of O₂ on the arterial and arteriolar wall. As discussed earlier, erythrocytes have the ability to sense changes in O₂ during hypoxic conditions and modulate vascular tone via release of ATP, thus leading to appropriate changes in blood flow and matching O₂ delivery with metabolic need (42). Therefore, large increases in O₂ availability during hyperoxic exercise could theoretically attenuate the release of ATP from erythrocytes (Fig. 1) (48).

A shift in the vasodilator/vasoconstrictor balance due to an attenuated release of or responsiveness to local vasodilators within the contracting muscle could also promote the reduced blood flow during hyperoxic exercise. In this context, prostaglandin-mediated vasodilation following isometric exercise is reduced during hyperoxia (162). Additionally, vasoconstriction via a reduction in basal NO production has been observed in porcine coronary arteries exposed to elevated levels of O₂ (106). Along the same lines, an increase in free radical production (i.e., superoxide anions) during hyperbaric oxygenation causes vasoconstriction in the cerebral circulation of rats via inactivation of NO (167). However, recent evidence suggests that NO metabolites are unaffected in humans during normobaric hyperoxic exercise (39). Therefore it is unclear whether alterations in the local vasodilator milieu are responsible for the blunted blood flow response to hyperoxic exercise.

LOCAL REDUCTIONS IN OXYGEN (VIA HYPOPERFUSION)

Over the past several years our laboratory has been interested in addressing whether the compensatory vasodilator signals that maintain oxygen delivery to active muscles during exercise with systemic hypoxia are the same or different than those that cause compensatory vasodilatation during normoxic exercise with hypoperfusion. During conditions of insufficient oxygen delivery to the active muscle (e.g., hypoperfusion or ischemia), metabolites can accumulate that either stimulate blood pressure, raising sensory nerves within the muscle, or evoke vasodilatation (1, 30, 67, 137, 155, 156). Either of these mechanisms might act to restore blood flow to the contracting muscle and relieve the flow/metabolism mismatch.

Reflex Pressor Response

Activation of chemosensitive afferent nerves in the active muscle evokes reflex increases in sympathetic outflow and arterial pressure, termed the muscle chemoreflex or metaboreflex (1, 30, 67, 155, 156). The increased pressure is thought to augment blood flow to the contracting muscle and partially restore the flow/metabolism matching. Evidence for restoration of blood flow to active muscle via a reflex pressor response comes primarily from studies in conscious animals. In dogs, the hemodynamic consequences of muscle chemoreflex activation, via graded reductions in flow and perfusion pressure, have been studied extensively using the "Seattle model" (53, 104, 105, 138, 139, 164). In this model, a terminal aortic occluder in combination with a flow probe in close proximity is used to suddenly reduce blood flow to the hindlimb muscles of dogs running on a treadmill. Using this model, imposed reductions in blood flow and oxygen delivery to active hindlimb muscles during dynamic exercise can evoke a powerful pressor response that restores ~50% of the flow deficit (105). The reflex pressor response to acute hypoperfusion during exercise in dogs is dependent on the intensity of the exercise (123) and apparently generated when O₂ delivery falls below some critical level causing accumulation of a pressor substance (Fig. 2) (139). The reflex pressor response in normal dogs is generated primarily by a rise in cardiac output (3, 53, 72, 104, 164), whereas in dogs with congestive heart failure the systemic pressor response is caused primarily by peripheral vasoconstriction (53). Taken together, the Seattle model clearly demonstrates that the reflex pressor response contributes to the restoration of blood flow in the hindlimbs of dogs during exercise. However, it should be noted that Britton et al. (14) demonstrated that autoregulation in the hindlimbs of dogs also contributes significantly to the regulation of blood flow in response to acute hypoperfusion during exercise.

![Fig. 1. Thigh plasma venous ATP responses at rest and during incremental knee-extensor exercise with exposure to normoxia, hypoxia, hyperoxia, and carbon monoxide (CO) + normoxia. *Significantly different from resting values (P < 0.05). [Adapted with permission from Ref. 48.](http://jap.physiology.org/)"
OXYGEN AVAILABILITY AND COMPENSATORY VASODILATION

Is the Pressor Response Apparent in Humans?

In humans, large increases in blood pressure during ischemic exercise were first described by Alam and Smirk (1). These investigators observed that the activity of even a small group of muscles may give rise to a substantial increase in systolic blood pressure (up to 70 mmHg) provided that the circulation of the blood through the exercising muscles was arrested completely. Lorensen (87) later demonstrated that the blood pressure response to plantar flexion in patients with unilateral intermittent claudication due to atherosclerosis obliterans was significantly greater during exercise with the diseased limbs compared with exercise with nondiseased limbs. Taken together, these studies suggest that the reflex pressor response in humans is engaged during exercise with ischemia and/or hypoperfusion. However, stimulation of the muscle chemoreflex evokes a large increase in vasoconstricting sympathetic nerve traffic directed toward the skeletal muscle (30, 89, 154). While the reflex increase in arterial pressure occurs at higher flows after arterial oxygen content is reduced with CO. [Adapted with permission from Ref. 139].

Fig. 2. Effects of CO on the rise of systemic arterial pressure to graded reductions in hindlimb perfusion during exercise (2 mph, 0% grade). Squares and solid lines are control (no CO) exercise data, and circles and dashed lines are exercise with CO data. Filled symbols represent free-flow data; open symbols represent data collected during reduced hindlimb perfusion. These data demonstrate that when terminal aortic flow is decreased during mild exercise the reflex rise in systemic arterial pressure occurs at higher flows after arterial oxygen content is reduced with CO. [Adapted with permission from Ref. 139].

To evaluate the blood flow response to hypoperfusion in contracting muscles the majority of studies in humans have relied on the use of external pressure to reduce limb blood flow during exercise, which have produced conflicting results (30, 66, 127, 149). Using O2 saturation of venous blood (%SvO2) as an indirect method of measuring blood flow, studies in the forearm reported that the reflex pressor response did not appear to restore blood flow to rhythmically contracting muscles (66). In contrast, Rowell et al. (127) concluded that the reflex pressor response partially restored the decrease in leg blood flow (%SvO2) induced by external positive pressure. Using a more direct measurement of flow (brachial artery mean blood velocity), Daley et al. (30) demonstrated that flow is not restored by a reflex pressor response at higher levels of external pressure (+50 mmHg) due to sympathetic vasoconstriction limiting the ability of the pressor response to restore the flow. Potential problems of these earlier studies mainly revolve around the indirect measures of blood flow (66, 127) and the method used to reduce limb blood flow (positive pressure) during exercise (30, 66, 127, 149). While external positive pressure clearly reduces perfusion pressure to the contracting muscles, it differs fundamentally with the Seattle model because it affects all elements of the vascular tree, including the microcirculation and veins, and might either limit expression of local vasodilation or limit the ability of changes in arterial pressure to improve blood flow.

To address the limitations of external pressure, our laboratory recently developed an experimental model in humans to directly measure the blood flow response in hypoperfused skeletal muscle produced by forearm exercise in the presence of a brachial artery occlusion. For this purpose a small balloon catheter is inserted into the brachial artery and inflated to reduce forearm blood flow and vascular conductance during handgrip exercise (Fig. 3) (23). With this experimental model there is a substantial restoration of flow to hypoperfused exercising human muscle. Interestingly, the restoration of flow occurs in the absence of a significant pressor response, thus suggesting local vasodilator and/or myogenic mechanisms are likely responsible. The absence of a significant pressor response (above exercise alone) during hypoperfusion suggests that a reflex increase in pressure is not necessary to restore blood flow to hypoperfused contracting human muscle. The lack of a pressor response in our model may be explained by the small muscle mass (forearm), moderate exercise intensity (20% MVC), magnitude of the reduction in forearm blood flow (~50%) induced by balloon inflation, or a combination of these being not sufficient enough to augment the pressor response beyond that of exercise alone. However, recent evidence suggests that using an upper arm cuff to reduce flow by ~40% during forearm exercise at 15% MVC was sufficient to evoke a reflex pressor response (63). It should be noted that the use of an upper arm cuff likely blocked venous outflow, leading to increased intramuscular pressure, which could activate sympatoexcitatory mechanosensitive afferents (93, 125). Therefore, the reflex pressor response observed might have been due to an enhanced mechanoreflex, which is not likely engaged using an intra-arterial balloon catheter to induce hypoperfusion.

Local Vasodilation

During systemic hypoxia there is a compensatory vasodilation that mirrors the decrease in O2 content (25, 26, 47, 160, 161). However, during local reductions in O2 availability (via hypoperfusion) the compensatory response appears to be less than perfect in humans (20–23). That is, flow does not return completely (100% recovery) to preinflation levels. One potential explanation for the incomplete compensatory vasodilation during acute hypoperfusion may be related to an initial rise in vascular resistance at the onset of balloon inflation. The initial rise in vascular resistance in these studies is in contrast to the classic view of autoregulation (a decrease in perfusion pressure
is followed by a reduction in resistance to blood flow through the muscle) (14, 50, 108, 146). However, the initial increase in vascular resistance is not unprecedented in that an immediate increase in vascular resistance has also been reported to occur in isolated perfused skeletal muscle of dogs (65). The reason for the acute increase in vascular resistance at the onset of balloon inflation in our model of hypoperfusion is not completely clear but may be related to dampening of pulsatile flow by balloon inflation. One possibility is that pulsatile flow is a critical component for the release of endothelium-derived vasodilators (128). Another possibility is that a sudden drop in perfusion pressure causes the resistance vessels to recoil before autoregulatory vasodilation, a response that was also noted by Koch et al. (76) during mild exercise in dogs. Alterations in vascular bed compliance at the onset of balloon inflation may also contribute to the acute increase in vascular resistance observed in our model of hypoperfusion (166). Since no major pressor response is observed at the onset of balloon inflation (20–23) it is unlikely that a marked rise in sympathetic outflow explains the acute increase in vascular resistance.

The increase in vascular resistance at the onset of balloon inflation is followed by gradual autoregulatory compensation such that the vascular resistance decreases over time toward and, in some cases, below preinflation values. In this context the magnitude of blood flow restoration following acute hypoperfusion in contracting human skeletal muscle is predicted by the reduction in downstream forearm vascular resistance (Fig. 4). Additionally, the recovery of flow is not associated with changes in blood resistance and systemic arterial pressure (i.e., pressor response). Therefore, local vasodilator mechanisms must be responsible for the reduction in vascular resistance and restoration of flow to hypoperfused contracting forearm muscles.

VASODILATOR MECHANISMS: USUAL SUSPECTS REVISITED?

The vasodilator mechanisms in the microcirculation that contribute to the regulation of flow distal to the occlusion likely include a myogenic response of the microcirculation and all the mechanisms that are involved in vasodilation in response to increased metabolic needs, including endothelial factors and metabolic messengers released from the muscle. As previously mentioned, NO appears to contribute to the regulation of skeletal muscle blood flow during systemic hypoxia (11, 19, 25, 29, 158). Similarly NOS inhibition during moderate intensity handgrip exercise blunts the magnitude of restoration of forearm blood flow and vascular conductance in hypoperfused contracting muscles (21). Moreover, the compensatory vasodilation to hypoperfusion in the contracting human forearm was slowed with NOS inhibition. To our knowledge this is the only study to examine the contribution of NO to the restoration of blood flow in hypoperfused contracting skeletal muscle. However, parallel findings have been reported in the coronary circulation (40, 142). Duncker and Bache (40) assessed the contribution of NO to the vasodilation of coronary resistance arteries during exercise in the presence of a flow-limiting coronary stenosis. Inhibition of NO production during partial inflation of a hydraulic coronary occluder in dogs performing moderate treadmill exercise resulted in a decreased mean myocardial blood flow in the region perfused by the stenotic artery, but not in the normally perfused control region. A substantial recovery of forearm blood flow still remains after NOS inhibition, thus suggesting that additional vasodila-
tor mechanisms are involved in the compensatory response. Previous evidence in the Seattle model suggests that adenosine receptor antagonism blunts the recovery of hindlimb blood flow in dogs during high-intensity exercise in response to partial vascular occlusion (76). Additionally, active hyperemia in dog skeletal muscle is potentiated during experimentally restricted flow in the presence of dipyridamole, thus suggesting a role of adenosine in the regulation of blood flow under conditions of arterial occlusion (73). Furthermore, adenosine production is positively correlated to the degree of hypoperfusion in the coronary circulation of dogs (34) and appears to contribute to vasodilation of the coronary resistance vessels during exercise in the presence of a flow-limiting stenosis (82). In agreement with the aforementioned studies in dogs, data in the human forearm suggest 1) adenosine contributes to the overall magnitude of compensatory vasodilation during exercise with acute hypoperfusion in a manner that can be independent of NO-mediated mechanisms and 2) combined inhibition of adenosine receptors and NO formation results in additive reduction in the compensatory vasodilation (20).

Lastly, prostaglandins have been reported to be involved in the regulation of skeletal muscle blood flow following periods of ischemia (18, 43, 71, 102) and during systemic hypoxia (29, 90, 114). However, non-selective cyclooxygenase (COX) inhibition with Ketorolac to block the production of prostaglandins failed to reduce the recovery of forearm blood flow and vascular conductance during exercise with acute hypoperfusion (22). These findings are in agreement with available data in the coronary circulation of pigs where COX inhibition with indomethacin did not alter coronary blood flow in response to an experimentally induced flow-limiting stenosis (129). However, COX inhibition in patients with coronary artery disease causes coronary vasoconstriction (38, 44), thus suggesting that vasodilator prostaglandins may play greater role in the regulation of coronary vasomotor control in chronic vs. acute ischemia and in blood vessels subjected to atherosclerotic disease processes. Taken together, the mechanisms involved in the compensatory vasodilator response to acute hypoperfusion in contracting human muscle suggests that adenosine and NO contribute, whereas prostaglandins are not obligatory (Fig. 5).

**SUMMARY AND PERSPECTIVES**

This review highlights the key vasodilator signals and/or pathways that contribute to the local control of skeletal muscle blood flow during exercise under conditions with reduced oxygen availability (Table 1). Both acute systemic (hypoxia) and local (hypoperfusion) mediated reductions in O2 availability elicit a compensatory vasodilator response. Although NO appears to be a common link between the hypoxia and hypoperfusion-induced vasodilation (Table 1), its stimulus and/or interactions with other vasodilator systems varies between the two conditions. Both NO and adenosine contribute to the compensatory vasodilator responses to hypoperfusion (20, 21). By contrast, adenosine does not seem to play a major role in the compensatory vasodilator responses to hypoxia (25, 26, 59). Thus the story with adenosine is mixed; during hypoperfusion it appears to contribute in a synergistic manner with nitric oxide to compensatory vasodilation. By contrast, during hypoxia it does not contribute. Although combined NOS/COX inhibition has been demonstrated to reduce the compensatory vasodilator response during hypoxic forearm exercise (29), it is unclear what the independent role of prostaglandins are in this response. Available evidence suggests prostaglandins are not obligatory to the compensatory dilatation observed during forearm exercise with hypoperfusion (22).

Despite the majority of the data presented in this review being from studies in young apparently healthy adults, it has

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**Table 1. Systemic vs. local reductions in oxygen availability: contribution of local vasodilators in the control of human skeletal muscle blood flow during exercise**

<table>
<thead>
<tr>
<th>Systemic Hypoxia</th>
<th>Local Hypoperfusion</th>
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<tbody>
<tr>
<td>(Low O₂)</td>
<td></td>
</tr>
<tr>
<td>Perfect (proportional to the fall in arterial O₂ content)</td>
<td>Compensation</td>
</tr>
<tr>
<td>++</td>
<td>β-adrenergic receptor activation*</td>
</tr>
<tr>
<td>++</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>-</td>
<td>Adenosine</td>
</tr>
<tr>
<td>?</td>
<td>Prostaglandins</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Low O₂ + ↓ perfusion)</td>
</tr>
<tr>
<td></td>
<td>Imperfect (&lt;100% recovery)</td>
</tr>
</tbody>
</table>

*Is exercise intensity dependent; contribution decreases with increased exercise intensity. ++Contributes to the compensatory vasodilation; – is not obligatory in the compensatory vasodilation; ?lack of evidence for or against a role in the compensatory vasodilation.
important implications for understanding conditions associated with impaired endothelial function or reduced NO bioavailability. In this context, data from aging humans clearly demonstrate an attenuated compensatory vasodilation during hypoxic exercise, which appears to be from reduced NO signaling (27). Additionally, the observation that NO contributes to the compensatory flow response in the microcirculation during an acute proximal occlusion (21) raises concerns that the ability to restore flow might be impaired in conditions with endothelial dysfunction and/or reduced NO bioavailability (i.e., vascular disease). Therefore, patients with impaired endothelium-dependent dilation are likely to be more susceptible to hyperperfusion and/or ischemia during exercise, especially in vascular regions distal to a stenosis. Finally, there appears to be a great deal of similarity between the regulation of resistance vessel tone in human skeletal muscle (20–22) with those observed in the coronary circulation of dogs and pigs during exercise with acute hypoperfusion (34, 40, 41, 82, 129). Thus an impaired compensatory vasodilator response in the forearm might reflect impairments in other vascular beds.

In conclusion, the available literature reviewed here shows that under most circumstances skeletal muscle vasodilation is tightly coupled to changes in available O₂. Indeed, the compensatory vasodilation observed during hypoxic exercise generally mirrors the fall in CaO₂. Conversely, under conditions of increased O₂ availability (i.e., hyperoxia), vascular conductance is reduced and mirrors the increase in CaO₂. Taken together, these findings suggest that skeletal muscle blood flow is perfectly matched to changes in systemic O₂ availability. In contrast, the compensatory vasodilation in response to local reductions in O₂ availability via hypoperfusion appears to be less than perfect in human skeletal muscle.

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REFERENCES


OXYGEN AVAILABILITY AND COMPENSATORY VASODILATION


