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CROSSTALK

CrossTalk proposal: Diffusion limitation of O_2 from microvessels into muscle does contribute to the limitation of $\dot{V}_{O_2max}$

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At maximal oxygen uptake ($\dot{V}_{O_2max}$) we know that (1) muscle O_2 extraction is not 100%, yet (2) hyperoxia increases $\dot{V}_{O_2max}$. The reason for (1) is diffusion limitation of O_2 from the muscle microvessels to the mitochondria. This does not exclude 'central' factors from also affecting $\dot{V}_{O_2max}$, as will be explained.

Two simple, direct, published, and undisputed observations document the first point. They are that, when the inspired O_2 fraction (F_{IO_2}) is acutely altered (in random order within a single day):

(1) $\dot{V}_{O_2max}$ is higher in hyperoxia and lower in hypoxia, compared to room air (Welch, 1982, 1987; Knight *et al.* 1993).
(2) Muscle venous blood still contains significant amounts of O_2 at $\dot{V}_{O_2max}$, in hypoxia, normoxia and hyperoxia (Roca *et al.* 1989; Knight *et al.* 1993).

This shows unequivocally that the muscles are capable of using more O_2 in normoxia (or hypoxia) than they can extract, proving the existence of an extraction limit, contributing to $\dot{V}_{O_2max}$ limitation.

The extraction limit could result from any of three possibilities: (a) shunting of arterial blood around exercising muscle; (b) heterogeneity in the distribution of blood flow with respect to metabolic demand; (c) diffusion limitation of O_2 transport from microvessels to mitochondria.

While there may be minor contributions from the first two, diffusion limitation appears to be the major basis of limited extraction. The most compelling evidence comes from studies of isolated *in situ*, canine gastrocnemius muscle in which maximal contractions (and $\dot{V}_{O_2}$) were produced by nerve stimulation, holding O_2 delivery into the muscle constant while one factor was varied – haemoglobin O_2 affinity defined by (P_{50}) (Hogan *et al.* 1991; Richardson *et al.* 1998). Arterial [O_2] and blood flow were kept constant (animals breathed 100% O_2; muscle blood flow was pump-controlled). Hogan's study reduced P_{50} (to impair diffusive extraction by reducing microvascular P_{O_2}); Richardson's study increased P_{50} (to enhance diffusive extraction by increasing microvascular P_{O_2}). Importantly, neither shunting nor heterogeneity would alter extraction at constant O_2 delivery and blood flow, as only P_{50} is varied. As predicted, $\dot{V}_{O_2max}$ increased as P_{50} was raised, and fell when P_{50} was reduced. Moreover, the amount by which $\dot{V}_{O_2max}$ changed was predicted by the laws of diffusion from the concomitant changes in mean microvascular P_{O_2}: $\dot{V}_{O_2max}$ was proportional to mean microvascular P_{O_2}, a finding also noted in humans (Roca *et al.* 1989; Knight *et al.* 1993).

Additional evidence for diffusion limitation of O_2 between muscle microvessels and mitochondria comes from computational modelling (Groebe & Thews, 1990), frozen myoglobin spectroscopy (Gayeski & Honig, 1988) and magnetic resonance spectroscopy (Richardson *et al.* 1995).

Scientific progress calls for not only supporting one's views with data, but also reconciling them with other views. The major difference with others' opinions is in understanding the role of cardiac output in limiting $\dot{V}_{O_2max}$. That cardiac output contributes to $\dot{V}_{O_2max}$ limitation is not in dispute. Pericardiectomy in dogs increases maximal cardiac output and $\dot{V}_{O_2max}$ (Stray-Gundersen *et al.* 1986). The Saltin group, comparing two-legged and one-legged cycling (Rowell *et al.* 1986), showed that specific $\dot{V}_{O_2max}$ is higher in one-legged than two-legged cycling, associated with higher specific muscle blood flow. Additionally, Powers *et al.* (1989) showed that pulmonary gas exchange inefficiency affected $\dot{V}_{O_2max}$; severe anaemia is also well known to reduce exercise capacity. That is exactly what would be expected of an in-series O_2 transport system – every step must play a role in affecting overall outcome ($\dot{V}_{O_2max}$).

Pro-cardiac-output-is-*the*-limiting-factor-advocates (PCOITLFA) cite the Fick principle (O_2 uptake = blood flow × arteriovenous [O_2] difference) applied to elite athletes *versus* the rest of us. The main, undisputed, difference is in cardiac output (blood flow) and not in arteriovenous [O_2] difference. Ergo, the PCOITLFA conclude that cardiac output, not extraction, explains the differences in $\dot{V}_{O_2max}$. What the PCOITLFA forget is that if all else were similar between us, the elite athlete's higher cardiac output would shorten red cell transit time for O_2 unloading in the muscle microvessels. This would offset much of the benefit of higher blood flow by reducing diffusive O_2 unloading (Wagner, 1996). However, despite higher blood flow, athletes are able to extract higher amounts of O_2: femoral venous P_{O_2} is usually lower than in the rest of us. This means that the athlete's diffusive conductance supporting O_2 movement from microvessels to mitochondria is greater than in the rest of us, allowing the maintenance of a large arteriovenous [O_2] difference in the face of higher blood flow. But even so, elite athletes increase $\dot{V}_{O_2max}$ with added O_2, which takes us back to the initial arguments of this article.

Peter Wagner is Distinguished Professor of Medicine and Bioengineering at the University of California, San Diego. His research addresses the theoretical and experimental basis of oxygen transport and its limitations in the lungs and skeletal muscles in health and disease. A particular focus is muscle capillary growth regulation using molecular biological approaches in integrated systems: the role of O_2, microvascular haemodynamics, physical factors, nitric oxide and inflammatory mediators in transcriptional regulation of angiogenic growth factors. Of particular interest is the role of VEGF in both pulmonary and skeletal muscle structure and function.

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The simplest way to understand how the O_2 transport system works, with every step contributing to limiting $\dot{V}_{O_2max}$, is graphically, using a diagram relating $\dot{V}_{O_2}$ to muscle venous P_{O_2} on the basis of the two main transport equations involved. One underlies the previously mentioned Fick principle (O_2 uptake = blood flow × arteriovenous [O_2] difference), i.e.

$$\dot{V}_{O_2} = \dot{Q} \times (C_{aO_2} - C_{vO_2}) \quad (1)$$

And the second is the equation underlying the Fick law of diffusion:

$$\dot{V}_{O_2} = D_{MO_2} \times \left(P_{O_2 microvascular} - P_{O_2 mitochondrial}\right) \quad (2)$$

D_{MO_2} is muscle O_2 diffusional conductance, $P_{O_2 microvascular}$ is mean microvascular P_{O_2} within muscle, and $P_{O_2 mitochondrial}$ is mitochondrial P_{O_2}, which appears to be so low compared to $P_{O_2 microvascular}$ (Richardson *et al.* 1995) that it can here be neglected. Because $P_{O_2 microvascular}$ and muscle venous P_{O_2} rise and fall in proportion to one another (Roca *et al.* 1989), we can replace $P_{O_2 microvascular}$ by P_{vO_2}, the venous P_{O_2}, times a constant, say, k. With these approximations, eqn (2) may be re-written:

$$\dot{V}_{O_2} = D_{MO_2} \times k \times P_{vO_2} \quad (3)$$

Equations (1) and (3) embody the same undisputed law: conservation of O_2 mass during its transport. As a consequence they apply simultaneously: at their solution, both $\dot{V}_{O_2}$ and P_{vO_2} must be the same in the two equations. Because they both relate $\dot{V}_{O_2}$ to muscle venous O_2 levels, they can be plotted on one diagram with $\dot{V}_{O_2}$ on the ordinate and P_{vO_2} on the abscissa (Fig. 1, modified from Wagner, 1996). Their intersection point is the only point where conservation of mass exists – the same $\dot{V}_{O_2}$ at the same P_{vO_2} – indicating the value of $\dot{V}_{O_2max}$ for the given values of $\dot{Q}$, C_{aO_2} and D_{MO_2}. Change *any one* of these three, and the lines will shift, yielding a different intersection point (i.e. different $\dot{V}_{O_2max}$). Since $\dot{Q}$ represents cardiac function, C_{aO_2} represents pulmonary gas exchange and blood [Hb], and D_{MO_2} represents muscle O_2 diffusional properties, it is evident that all steps of the O_2 pathway significantly impact $\dot{V}_{O_2max}$. That is how an in-series system must work, and why muscle O_2 diffusion limitation *does* contribute to limitation of $\dot{V}_{O_2max}$.

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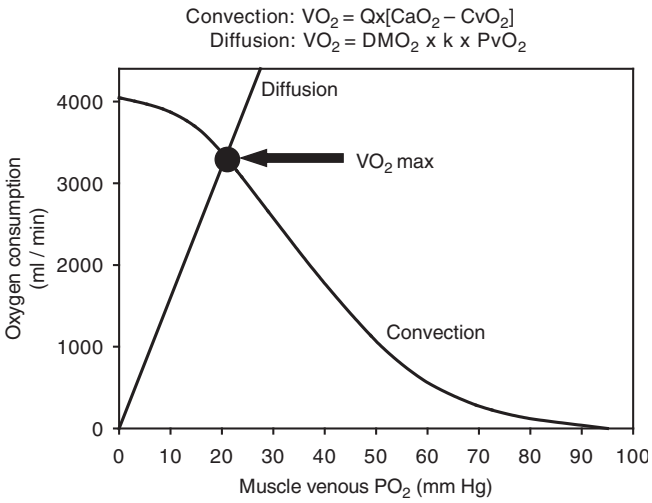

Figure 1. Determinants of V_{O_2max}
Plot of O_2 consumption ($\dot{V}_{O_2}$) against muscle venous P_{O_2} showing the two conservation of mass equations describing convective flow of O_2 into the muscle microcirculation (Fick principle), and subsequent diffusive flow of O_2 from the microcirculation to the mitochondria (Fick law of diffusion). Conservation of mass occurs only at their point of intersection, indicating the value of $\dot{V}_{O_2max}$ when the independent variables $\dot{Q}$, C_{aO_2} and D_{MO_2} are those at $\dot{V}_{O_2max}$ (modified from Wagner, 1996).

References

Gayeski TE & Honig CR (1988). Intracellular PO_2 in long axis of individual fibers in working dog gracilis muscle. *Am J Physiol* **254**, H1179–H1186.

Groebe K & Thews G (1990). Calculated intra- and extracellular gradients in heavily working red muscle. *Am J Physiol* **259**, H84–H92.

Hogan MC, Bebout DE & Wagner PD (1991). Effect of increased Hb-O_2 affinity on VO_{2max} at constant O_2 delivery in dog muscle in situ. *J Appl Physiol (1985)* **70**, 2656–2662.

Knight DR, Schaffartzik W, Poole DC, Hogan MC, Bebout DE & Wagner PD (1993). Effects of hyperoxia on maximal leg O_2 supply and utilization in men. *J Appl Physiol (1985)* **75**, 2586–2594.

Powers SK, Lawler J, Dempsey J, Dodd JA & Landry G (1989). Effects of incomplete pulmonary gas exchange on VO_2 max. *J Appl Physiol (1985)* **66**, 2491–2495.

Richardson RS, Noyszewski EA, Kendrick KF, Leigh JS & Wagner PD (1995). Myoglobin O_2 desaturation during exercise: evidence of limited O_2 transport. *J Clin Invest* **96**, 1916–1926.

Richardson RS, Tagore K, Haseler L, Jordan M & Wagner PD (1998). Increased VO_2max with a right shifted Hb-O_2 dissociation curve at a constant O_2 delivery in dog muscle in situ. *J Appl Physiol (1985)* **84**, 995–1002.

Roca J, Hogan MC, Story D, Bebout DE, Haab P, Gonzalez R, Ueno O & Wagner PD (1989). Evidence for tissue diffusion limitation of VO_2max in normal humans. *J Appl Physiol (1985)* **67**, 291–299.

Rowell LB, Saltin B, Kiens B & Christensen NJ (1986). Is peak quadriceps blood flow in humans even higher during exercise with hypoxemia? *Am J Physiol* **251**, H1038–H1044.

Stray-Gundersen J, Musch TI, Haidet GC, Swain DP, Ordway GA & Mitchell JH (1986). The effect of pericardiectomy on maximal oxygen consumption and maximal cardiac output in untrained dogs. *Circ Res* **58**, 523–530.

Wagner PD (1996). A theoretical analysis of factors determining VO_2max at sea level and altitude. *Respir Physiol* **106**, 329–343.

Welch HG (1982). Hyperoxia and human performance: a brief review. *Med Sci Sports Exerc* **14**, 253–262.

Welch HG (1987). Effects of hypoxia and hyperoxia on human performance. *Exerc Sports Sci Rev* **15**, 191–221.

Additional information

Competing interests

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