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SYMPOSIUM REVIEW

Compensatory vasodilatation during hypoxic exercise: mechanisms responsible for matching oxygen supply to demand

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Abstract Hypoxia can have profound influences on the circulation. In humans, acute exposure to moderate hypoxia has been demonstrated to result in vasodilatation in the coronary, cerebral, splanchnic and skeletal muscle vascular beds. The combination of submaximal exercise and hypoxia produces a 'compensatory' vasodilatation and augmented blood flow in contracting skeletal muscles relative to the same level of exercise under normoxic conditions. This augmented vasodilatation exceeds that predicted by a simple sum of the individual dilator responses to hypoxia alone and normoxic exercise. Additionally, this enhanced hypoxic exercise hyperaemia is proportional to the hypoxia-induced fall in arterial oxygen (O_2) content, thus preserving muscle O_2 delivery and ensuring it is matched to demand. Several vasodilator pathways have been proposed and examined as likely regulators of skeletal muscle blood flow in response to changes in arterial O_2 content. The purpose of this review is to put into context the present evidence regarding mechanisms responsible for the compensatory vasodilatation observed during hypoxic exercise in humans. Along these lines, this review will highlight the interactions between various local metabolic and endothelial derived substances that influence vascular tone during hypoxic exercise.

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Exercise hyperaemia: matching blood flow to metabolism

ATP turnover stimulates oxygen (O_2) consumption in contracting skeletal muscles. For contractions to be sustained, as is the case during endurance exercise, there must be continuous supply of O_2 to the contracting muscles. At the systemic level, ventilation and gas exchange in the lung, along with increases in cardiac output, are critical to meet the demands of the contracting skeletal muscle for oxygen, and within skeletal muscle there is typically an increase in blood flow (O_2 delivery) that is proportional to what might generally be termed as 'metabolic demand.' Presented in Fig. 1 is an example of the tight matching between indices of O_2 demand and increases in skeletal muscle blood flow during different modes of exercise (Mortensen *et al.* 2008).

It is important to note that at rest, skeletal muscle O_2 consumption is quite low and blood flow is on the order of 3 ml (100 g)$^{-1}$ min^{-1}. This is consistent with the general concept that resting oxygen consumption in normal-sized humans is ∼250 ml min^{-1}. However, during maximal exercise O_2 consumption can increase 10- to 15-fold in untrained young subjects, and 20- to 25-fold in elite highly trained endurance athletes. These increases in O_2 consumption are facilitated by vast increases in cardiac output and, more importantly, increases in skeletal muscle blood flow of 50- to 100-fold (Andersen & Saltin, 1985; Armstrong & Laughlin, 1985; Musch, 1988). So, exercising skeletal muscles can increase their O_2 consumption markedly, and this increase in O_2 consumption drives vast increases in blood flow.

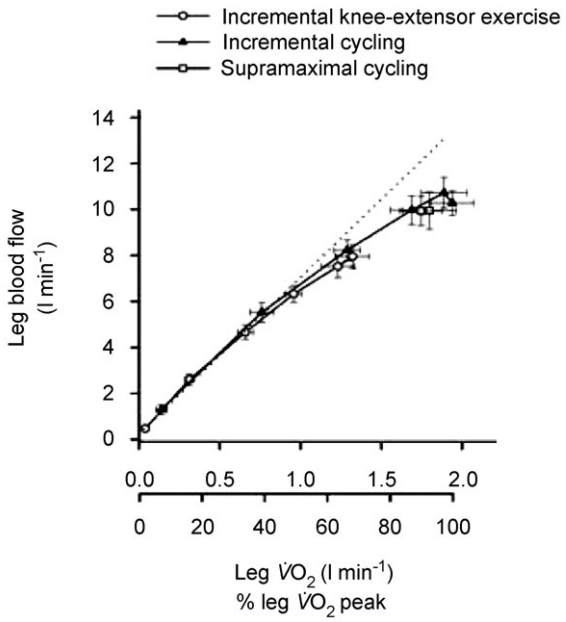

Figure 1. Matchingblood flow to metabolism during exercise
One-legged blood flow during incremental knee-extensor exercise and incremental and supramaximal cycling to exhaustion plotted against one-legged V_{O2}. Adapted with permission from Mortensen *et al.* (2008).

Table 1. Potential mechanisms responsible for increasing blood flow in contracting muscle

1. Mechanical
a. Muscle pump (↑ in the arterio-venous pressure gradient for flow)
b. Mechanical deformation of the vessel wall
2. Neural
a. Blunting of sympathetic α-adrenergic vasoconstriction (functional sympatholysis)
b. Sympathetic cholinergic vasodilatation
c. Acetylcholine spillover from motor-end plates
3. Metabolic
Substances produced and/or released from skeletal muscle, endothelial, and red blood cells (NO, adenosine, prostanoids, ATP, hydrogen ion, potassium, EDHF)
4. Flow- or shear stress-induced vasodilatation
5. Conducted vasodilatation

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 and neural factors and various local metabolic and endothelial derived substances that influence vascular tone (Clifford, 2007). These potential mechanisms are listed in Table 1 and have previously been reviewed in detail (Shepherd, 1983; Clifford, 2007; Joyner & Wilkins, 2007).

What happens when O_2 availability is limited?

The general principles outlined above reflect the synthesis of ideas and data generated in healthy humans with normal haematocrit levels, exercising at low altitude. This means that under most circumstances arterial O_2 saturation remains high (95% or greater). What happens when arterial O_2 content is lowered by hypoxia or anaemia, or when the ability of red cells to carry and release O_2 is limited by carbon monoxide (CO)? Under these circumstances, the relationship between blood flow and O_2 demand is shifted upward so that blood flow increases but O_2 delivery to the exercising muscle remains constant. For example, if arterial O_2 saturation falls from 100% to 80% as a result of hypoxia, there is a ∼20% increase in blood flow so that total O_2 delivery to the skeletal muscles remains constant. The compensatory vasodilatation exceeds that predicted by a simple sum of the individual dilator responses to hypoxia alone and normoxic exercise. This general principle is also seen when O_2 delivery is limited by CO or anaemia and the general concept of 1:1

compensation is seen under all three conditions (Roach *et al.* 1999; Gonzalez-Alonso *et al.* 2001).

Compensatory vasodilatation in the face of sympathetic vasoconstrictor activity

One especially interesting feature associated with compensatory vasodilatation is that during hypoxia there is increased sympathetic vasoconstrictor activity directed towards skeletal muscle (Hanada *et al.* 2003) (Fig. 2). This means that the signals associated with the compensatory vasodilatation are opposed by the vasoconstrictor activity. To better understand this interaction, we evaluated the effects of α-adrenergic blockade on the compensatory vasodilatation during hypoxic forearm exercise (Wilkins *et al.* 2008). Similar to findings under resting conditions (Weisbrod *et al.* 2001), α-adrenergic receptor blockade revealed a substantially greater vasodilatation during hypoxic exercise compared to control hypoxic exercise conditions (i.e. during saline infusion). However, despite elevated sympathetic vasoconstrictor activity during hypoxic exercise (compared to normoxic exercise or hypoxia alone), substantial compensatory vasodilatation persists.

Under normoxic conditions sympathetic vasoconstrictor responses are blunted in the vascular beds of contracting limbs (Remensnyder *et al.* 1962; Dinenno & Joyner, 2003), a phenomenon referred to as 'functional sympatholysis'. Moreover vasoconstrictor responses to sympathetic stimulation and exogenous noradrenaline are attenuated during hypoxia (Heistad & Wheeler, 1970; Heistad *et al.* 1975). These findings raise the possibility that blunted vasoconstrictor responsiveness (augmented functional sympatholysis) contributes to the compensatory vasodilatation during hypoxic exercise. However, we found that the compensatory vasodilator response to hypoxic forearm exercise was not due to an augmented functional sympatholysis (Wilkins *et al.* 2006). These observations suggest that enhanced vasodilator signals and not blunted vasoconstriction are primarily responsible for the compensatory vasodilatation in skeletal muscle during hypoxic exercise.

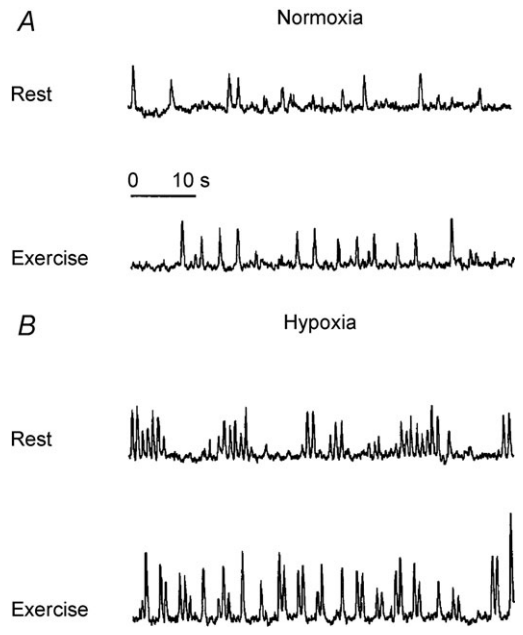

Figure 2. Hypoxia induced increases in muscle sympathetic nerve activity (MSNA)
Representative recordings of leg MSNA at rest and during exercise under normoxia (F_{I,O_2} 21%; *A*) and hypoxia (F_{I,O_2}) ~10%; *B*). Adapted with permission from Hanada *et al.* (2003).

Role of local vasodilator pathways

Our lab has conducted a series of studies to evaluate at least some of the putative metabolic vasodilating substances (adenosine, nitric oxide (NO), prostaglandins, etc.) as potential mediators of compensatory vasodilatation during hypoxia. During mild rhythmic hand gripping we found evidence that at least some of the compensatory vasodilatation was mediated by vasodilating β-adrenergic receptors in the active limb, stimulating the release of NO (Wilkins *et al.* 2008; Casey *et al.* 2010). As exercise intensity increased, there still appeared to be a role for NO but the β-adrenergic-NO pathway was absent and there must have been some other mechanism evoking NO release as a mediator of compensatory vasodilatation (Wilkins *et al.* 2008; Casey *et al.* 2011). These mechanisms may include direct release of NO from the endothelium as a result of luminal hypoxia (Pohl & Busse, 1989), shear stress mediated NO release (Kooijman *et al.* 2008), NO from erythrocytes in the form *S*-nitrosohaemoglobin (Stamler *et al.* 1989), and/or increased NO release via ATP and prostaglandins (Mortensen *et al.* 2007; Mortensen *et al.* 2009). Nonetheless, evidence that hypoxia increases plasma but not skeletal muscle interstitial NO in humans is likely to suggest an endovascular or endothelial source (Leuenberger *et al.* 2008).

Adenosine has also been suggested to play a role in compensatory vasodilator responses (Bryan & Marshall, 1999*a*,*b*). However, in several human studies we (Casey *et al.* 2009) and others (Heinonen *et al.* 2010) were unable to find clear evidence for a primary role for adenosine. Moreover, adenosine does not contribute to the compensatory vasodilatation after NO synthase inhibition, thus indicating that adenosine does not act through a NO-independent pathway in the compensatory vasodilator response during hypoxic exercise (Casey *et al.* 2010). This is important because in the coronary circulation adenosine appears to play an important role in regulating blood flow to ischaemic tissue in various models

of coronary artery disease (Laxson *et al.* 1993). Likewise, in exercising human forearm muscles, inflation of a balloon in the brachial artery upstream from the forearm causes an immediate decrease in forearm blood flow followed by recovery to control values and we have evidence that adenosine does in fact contribute to the recovery of flow under these circumstances (Casey & Joyner, 2011).

Over the past several years it has been proposed that erythrocytes are not only responsible for sensing and carrying O_2, but also participate in the regulation of blood flow and its distribution by releasing ATP (Ellsworth *et al.* 2009). In this context, acute exposure to hypoxia at rest as well as exercise under normoxic conditions leads to increases in venous plasma levels of ATP (Gonzalez-Alonso *et al.* 2002; Mortensen *et al.* 2011). Whether erythrocyte derived ATP contributes to the compensatory vasodilatation observed during hypoxic exercise is still unclear. Unfortunately, specific pharmacological antagonists for P_2 receptors to address the role of ATP in the hypoxia-induced compensatory vasodilatation are currently unavailable for human use. Therefore, we are left to rely on plasma measures to gain insight into the contribution of ATP in the compensatory vasodilator response to hypoxic exercise. Along these lines, arterial and venous plasma levels of ATP measured via intravascular microdialysis are not greater during hypoxic compared to normoxic exercise (Mortensen *et al.* 2011). Thus the question whether ATP contributes to compensatory vasodilatation during hypoxic exercise remains somewhat elusive. Figure 3 illustrates well established as well as potential dilator signals that contribute to compensatory vasodilatation during submaximal hypoxic exercise.

What happens during whole body maximal exercise?

Under the assumption that increases in cardiac output during exercise are directed at the active skeletal muscle, there is evidence for compensatory vasodilatation during submaximal whole body exercise (Stenberg *et al.* 1966; Hughes *et al.* 1968; Vogel & Gleser, 1972). For example, when the arterial O_2 content and saturation are reduced via acute hypoxia, there is an increase in cardiac output that keeps O_2 delivery to the skeletal muscles constant

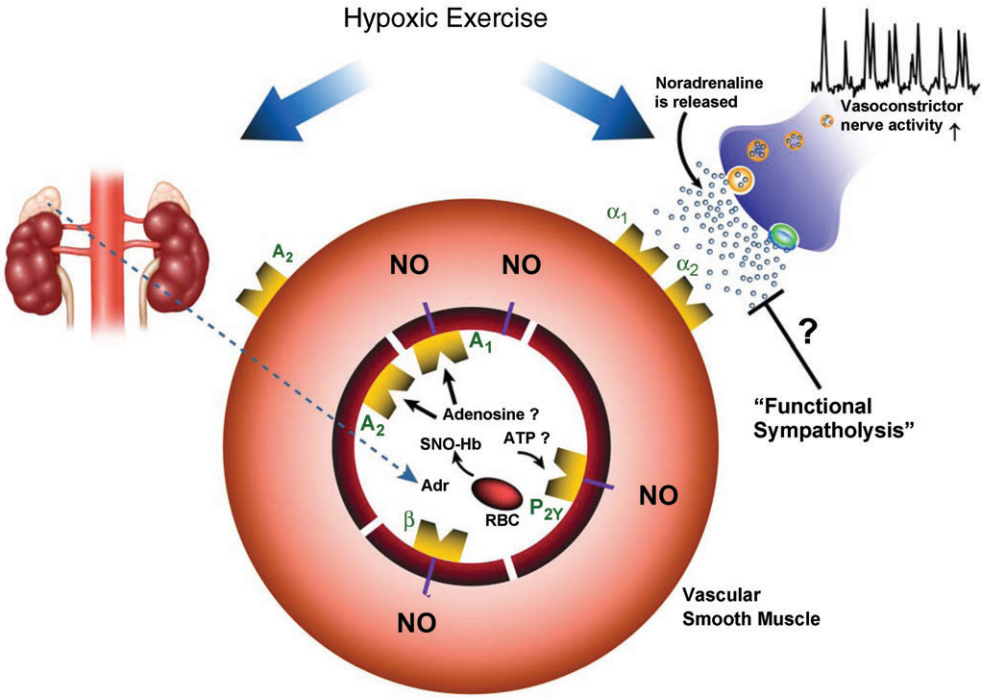

Figure 3. Proposed mechanisms for hypoxia-induced vasodilatation at rest and during exercise
During hypoxic exercise NO is the final common pathway for the compensatory dilator response. Systemic adrenaline release, acting via β-adrenergic receptors, contributes to the NO-mediated vasodilatation at lower exercise intensities, but this β-adrenergic contribution decreases with increasing exercise intensity. ATP released from the red blood cell remains an attractive candidate for stimulating NO during higher intensity hypoxic exercise. Adenosine receptor activation does not appear to play a major role (either dependent or independent of NO) in the compensatory vasodilator response during hypoxic exercise in humans. Compensatory vasodilatation persists despite an increased sympathetic vasoconstrictor activity directed towards skeletal muscle during hypoxic exercise. Blunted vasoconstrictor responsiveness (augmented functional sympatholysis) does not appear to contribute to the compensatory vasodilatation during hypoxic exercise. α_1 and α_2 indicate α_1 and α_2 adrenergic receptors, respectively; A1 and A2, adenosine receptors; β, β_2 adrenergic receptors; Adr, adrenaline.

(Hughes *et al.* 1968). However, during maximal exercise involving a large muscle mass (i.e. cycling or running), blood flow and vasodilatation in the exercising limbs are reduced under hypoxic compared to normoxic conditions (Calbet, 2000). The lower blood flow in exercising skeletal muscle is likely to be related to the significant reductions in maximal cardiac output observed during hypoxic exercise (Calbet *et al.* 2003, 2009*a*; Lundby *et al.* 2006). The potential mechanisms for reductions in maximal cardiac output during acute hypoxia have been recently reviewed by others (Calbet *et al.* 2009*b*). Conversely, when small muscle mass is activated and cardiac output is not limited, skeletal muscle blood flow is maintained at peak exercise under hypoxic conditions (Calbet *et al.* 2009*a*).

It is apparent that exercise intensity (submaximal *vs.* maximal), the amount of muscle mass, and the severity and duration of hypoxia are all important factors in determining the blood flow and compensatory vasodilator responses during hypoxic exercise. The studies related to the mechanisms responsible for compensatory vasodilatation during hypoxic exercise highlighted in this review have mainly been derived using a forearm exercise model and local infusions of various study drugs. This approach has allowed us, as well as others, to investigate local vascular control without additional confounding variables (i.e. cardiovascular reflexes) that occur with exercise involving larger muscle mass or systemic drug infusions. However, it is currently unclear whether the regulatory mechanisms involved in compensatory vasodilatation during forearm exercise continue to contribute to muscle blood flow as exercise intensity and/or the amount of active muscle mass increases. In this context, future studies will be needed to examine vascular responses to hypoxic exercise during 'real world' settings (such as whole body exercise at altitude).

Summary

It is clear that acute reductions in available O_2 via systemic hypoxia promote compensatory vasodilatation and an augmented blood flow in contracting skeletal muscle during submaximal workloads. The compensatory response is essential to preserving muscle O_2 delivery and ensuring it is matched to demand. Interestingly, the compensatory vasodilatation and augmented flow persist despite large increases in sympathetic vasoconstrictor activity directed towards skeletal muscle. Thus, the degree of vasodilatation prevails over the vasoconstrictor response in determining vasomotor tone during hypoxic exercise.

We have demonstrated that a key vasodilator signal in the compensatory response is NO. However, it appears that the NO-mediated component of the compensatory vasodilatation 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 dilatation 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 release during higher intensity hypoxic exercise.

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