Respiratory Physiology & Neurobiology 189 (2013) 477–483

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Importance of mitochondrial P_{O_2} in maximal O_2 transport and utilization: A theoretical analysis

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ARTICLE INFO

Article history:
Accepted 29 August 2013

Keywords:
Bioenergetics
Mitochondrial respiration
Mitochondrial P_{O_2}
Oxygen transport
$\dot{V}_{O_2}$max

ABSTRACT

In previous calculations of how the O_2 transport system limits $\dot{V}_{O_2}$max, it was reasonably assumed that mitochondrial P_{O_2} (Pm_{O_2}) could be neglected (set to zero). However, in reality, Pm_{O_2} must exceed zero and the red cell to mitochondrion diffusion gradient may therefore be reduced, impairing diffusive transport of O_2 and $\dot{V}_{O_2}$max. Accordingly, we investigated the influence of Pm_{O_2} on these calculations by coupling previously used equations for O_2 transport to one for mitochondrial respiration relating mitochondrial $\dot{V}_{O_2}$ to P_{O_2}. This hyperbolic function, characterized by its P_{50} and $\dot{V}_{MAX}$, allowed Pm_{O_2} to become a model output (rather than set to zero as previously). Simulations using data from exercising normal subjects showed that at $\dot{V}_{O_2}$max, Pm_{O_2} was usually <1 mm Hg, and that the effects on $\dot{V}_{O_2}$max were minimal. However, when O_2 transport capacity exceeded mitochondrial $\dot{V}_{MAX}$, or if P_{50} were elevated, Pm_{O_2} often reached double digit values, thereby reducing the diffusion gradient and significantly decreasing $\dot{V}_{O_2}$max.

1. Introduction

At rest or during exercise, production of ATP requires both physical O_2 transport from the environment to the mitochondria and subsequent chemical utilization of O_2 by oxidative phosphorylation. Oxygen transport has been well described (Dejours and Kayser, 1966; Gnaiger et al., 1998; Weibel et al., 1981) based on the O_2 transport pathway, consisting of the lungs/chest wall, the heart, vascular tree and blood, and the tissues. These structures conduct O_2 as an in-series system in which the main sequential transport steps are ventilation, alveolar-capillary diffusion, circulatory transport, and tissue capillary to mitochondrial diffusion. At each step, the mass of O_2 must be conserved, and this allows a set of simple equations to be defined (Wagner, 1993, 1996b) that quantifies how the transport process at each step integrates with those of the other steps to determine how much O_2 is delivered to the mitochondria per minute (Wagner, 1996a). In this construct, it is shown that each of the four steps contributes to limitation to $\dot{V}_{O_2}$max and that the quantitative effects of changes at each step are similar.

Systems physiological investigations (Wagner, 1993, 1996b) targeting the understanding of the limits to maximal $\dot{V}_{O_2}$, have previously been performed on the basis of an important simplifying approximation. This has been that the downstream mitochondrial P_{O_2} (Pm_{O_2}) is so small in comparison to tissue capillary P_{O_2} that it can be ignored and therefore set to zero, thus making the analyses of O_2 transport much more tractable. However, because O_2 is one of the molecules that drive oxidative phosphorylation according to the law of mass action, this approximation cannot be physiologically correct, or otherwise $\dot{V}_{O_2}$ would itself be zero.

Given that Pm_{O_2} must exceed zero, the P_{O_2} difference between red cells and mitochondria must be less than when Pm_{O_2} is assumed to be zero, and thus the diffusive movement of O_2 between them must also be reduced. Therefore, if Pm_{O_2} is now considered as greater than zero, there is an additional resistance, from the process of mitochondrial respiration, to O_2 movement through the entire pathway of O_2 transport and utilization. We therefore hypothesize that this additional resistance must reduce maximal $\dot{V}_{O_2}$ below that which would be expected if this resistance were ignored. Clearly, the degree to which $\dot{V}_{O_2}$max would be reduced will depend on how the high mitochondrial P_{O_2} rises above zero. This in turn will depend broadly on the capacity for O_2 transport (how many O_2 molecules can be delivered to the mitochondria per minute) compared to the capacity for metabolism (how many O_2 molecules can be consumed by the mitochondria per minute).

The importance of including consideration of oxidative phosphorylation goes beyond asking how much does mitochondrial respiration contribute to the overall impedance to $\dot{V}_{O_2}$. Because the value of Pm_{O_2} is dependent on the mitochondrial respiration curve/O_2 transport interaction, hypoxia-induced biological

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http://dx.doi.org/10.1016/j.resp.2013.08.020

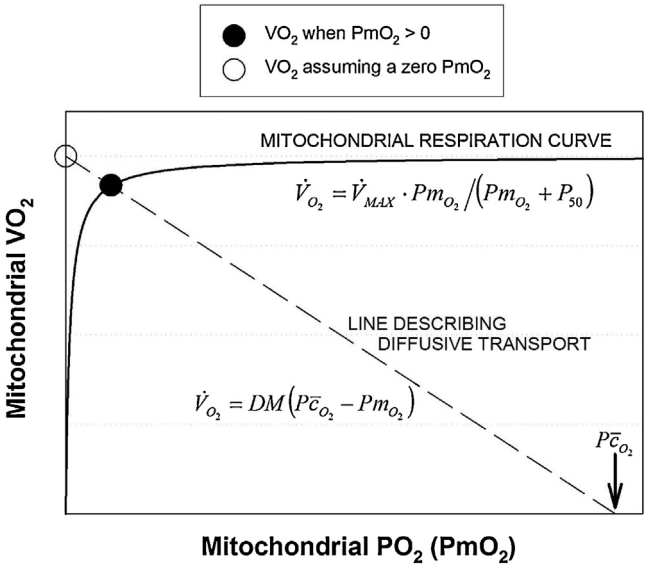

Fig. 1. Graphical analysis of diffusive transport of O_2 from muscle capillary to the mitochondria (dashed line) and subsequent utilization of O_2 through oxidative phosphorylation (solid line). See text for details.

changes may be affected by this interaction. Thus, the significance of the present study is in the degree to which $\dot{V}_{O_2}$max is reduced by the resistance imparted by oxidative phosphorylation and the consequent effect on mitochondrial P_{O_2}, which in turn may affect processes such as generation of reactive oxygen species and hypoxia-induced gene expression.

The purpose of the present paper is therefore to expand the prior theoretical analysis of the integrated O_2 transport pathway (Wagner, 1993, 1996a) by analyzing the consequences for O_2 transport of allowing mitochondrial P_{O_2} to be greater than zero. This requires integration of the previously described O_2 transport equations with an equation for mitochondrial respiration, followed by the application of mass conservation principles to solve this new equation system. The same data that were used in (Wagner, 1993, 1996a) are used here.

2. Material and methods

2.1. Principles

Oxidative phosphorylation ensues via the following Eq. (1) that embodies the law of mass action:

$$3ADP + 3Pi + NADH + H^+ + 1/2O_2 \rightarrow 3ATP + NAD + + H_2O \quad (1)$$

In this equation, Pm_{O_2} corresponds to O_2. Clearly, this mass action equation can only move from left to right and produce ATP if Pm_{O_2} is greater than zero.

To illustrate this effect, a graphical depiction of mitochondrial respiration is presented in Fig. 1. Here, the solid line is the relationship between velocity of the reaction (i.e., mitochondrial $\dot{V}_{O_2}$), and Pm_{O_2}, similar to what has been found experimentally (Gnaiger et al., 1998; Scandurra and Gnaiger, 2010; Wilson et al., 1977). It shows how $\dot{V}_{O_2}$ is a positive but non-linear function of mitochondrial P_{O_2}, and indicates that at low Pm_{O_2}, $\dot{V}_{O_2}$ is very sensitive to (and thus limited by) P_{O_2}, while at higher Pm_{O_2}, $\dot{V}_{O_2}$ becomes independent of P_{O_2}, and is limited by factors other than O_2.

The hyperbolic curve through the origin displayed in Fig. 1 represents mitochondrial respiration. It is of note that despite mitochondrial respiration kinetics is not really a Michaelis–Menten type (Johnson and Goody, 2011; Michaelis and Menten, 1913), experimental data (Gnaiger et al., 1998; Scandurra and Gnaiger, 2010) are well fitted by such a curve. As a hyperbola, it can be represented by Eq. (2):

$$\dot{V}_{O_2} = \frac{\dot{V}_{MAX} \cdot Pm_{O_2}}{Pm_{O_2} + P_{50}} \quad (2)$$

where $\dot{V}_{O_2}$ is mitochondrial $\dot{V}_{O_2}$ (the ordinate in Fig. 1); $\dot{V}_{MAX}$ is the asymptote of the curve, and represents the maximal rate of use of O_2 when O_2 is in excess; Pm_{O_2} is mitochondrial P_{O_2} (the abscissa in Fig. 1) and P_{50} is the P_{O_2} at 50% of $\dot{V}_{MAX}$. Thus, the mitochondrial respiration curve is defined by two parameters: $\dot{V}_{MAX}$ and P_{50}.

Also shown in Fig. 1 is a straight (dashed) line of negative slope. It represents the Fick law of diffusion and depicts diffusive O_2 transport between the tissue capillary and the mitochondria as a function of mitochondrial P_{O_2} for a given tissue O_2 diffusional conductance (DM) and a given tissue mean capillary P_{O_2} ($P\bar{c}_{O_2}$), both at maximal exercise. We previously utilized this representation as a tool for interpreting intracellular oxygenation data obtained using magnetic resonance spectroscopy (Richardson et al., 1999). The equation is as follows:

$$\dot{V}_{O_2} = DM \cdot (P\bar{c}_{O_2} - Pm_{O_2}) \quad (3)$$

As the figure indicates, as Pm_{O_2} is increased, $\dot{V}_{O_2}$ in Eq. (3) must fall because the P_{O_2} difference between mean capillary and mitochondrial P_{O_2} is reduced. Thus, Fig. 1 shows how $\dot{V}_{O_2}$ *increases* with mitochondrial P_{O_2} according to oxidative phosphorylation, but *decreases* with mitochondrial P_{O_2} according to the laws of diffusion.

The key concept in Fig. 1 is that in a steady state of O_2 consumption, $\dot{V}_{O_2}$ given by both Eqs. (2) and (3) must be the same at the same mitochondrial P_{O_2} (i.e., the law of mass conservation applies). This can occur only at the single point of intersection between the two relationships, as indicated by the solid circle placed there. If, as previously approximated (Wagner, 1996b), mitochondrial P_{O_2} were truly zero, $\dot{V}_{O_2}$ would be higher, as indicated by the open circle at the left end of the dashed straight line in Fig. 1. For a given O_2 transport system defined by the conductances for O_2 allowed by ventilation, alveolar-capillary diffusion, circulation, and capillary to mitochondrial diffusion, the values of mitochondrial $\dot{V}_{MAX}$ and P_{50} (Eq. (2)) will thereby influence maximal rate of O_2 utilization, $\dot{V}_{O_2}$max. In the remainder of this paper, it will be important to distinguish between $\dot{V}_{MAX}$ (the asymptote to the mitochondrial respiration curve) and $\dot{V}_{O_2}$max (actual maximal rate of O_2 utilization, solid circle in Fig. 1) to avoid confusion. In general, $\dot{V}_{MAX}$ can exceed $\dot{V}_{O_2}$max, but $\dot{V}_{O_2}$max cannot exceed $\dot{V}_{MAX}$.

2.2. Modeling the O_2 transport/utilization system

The present study augments our prior approach (Wagner, 1993, 1996b) by adding Eq. (2) to the equation system used previously. Fig. 2 recapitulates the O_2 transport pathway, and the associated four mass conservation equations governing O_2 transport at each step. It adds Eq. (2), describing O_2 utilization as a function of Pm_{O_2}. The important point is that in this way, the system has expanded from four equations with four unknowns into a system of five equations and five unknowns.

Briefly, using specified input values for O_2 transport step parameters (i.e., values of inspired O_2 fraction (FI_{O_2}), ventilation ($\dot{V}$I, inspired; $\dot{V}$A, expired), lung diffusing capacity (DL), cardiac output ($\dot{Q}$), [Hb], acid base status, tissue (muscle) diffusing capacity (DM), and mitochondrial respiration curve parameters ($\dot{V}_{MAX}$ and P_{50})), five mass conservation equations are written for O_2 (see Fig. 2). They describe (a) ventilatory transport; (b) alveolar–capillary diffusion; (c) circulatory transport; (d) muscle