Muscle blood flow, hypoxia, and hypoperfusion

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Joyner MJ, Casey DP. Muscle blood flow, hypoxia, and hypoperfusion. J Appl Physiol 116: 852–857, 2014. First published July 25, 2013; doi:10.1152/japplphysiol.00620.2013.—Blood flow increases to exercising skeletal muscle, and this increase is driven primarily by vasodilation in the contracting muscles. When oxygen delivery to the contracting muscles is altered by changes in arterial oxygen content, the magnitude of the vasodilator response to exercise changes. It is augmented during hypoxia and blunted during hyperoxia. Because the magnitude of the increased vasodilation during hypoxic exercise tends to keep oxygen delivery to the contracting muscles constant, we have termed this phenomenon “compensatory vasodilation.” In a series of studies, we have explored metabolic, endothelial, and neural mechanisms that might contribute to compensatory vasodilation. These include the contribution of vasodilating substances like nitric oxide (NO) and adenosine, along with altered interactions between sympathetic vasoconstriction and metabolic vasodilation. We have also compared the compensatory vasodilator responses to hypoxic exercise with those seen when oxygen delivery to contracting muscles is altered by acute reductions in perfusion pressure. A synthesis of our findings indicate that NO contributes to the compensatory dilator responses during both hypoxia and hypoperfusion, while adenosine appears to contribute only during hypoperfusion. During hypoxia, the NO-mediated component is linked to a β-adrenergic receptor mechanism during lower intensity exercise, while another source of NO is engaged at higher exercise intensities. There are also subtle interactions between β-adrenergic vasoconstriction and metabolic vasodilation that influence the responses to hypoxia, hyperoxia, and hypoperfusion. Together our findings emphasize both the tight linkage of oxygen demand and supply during exercise and the redundant nature of the vasomotor responses to contraction.

This review is broadly about the phenomenon we have termed “compensatory vasodilation” and is based on a presentation given at the 18th International Hypoxia Symposia held in early 2013. This phenomenon describes the tendency of muscle blood flow to increase (or decrease), depending on changes in arterial oxygen content. This is especially true during exercise, when the ability to maintain oxygen consumption by changes in extraction alone is somewhat limited, because extraction is already high during exercise (1). The basic idea is that, when arterial oxygen content is reduced by hypoxia, anemia, or other reductions of functional oxygen-carrying capacity (carbon monoxide, for example), there is an increase in blood flow to active muscles that “compensates” for the reduced arterial oxygen content and keeps oxygen delivery to the active muscles relatively constant. It should also be noted that the opposite occurs during hyperoxia, when there are increases in arterial oxygen content and vasodilation is reduced. In this paper, we briefly review our data and data from others and discuss potential mechanisms responsible for these observations. Figure 1 is a classic slide adapted from Rowell and colleagues (39) showing this phenomenon.

Our interest in this topic stems from our general interest in exercise hyperemia. In this context, there appears to be redundant mechanisms that contribute to exercise hyperemia, including various “metabolic” vasodilators (28). The idea is that vasodilating substances released by the contracting muscles or other tissues in proportion to the level of contractile activity are responsible for the well-known matching of blood flow and metabolism. However, identifying the dominant metabolic dilating substance (if there is one) or substances has proven challenging, and we hoped that, by altering oxygen delivery to the active muscle, we might either amplify or suppress one or more of the major contributors to this response.

How have we studied this in humans?

Our basic strategy to study compensatory vasodilation in humans has used the isolated forearm handgripping model, which involves a handgrip device that allows subjects to perform rhythmic forearm exercise by lifting a given weight 4–5 cm over a pulley 20 times/min. This model has a number...
Our final strategy to manipulate arterial oxygen content has been local hypoperfusion. In this technique, we place a balloon in the brachial artery and inflate the balloon to partially occlude it (5–8). Using this technique, we can acutely reduce perfusion pressure to the contracting skeletal muscles of the forearm by 15–20% and forearm blood flow by 40–50%. We have not used anemia or carbon monoxide in our studies.

**HYPOXIA IS SYMPATHOEXCITATORY**

The first thing to remember about hypoxia is that it is sympathoexcitatory. This sympathetic activation is due to stimulation of the carotid body chemoreceptors, and there is a 50–60% rise in muscle sympathetic nerve activity during systemic hypoxia (25). Normally, this increase in sympathetic traffic would potentially compete with or limit any local vasodilation caused by the hypoxia, and at rest this is clearly the case (43, 45). In other words, the vasodilation seen with hypoxia is greater after α-adrenergic blockade of the forearm than with hypoxia alone. As demonstrated in Fig. 2, there also appears to be enhanced sympathetic vasoconstrictor restraint of the skeletal muscle vasculature during hypoxic exercise, as α-adrenergic blockade reveals a greater vasodilation during hypoxic exercise compared with control hypoxic exercise conditions (no pharmacological blockade) (45). Thus while the ability of norepinephrine released from sympathetic nerves to cause vasoconstriction in active skeletal muscle is blunted during exercise, the additional sympathetic outflow evoked by systemic hypoxia can still cause vasoconstriction in the active muscles.

So our first question was to determine whether functional sympatholysis was augmented during exercise under hypoxic conditions. In this study, we used tyramine to cause local release of norepinephrine from the sympathetic nerves in the forearm. We showed that exercise clearly caused functional sympatholysis, and that functional sympatholysis (compared with rest) was greater during rhythmic handgripping at 10 and
20% of maximum voluntary contraction (46). However, compared with what is observed during normoxic exercise, hypoxia did not augment sympatholysis. So the classic compensatory vasodilation seen during hypoxia could not be ascribed simply to augmented sympatholysis during hypoxia: clearly something else, perhaps related to a “metabolic signal” from the active muscles or circulating factor, drives the compensatory dilator response.

**CANDIDATE DILATORS AND COMPENSATORY VASODILATION**

Along these lines, in our hypoxia studies, we have focused on the role of β-adrenergic receptors, adenosine, and nitric oxide (NO) acting alone or in combination as potential candidate dilators, which might contribute to compensatory vasodilation during hypoxia. During mild rhythmic handgripping (10% of maximum voluntary contraction), there is evidence that β-adrenergic receptor stimulation plays a role in compensatory vasodilation. However, this role is not as prominent during heavier rhythmic handgripping (20% maximum voluntary contraction) (45). It is also likely that some or all of this β2-mediated vasodilation is due to stimulation of NO release from the vascular endothelium (3).

We have also studied the interactions of adenosine and NO in a complex series of experiments that have blocked both pathways alone and in combination. Based on our data, we have concluded that NO plays a major role (~50% or more) in compensatory vasodilation, and that adenosine is not obligatory for this response (11, 12). Our findings that adenosine is not obligatory for the compensatory vasodilation in the forearm is in agreement with what is observed in exercising human quadriceps femoris muscle during hypoxia (27). However, it should be noted that, under resting conditions, adenosine plays a major role in skeletal muscle vasodilation in experimental animals when oxygen is reduced by acute systemic hypoxia, and a substantial amount of the response is mediated by NO (19, 33, 34). Recent evidence from others has demonstrated that the combined blockade of NO and prostaglandin pathways also reduces the vasodilator response to hypoxic exercise by ~50% (17). However, single inhibition trials of NO and prostaglandins were not performed in the aforementioned study, and, therefore, it is difficult to discern the relative contribution of prostaglandins and its interaction with NO in the compensatory vasodilation during hypoxic exercise. As is the case for both β2-adrenergic receptor- and adenosine-mediated vasodilation, at least some of the vasodilator response to prostaglandins is NO mediated (37).

There are a variety of other pathways that might contribute to compensatory vasodilation, including direct effects of hypoxia on vascular smooth muscle and ATP release from red blood cells as they desaturate. This latter pathway has emerged as an exciting new mechanism to help match blood flow, metabolism, and oxygen delivery in contracting skeletal muscles (20). However, in some models, ATP-mediated dilation is due in part to stimulation of NO release from the vascular endothelium (14, 35, 36). There has also been speculation about NO release from hemoglobin as a contributor to vasodilation during hypoxia (42), but at least in our model the dramatic effects of a local blockade of NO synthesis by selective infusions of NO synthase inhibitors into the forearm would tend to argue against a systemic mechanism centered on NO release from circulating hemoglobin as predominant. In both the case of ATP and NO release from desaturating hemoglobin, there are parallels to historic ideas about either oxygen or carbon dioxide per se playing a role in exercise hyperemia (41). Additionally, neuronal NO synthase (NOS)-derived NO plays a significant role in the regulation of skeletal muscle vascular tone at rest in humans (40) and in low-oxidative muscles of rats during high-intensity treadmill running (15). Therefore, it is possible that neuronal NOS-derived NO might be another contributor to compensatory vasodilation during hypoxic exercise. Lastly, accumulating evidence suggests that nitrite reduction (i.e., nitrate-nitrite-NO pathway) represents an alternative and differentially regulated system for NO generation that operates in parallel to the classic L-arginine-NOS pathway (32). Interestingly, the nitrate-nitrite-NO pathway is greatly enhanced under hypoxic conditions (29). Moreover, recent evidence in experimental animals suggests that dietary nitrate supplementation increases skeletal muscle blood flow and vasodilation during exercise (21). Taken together, these findings might suggest that the nitrate-nitrite NO pathway potentially can contribute to compensatory vasodilation. Lastly, other hypotheses and models have been proposed to explain the regulation of local blood flow under various levels of oxygen availability. For a provocative review of an alternative mechanism that may contribute to hyperemia within skeletal muscle and the compensatory vasodilation during hypoxic exercise, please see Ref. 22.

Based on our previous data demonstrating that β-adrenergic receptor activation is responsible for a portion of hypoxic vasodilation (45) and evidence supporting the idea that β-adrenergic receptors are either more sensitive or upregulated in young women compared with men (26, 31), we recently examined whether hypoxic vasodilation is influenced by sex. Our retrospective analysis of the blood flow and vasodilator responses during hypoxic exercise revealed that young women demonstrated a greater compensatory vasodilation compared with young men (12a). The mechanisms responsible for the discrepancies between sexes are currently unclear. Compensatory dilation is also blunted with aging (13). In this context, a loss of NO-mediated endothelial dilator responses with aging likely explains these observations. Additionally, the ATP mechanisms mentioned above are also blunted by aging (30), and, unlike younger subjects, there do not appear to be major sex differences in the compensatory dilator responses seen in older men and women.

**WHAT ABOUT HYPOXIA?**

We have used hyperbaric hypoxia (100% oxygen at 2.82 ATA) and also hyperbaric normoxia (7.4% oxygen at 2.82 ATA) to study the effects of increased oxygen content on blood flow responses to contracting muscle (9). The studies conducted at 7.4% fraction of inspired O2 served as an atmospheric pressure control trial and are done to control for the effects of chamber pressurization on any observed responses. The fundamental observations with this approach are that, when arterial oxygen content is increased by an estimated 25%, the blood flow responses are reduced by a similar amount. In other words, the opposite directional changes are seen compared with hypoxia. Additionally, this reduction in flow during
hyperoxia is not due to a loss of functional sympatholysis and an augmented sympathetic vasoconstrictor response in the active skeletal muscles (10). The extent to which hyperbaric hyperoxia affects other potential vasodilator pathways, such as NO, adenine nucleotides, or other factors, is currently under investigation.

**HYPOPERFUSION**

When we use our balloon catheter system to reduce perfusion pressure in the contracting forearm, we see a brief reduction in flow, followed by local vasodilation, which tends to return flow to normal (8). Interestingly, the compensatory response appears to be “less than perfect” (4–8). That is, in the majority of the studies we have conducted, flow does not return completely (100% recovery) to preinflation levels. Figure 3 is an individual record of such a response. During a series of studies aimed at identifying the potential vasodilators involved in the partial restoration of blood flow in the hypoperfused muscles, we have shown that most of the compensatory vasodilation is due to either NO or adenosine acting alone or in combination with NO (5, 6). In this context, 1) the magnitude of compensatory vasodilation is reduced by both single inhibition of NOS or adenosine receptor antagonism; and 2) the combined inhibition of the two pathways results in additive reduction in the compensatory response (5). At some level, these responses are an important confirmation of the so-called “adenosine hypothesis” postulated in the 1960s. This hypothesis, primarily directed at coronary circulation, suggested that, when there was a mismatch between flow and metabolism, which caused local tissue hypoxia, adenosine released from hypoperfused muscle as a metabolic “error signal” might be a critical mediator of vasodilator responses (2). It is of interest to note that there was discussion of adenosine, ADP, and ATP as potential candidate dilators during the initial wave of interest in these mechanisms as part of the adenosine hypothesis (41).

In this context, it is interesting to note that adenosine does not appear to be an important contributor to responses seen during systemic hypoxia in humans (12, 27), but is an impor-
Compensatory Vasodilation • Joyner MJ et al.

SUMMARY AND FUTURE DIRECTIONS

Blood flow to contracting skeletal muscles has a remarkable ability to adapt to changes in arterial oxygen content. Our studies have shown this both with systemic hypoxia and hyperoxia, along with skeletal muscle hypoperfusion. Others have shown similar responses during anemia and systemic carbon monoxide administration (24, 38).

During both hypoxia and hyperoxia, alterations in the way that the sympathetic nervous system interacts with local vasodilator mechanisms (functional sympatholysis) probably do not play a major role in modulating these responses. During systemic hypoxia, there can be release of epinephrine, and this epinephrine release and increase in circulating epinephrine could in fact contribute to the compensatory vasodilator response.

At this time, NO appears to be a major contributor to the compensatory dilator responses seen during both hypoxia and hyperperfusion, but it is unclear whether this NO release is due to direct stimulation of the vascular endothelium, NO release from the active skeletal muscles, potentiation of a non-NOS NO pathway, release of some mediator (ATP?) that then evokes NO release from the vascular endothelium, or perhaps a direct effect of hypoxia on vascular smooth muscle that then stimulates flow-induced NO release. The contribution and interactions between potential vasodilator substances are illustrated in Figure 4. These responses appear to be augmented in healthy young women. Our studies in healthy older humans demonstrate that compensatory vasodilation during hypoxic exercise is blunted with aging in both sexes and likely due to a loss of NO-mediated endothelial vasodilator function. In this context, there may be further reductions in compensatory vasodilator responses with pathophysiological conditions such as hypertension and diabetes. If these responses also occurred in other vascular beds, then the consequences of tissue hypoxia or hypoperfusion might be even more problematic in disease states. As always for both exercise hyperemia and NO, it could be “some of the above” or “all of the above,” when thinking about vasodilator mechanisms and exercise. The fact that differences in dilator mechanisms are seen when different approaches are used to alter oxygen delivery to contracting muscles is not surprising to us, given the highly redundant regulatory control mechanisms associated with exercise hyperemia.

REFERENCES


AUTHOR CONTRIBUTIONS

Author contributions: M.J.J. conception and design of research; M.J.J. and D.P.C. interpreted results of experiments; M.J.J. and D.P.C. drafted manuscript; M.J.J. and D.P.C. approved final version of manuscript; D.P.C. performed experiments; D.P.C. analyzed data; D.P.C. prepared figures; D.P.C. edited and revised manuscript.

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DISCLOSURES

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