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CROSSTALK

CrossTalk opposing view: Diffusion limitation of O_2 from microvessels into muscle does not contribute to the limitation of $\dot{V}_{O_2max}$

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Oxygen is transferred from air to mitochondria in sequential steps by means of diffusion and convection. The theoretical ceiling for whole body aerobic uptake may be determined by any factor influencing the O_2 transport and utilization chain. The dispute considered here is whether peripheral O_2 diffusion from microvessels, particularly capillaries, into active skeletal muscle fibres limits/regulates maximal oxygen uptake ($\dot{V}_{O_2max}$) in healthy humans.

Peripheral O_2 diffusion does not limit $\dot{V}_{O_2max}$

$\dot{V}_{O_2max}$ is experimentally determined by the levelling off in O_2 uptake observed with increasing workload during dynamic exercise involving more than half of total muscle mass (e.g. running, cycling) (Levine, 2008). This indicates that, empirically, $\dot{V}_{O_2max}$ is limited, i.e. primarily restricted prior to peak muscle activation. Moreover, such limitation is attributed to a finite oxygen supply to muscle given that mitochondrial oxidative capacity exceeds that of oxygen delivery at $\dot{V}_{O_2max}$ (Boushel *et al.* 2011). Thus, any factor related to the transport of O_2 into the mitochondria might limit $\dot{V}_{O_2max}$. In this regard, there is sound evidence that $\dot{V}_{O_2max}$ is proportionally modified in accordance with acute changes in blood O_2-carrying capacity and content (Calbet *et al.* 2006*a*). In contrast, a decrease in arterial O_2 partial pressure, and thereby reducing the driving force for O_2 diffusion, does not affect maximal O_2 uptake if O_2 delivery to the exercising limbs at the same time remains preserved (Calbet *et al.* 2003, 2009). Importantly, these observations were not associated with any particular individual's fitness status. Accordingly, at $\dot{V}_{O_2max}$ in healthy individuals there must be a physiologically relevant reserve in muscle O_2 diffusing capacity, which also precludes that $\dot{V}_{O_2max}$ is limited by peripheral O_2 diffusion from capillary into muscle.

Does muscle O_2 diffusion regulate $\dot{V}_{O_2max}$?

While peripheral O_2 diffusion does not limit $\dot{V}_{O_2max}$, the question arises as to whether $\dot{V}_{O_2max}$ could be influenced by muscle O_2 diffusing capacity in healthy individuals. This would be entirely refuted if O_2 were fully extracted from capillaries supplying active muscle fibres. However, such level of resolution for O_2 extraction within human muscle fibres is beyond reach with current methods (Koga *et al.* 2014). Instead, the large body of empirical evidence derives from O_2 measures in venous blood exiting the active limb (Rud *et al.* 2012), in which a 100% O_2 extraction seems unachievable considering temporal and spatial characteristics (Heinonen *et al.* 2015). For instance, the high intramuscular pressure generated during the contraction phase partly diverts blood flow toward less metabolically active tissue (Clark *et al.* 2000). Also, the perfusion of active muscle fibres is inherently inefficient as regards O_2 delivery, since microvascular units (i.e. terminal arteriole and downstream capillaries) are not spatially coordinated with individual motor units and this may result in the overperfusion of inactive fibres (Emerson & Segal, 1997). In addition, O_2 extraction may be a function of the physiological distribution of blood flow among active/inactive muscle fibres and other tissues (Kalliokoski *et al.* 2001, 2005; Calbet *et al.* 2006*b*). Of note, blood flow distribution is determined by the complex interplay of factors including the sympathetic drive, concentration of vasoactive substances, arterial dilator/constrictor function and microvascular structure. Therefore, a perfect matching between leg O_2 delivery and metabolic demand during exercise is not expected even if neglecting the previously mentioned temporal and spatial intrinsic constraints; here, blood flow distribution is improved and O_2 extraction enhanced within exercising muscles in long-term trained individuals (Kalliokoski *et al.* 2001). Ignoring or trivializing this fact may have distorted the contribution of muscle O_2 diffusion to the limitation $\dot{V}_{O_2max}$ (Piiper, 2000; Koga *et al.* 2014). Yet O_2 extraction across the leg commonly rises to 85% or more at $\dot{V}_{O_2max}$ in untrained and trained individuals (Lundby *et al.* 2006; Rud *et al.* 2012), attaining an astonishing 97% in some elite athletes (Calbet *et al.* 2005). It follows that for muscle O_2 diffusing capacity to contribute to the limitation of $\dot{V}_{O_2max}$, an average of approximately 85% or more of leg blood flow should be *continuously* perfusing active muscle fibres.

If leg O_2 extraction, and thus $\dot{V}_{O_2max}$, were regulated by leg muscle O_2 diffusing capacity, any increase in diffusion capacity would be reflected, at least to a degree, in an augmented leg O_2 extraction. In this respect, one-leg training studies have provided compelling evidence because the impact of peripheral adaptations on $\dot{V}_{O_2max}$ may be isolated from central haemodynamic adaptations (Gleser, 1973; Saltin *et al.* 1976; Klausen *et al.* 1982; Rud *et al.* 2012). All these studies have shown marked increases in one-legged cycling peak blood flow, O_2 diffusing capacity, and uptake in individuals

Carsten Lundby (left) and **David Montero** (right) both work at the University of Zürich in a small team focusing on Oxygen Transport and Utilization in its broadest sense. The strength of the group is its integrative approach which allows them to study O_2 as it is transported all the way from inspired air and until it is oxidized in the mitochondrion. Their most recent work has focused on the relative importance of skeletal muscle and circulatory adaptations to exercise training for improvements in $\dot{V}_{O_2max}$ and hence is in direct line with the current cross talk.

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who, before training, had $\dot{V}_{O_2max}$ in the normal range (Gleser, 1973; Saltin *et al.* 1976; Klausen *et al.* 1982; Rud *et al.* 2012). However, peak O_2 uptake during two-legged cycling (i.e. $\dot{V}_{O_2max}$) remained unaltered in the presence of unchanged maximal cardiac output ($\dot{Q}_{max}$) following one-legged training (Gleser, 1973). In line with this, the increase in $\dot{V}_{O_2max}$ following two-legged training was reverted to the baseline level after negating the training-induced gain in $\dot{Q}_{max}$ by means of phlebotomy (Bonne *et al.* 2014). Likewise, $\dot{V}_{O_2max}$ was identical prior to and after one-legged training despite the fact that blood flow, O_2 extraction and uptake were enhanced during two-legged cycling in the trained *versus* control leg (Rud *et al.* 2012). This strongly suggests that two-legged O_2 extraction (~85%) was maximized relative to blood flow at $\dot{V}_{O_2max}$, irrespective of any training adaptation in muscle O_2 diffusing capacity. Overall, these data indicate that $\dot{V}_{O_2max}$ is not modulated by muscle O_2 diffusing capacity. Rather, $\dot{V}_{O_2max}$ seems to be governed, in a tyrannical manner, by the amount of blood flowing into the exercising limbs.

Several canine studies have been aimed aet examining the contribution of muscle O_2 diffusing capacity to O_2 extraction (Schumacker *et al.* 1985; Barclay, 1986; Hogan *et al.* 1989, 1991; Richardson *et al.* 1998). In these, blood flow or haemoglobin O_2 affinity (P_{50}) have been manipulated while maintaining O_2 delivery constant to contracting muscle. Hence a regulatory role for O_2 diffusion from capillary into muscle in O_2 extraction could be pinpointed, provided that O_2 delivery to active muscle fibres is not influenced by blood flow or P_{50} (Schumacker *et al.* 1987). Regardless, the majority of the evidence comparing experimental *versus* control conditions indicates that muscle O_2 uptake is uniquely dependent on O_2 delivery (Schumacker *et al.* 1985, 1987; Barclay, 1986; Richardson *et al.* 1998). Furthermore, the presence of statistical procedures raising the likelihood for type I errors to occur (i.e. the probability of making false discoveries) in divergent findings is noteworthy (Hogan *et al.* 1989). Taken together, the proposed regulatory role for O_2 diffusion from capillary into muscle during exercise (Wagner, 1992) cannot be induced from the above animal experiments, let alone extrapolating it to humans exercising at $\dot{V}_{O_2max}$, in which, as a matter of fact, such a role is empirically absent (Calbet *et al.* 2003; Lundby *et al.* 2006).

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Additional information

Competing interests

None declared.