

Published in final edited form as:

Comput Methods Programs Biomed. 2011 February ; 101(2): 109–114. doi:10.1016/j.cmpb.2010.03.013.

Modeling O₂ Transport as an Integrated System Limiting $\dot{V}O_2\text{MAX}$

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Abstract

Maximal endurance exercise capacity is determined by a variety of factors, including maximal ability to transport O₂ to the muscle mitochondria and to use this O₂ for ATP generation ($\dot{V}O_2\text{MAX}$). This analysis combines the individually well-known O₂ mass conservation equations for the four critical steps in the O₂ transport pathway (ventilation, alveolar/capillary diffusion, circulation and muscle diffusion) into an analytical, closed form, model showing how $\dot{V}O_2\text{MAX}$ depends on all four steps. It further shows how changes in any one step affect the function of the others. This analytical approach however requires approximating the O₂Hb dissociation curve as linear. Removing this condition to allow for the real O₂Hb curve requires numerical analysis best explained graphically. Incorporating maximal mitochondrial metabolic capacity to use O₂ allows prediction of when $\dot{V}O_2\text{MAX}$ is limited by transport or by metabolic capacity. This simple approach recapitulates in vivo behavior and clarifies the determinants of maximal exercise.

Keywords

maximal O₂ consumption; maximal exercise capacity; oxygen transport; oxygen utilization

Endurance exercise depends on delivering O₂ from the air to the contracting muscle mitochondria. This O₂ pathway is very well understood in terms of its individual steps [1] (Figure 1), but there remains considerable misunderstanding about how the steps relate to one another and combine to determine maximal O₂ throughput. Modeling O₂ transport as an integrated system offers the opportunity to clarify how the system works and which steps are important to overall function. To do this requires appreciation of three principal issues: First, the four main steps shown in Figure 1 (ventilation, alveolar-capillary diffusion, circulation, and muscle diffusion) form an *in series* set of steps for O₂ as molecules are passed from the air to the lungs to the blood and finally to the mitochondria. Second, O₂ throughput at each step must conserve O₂ mass. Finally, for present purposes, the system should be considered in a steady state, such that the transients at the onset and cessation of exercise are removed from consideration.

Under these constraints, well known transport equations exist for each step. These were described some 60 years ago [2–5]. The equations describing transport by convective processes (ventilation and circulation) simply conserve mass; those describing transport by

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diffusive processes start as first order linear differential equations that must be integrated along the relevant capillary path to yield overall mass conservation and O_2 throughput from start to end of the capillary.

The purpose of this analysis is to bring these separate equations together as a system, and from this to examine how the system functions. To do this, either of two approaches could be used. One is to approximate the O_2 Hb dissociation curve by a straight line (the slope being modeled by a single constant) rather than using the complex non-linear function that it really is [5–6]. The other is to use the actual O_2 Hb dissociation curve [7]. The former allows algebraic analysis with closed form solutions that give a clear overview of the principles of system function at the cost of strict numerical accuracy. The latter provides accurate simulation for O_2 transport, but the complex nature of the dissociation curve precludes analytical solutions. Thus, numerical analysis must be applied, and this means that each such computation yields a particular solution correct and applicable only for the values of the chosen variables. These two approaches are nicely complementary and both will be addressed in what follows.

O_2 transport modeled using linear approximation to the O_2 Hb dissociation curve

Figure 2 presents at the top the mass balance equations for each of the four processes [4–5]. Those describing diffusion (at both the lungs and muscles) have already been integrated to provide the overall solution. These equations are each far from novel as mentioned above. What should be realized is that these four equations contain precisely four unknowns as set out in Figure 2. Therefore, this equation set can be solved algebraically, and the solutions for the four unknowns are also laid out in Figure 2.

In Figure 3, the top section shows these solutions graphically as just one of the input variables, maximal cardiac output, is systematically altered across the spectrum from 0 to 50 l/minute using data for all variables corresponding to maximal exercise for normal fit young adults. Oxygen uptake varies as would be expected, cardiac output being just one component of an *in series* transport system. It governs $\dot{V}O_2$ when low (<10 L/min), but has little effect when higher. This characteristic non-linear behavior of $\dot{V}O_2$ is explained by the basic governing equations (top of Figure 2). The higher the cardiac output, the greater is the convective flow of O_2 within the circulatory system (blood flow equation). However, the two equations describing diffusion each have an exponential term with blood flow, \dot{Q} , in the denominator of the exponent. Thus, as \dot{Q} increases, there is less and less complete diffusive equilibration in both the lungs and muscles, offsetting the enhancement by the circulatory component mentioned above. As \dot{Q} increases, the fall in arterial PO_2 and rise in venous PO_2 shown in figure 3 reflect this interference to diffusive transport and limit the gain in $\dot{V}O_2$ MAX with increasing \dot{Q} .

This pattern of behavior is seen when any of the independent transport variables (Figure 2) is altered, as shown in the bottom panel of Figure 3. Except for the linear relationship between $\dot{V}O_2$ MAX and PIO_2 (which is an artifact of assuming the O_2 Hb dissociation curve is linear as PIO_2 increases), the effects of changing any of the independent variables are similar as Figure 3 shows. The major point of this analysis is that in an *in series* system such as that for O_2 transport, every component has the potential to affect $\dot{V}O_2$ MAX. The standard question of “what limits $\dot{V}O_2$ MAX: is it the heart, the lungs or the muscle?” needs to be replaced by the question “how important are the various independent variables to $\dot{V}O_2$ MAX?” There is no one determinant of maximal $\dot{V}O_2$.

O₂ transport modeled using the actual O₂Hb dissociation curve

Figures 2 and 3 demonstrate the power of analytical approaches to the O₂ transport system, but also reveal the approximations resulting from assuming a linear O₂Hb dissociation curve. Numerical analysis to solve the equation system of Figure 2 reconfigured to use the actual dissociation curve is feasible. Because each simulation produces a particular result [7], a more efficient way to present system behavior is to use a graphical approach [8]. Figure 4 shows the conceptual basis for this approach. Panel A describes the coexistent transport processes of blood flow to, and diffusion within, muscle. Panel B focuses on the convective, circulatory transport component using the well-known Fick principle of mass conservation (as also used in Figure 2). Panel C focuses on the diffusive transport of O₂ from muscle microvascular red cells to muscle mitochondria, using the laws of diffusion. The equations now reflect the actual dissociation curve. For the diffusive component, P_{cap}O₂ represents mean capillary PO₂ between the artery and vein, which in effect serves to integrate O₂ diffusion along the capillary length. In panel C, O₂ flux is given by the product of the muscle diffusing capacity, D, and the difference between the mean capillary PO₂ (P_{cap}O₂) and the mitochondrial PO₂ (P_{mito}O₂).

Two important approximations are now made to simplify the presentation: First, mitochondrial PO₂ is taken to be zero. It must be less than 3–4 mm Hg, which is the measured value of the PO₂ associated with myoglobin in the cytoplasm during heavy exercise [9]. Mean capillary PO₂ on the other hand is about 40–50 mm Hg, calculated by numerical analysis between measured values of arterial and muscle venous PO₂ [10]. The second approximation is to replace P_{cap}O₂ by a constant, k, multiplying P_vO₂ (muscle venous PO₂). This too has been shown to be reasonable [10]. The two transport equations of Figure 4 may now be written:

$$\dot{V} O_2 = \dot{Q} \times [CaO_2 - CvO_2] \quad 1$$

$$\dot{V} O_2 = D \times [P_{CAPO_2} - P_{MITOO_2}] = D \times k \times P_vO_2 \quad 2$$

These two equations are plotted in Panel A of Figure 5, with $\dot{V}O_2$ on the ordinate and P_vO_2 on the abscissa, assuming $P_{mito}O_2=0$. The square symbols indicate the boundaries of equation 1 above, the equation describing convective blood flow. The open square marks what would be seen if all O₂ was extracted from the flowing blood; the closed square if no O₂ at all were extracted from the flowing blood. Neither extreme is ever seen in practice.

It can be seen that the only point in the figure where both equations yield the same $\dot{V}O_2$ and P_vO_2 – requirements of mass conservation – is that point marked by the solid circle. The values for the independent variables (\dot{Q} , D, [Hb]) are those at maximal exercise, with arterial O₂ concentration additionally depending on lung diffusing capacity and ventilation at maximal exercise. Thus, the solid circle identifies $\dot{V}O_2MAX$, and shows it to be a function of all of the independent variables listed in Figure 2.

Panels B, C and D indicate how individual changes in key independent variables (inspired PO₂, ventilation and lung diffusing capacity and hence arterial PO₂ (B); muscle diffusing capacity (C); and blood flow (D)) would affect $\dot{V}O_2MAX$ (and P_vO_2). In particular, changing inspired PO₂ is predicted to produce a linear and proportional relationship between $\dot{V}O_2MAX$ and P_vO_2 , and this has been found repeatedly [10–11]. Panels C and D contrast the effects of reduced diffusing capacity versus impaired blood flow: the former reduces

$\dot{V}O_2\text{MAX}$ but increases PvO_2 , while the latter reduces PvO_2 as $\dot{V}O_2\text{MAX}$ is lowered. Thus, different causes of any observed reduction in $\dot{V}O_2\text{MAX}$ can be analyzed on Figure 5 if the relevant data are available, allowing the separate contributions of any changes in each transport variable to be determined.

Mitochondrial metabolic capacity: interaction with O_2 transport in determining $\dot{V}O_2\text{MAX}$

To this point, it has been implicitly assumed that O_2 transport governs maximal $\dot{V}O_2$. In other words, that the capacity to use O_2 for ATP generation exceeds the capacity of the transport system to deliver O_2 to the mitochondria. However, it is also possible that the O_2 transport system can supply enough O_2 to meet the maximal demands of the mitochondria for O_2 . In this case, it would be maximal mitochondrial oxidative capacity (MMOC) and not transport that limited maximal O_2 consumption. Figure 6 explores this possibility, integrating it with O_2 transport. In panel A are shown data from Wilson et al showing how isolated mitochondrial $\dot{V}O_2$ depends on ambient PO_2 . Above a PO_2 of about 2 mm Hg, mitochondrial $\dot{V}O_2$ is independent of PO_2 , and this plateau $\dot{V}O_2$ value constitutes MMOC. This can be added to the diagrams of Figure 5. In panels B and C are shown hypothetical effects of a high (B) and low (C) MMOC. In B, MMOC exceeds O_2 transport capacity even at the highest of the three levels of oxygenation shown. In this example, $\dot{V}O_2\text{MAX}$ falls as FIO_2 is reduced, exactly as in Figure 5B. However, in a subject with very low MMOC (Figure 6C), but identical O_2 transport capacity as the subject in Figure 6B, a different outcome will be seen. With changes in FIO_2 , $\dot{V}O_2\text{MAX}$ will vary in proportion to PvO_2 only when FIO_2 is low enough that $\dot{V}O_2$ is less than MMOC. At higher FIO_2 , $\dot{V}O_2\text{MAX}$ fails to increase linearly, and plateaus at the MMOC value. Figure 6D shows that indeed these two patterns can be seen in healthy subjects [11–12]. By and large, trained athletes emulate Figure 6B while sedentary untrained subjects follow Figure 6C. Thus, this analysis suggests that in fit subjects, O_2 transport limits $\dot{V}O_2\text{MAX}$, while in unfit subjects, mitochondrial oxidative enzyme capacity sets the limit to $\dot{V}O_2\text{MAX}$, until imposed hypoxia becomes severe.

In summary, the O_2 transport and utilization system is an *in series* system in which every component is important to overall system throughput of O_2 . Bringing together the well-established O_2 transport equations for the four main O_2 transport processes (ventilation, alveolar-capillary diffusion, circulation and muscle diffusion), analytical solutions for transport can be found if the $O_2\text{Hb}$ dissociation curve is approximated by a straight line. This shows how every transport component has the power to affect $\dot{V}O_2\text{MAX}$ – there is no single limiting factor. To account for the non-linearity of the dissociation curve, numerical analysis is required, but a simple diagram plotting $\dot{V}O_2$ against muscle venous PO_2 can achieve this and yields great insight into the integrative nature of the O_2 transport and utilization process.

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The O₂ transport system

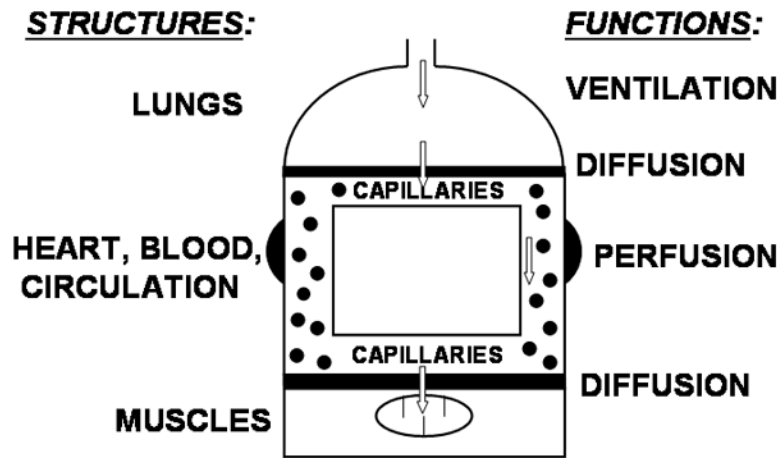


Figure 1.

Diagram of the O₂ transport system, consisting of four major organs/tissues (lungs, cardiovascular system, blood and muscle) supporting the four principal transport functions (ventilation, alveolar-capillary diffusion, circulatory perfusion and muscle diffusion).

FOUR EQUATIONS, WITH FOUR UNKNOWN

Ventilation: $VO_2 = VA \times [PIO_2 - PAO_2] \times k$
Lung diffusion: $(PAO_2 - PaO_2) / (PAO_2 - PvO_2) = \exp[-DLO_2 / (\beta \times Q)]$
Blood flow: $VO_2 = Q \times \beta \times [PaO_2 - PvO_2]$
Muscle diffusion: $(PvO_2 - PmitoO_2) / (PaO_2 - PmitoO_2) = \exp[-DMO_2 / (\beta \times Q)]$

Known (independent, input) variables:

VA: Ventilation (constant, l)
PIO₂: Inspired PO₂
DLO₂: Lung diffusing capacity
β: Slope of O₂Hb dissociation curve
Q: muscle blood flow
PmitoO₂: Mitochondrial PO₂
DMO₂: Muscle diffusing capacity

Unknown (dependent) variables:

PAO₂: Alveolar PO₂
PaO₂: Arterial PO₂
PvO₂: Venous PO₂
VO₂: Oxygen uptake

AND THEIR SOLUTIONS

$$PAO_2 = PIO_2 \times VA/Q \times (1-ML) / \text{DENOM}$$

$$PaO_2 = PIO_2 \times VA/Q \times (1-L) / \text{DENOM}$$

$$PvO_2 = PIO_2 \times VA/Q \times M(1-L) / \text{DENOM}$$

$$VO_2 = PIO_2 \times VA \times \beta \times (1-M)(1-L) / \text{DENOM}$$

$$\begin{aligned}
 M &= \exp[-DMO_2 / (\beta \times Q)] & L &= \exp[-DLO_2 / (\beta \times Q)] \\
 \text{DENOM} &= VA/Q \times (1-ML) + 0.863 \times \beta \times (1-M) \times (1-L)
 \end{aligned}$$

Figure 2.

By approximating the O₂Hb dissociation curve as a straight line, the four O₂ transport functions are each described by explicit equations that can be solved simultaneously to yield analytical solutions for the four indicated dependent variables in terms of given values of the seven independent variables listed. These solutions are given in the lower section of the figure.

CONSEQUENCES OF CHANGES IN TRANSPORT VARIABLES

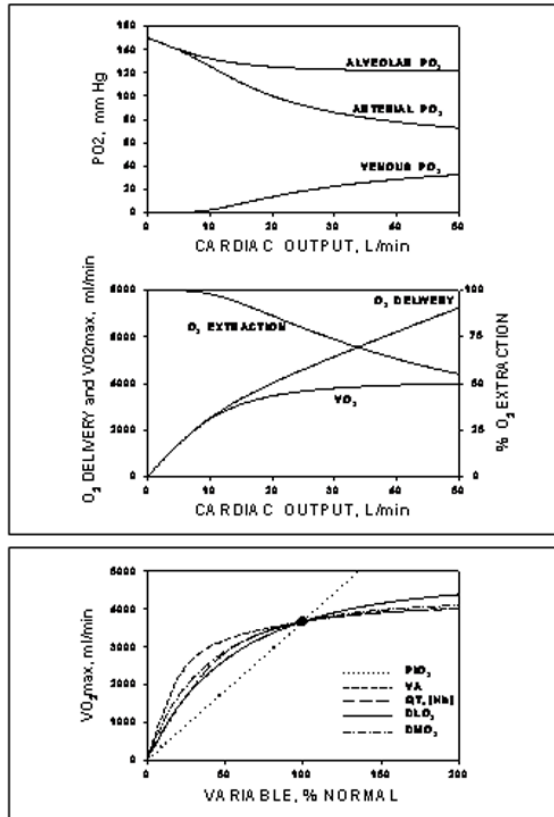


Figure 3.

Upper box: Graphical expression of the solutions listed in Figure 2 for the case of changing cardiac output. Lower box: Summary solutions for the effects on $\dot{V}O_2\text{MAX}$ of varying each independent variable one at a time. Except for the effects of PIO_2 (which reflect the linear approximation to the $O_2\text{Hb}$ dissociation curve), the effects of all other variables are similarly non-linear.

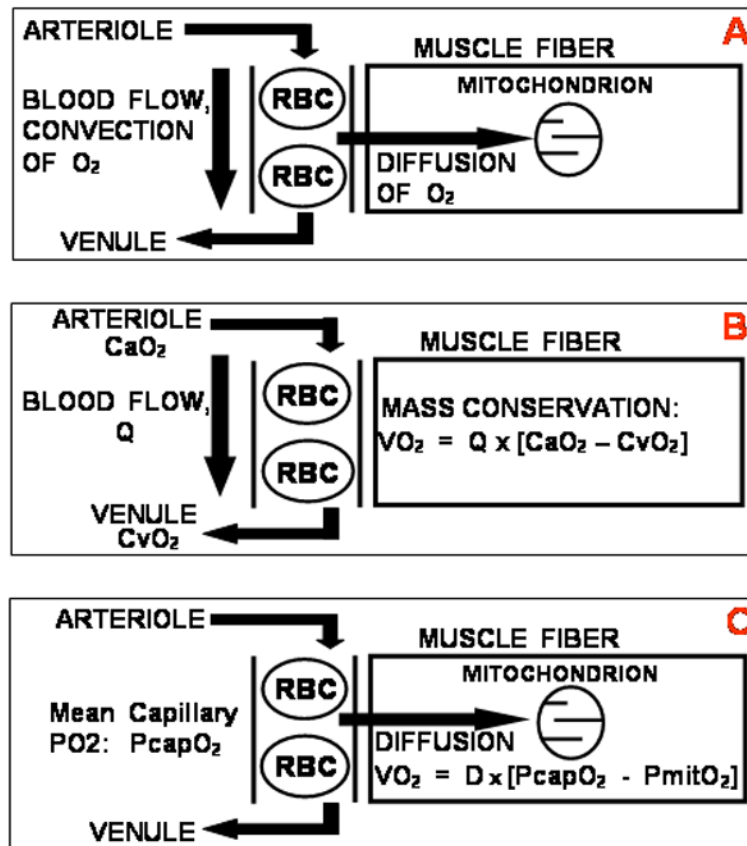


Figure 4.
 Panel A: Concept of convective transport of O₂ to the muscle by blood flow and simultaneous diffusive transport of O₂ from red cells to mitochondria in muscle. Panel B: The convective transport component must obey the Fick principle of mass conservation. Panel C: The diffusive component must obey the laws of diffusion.

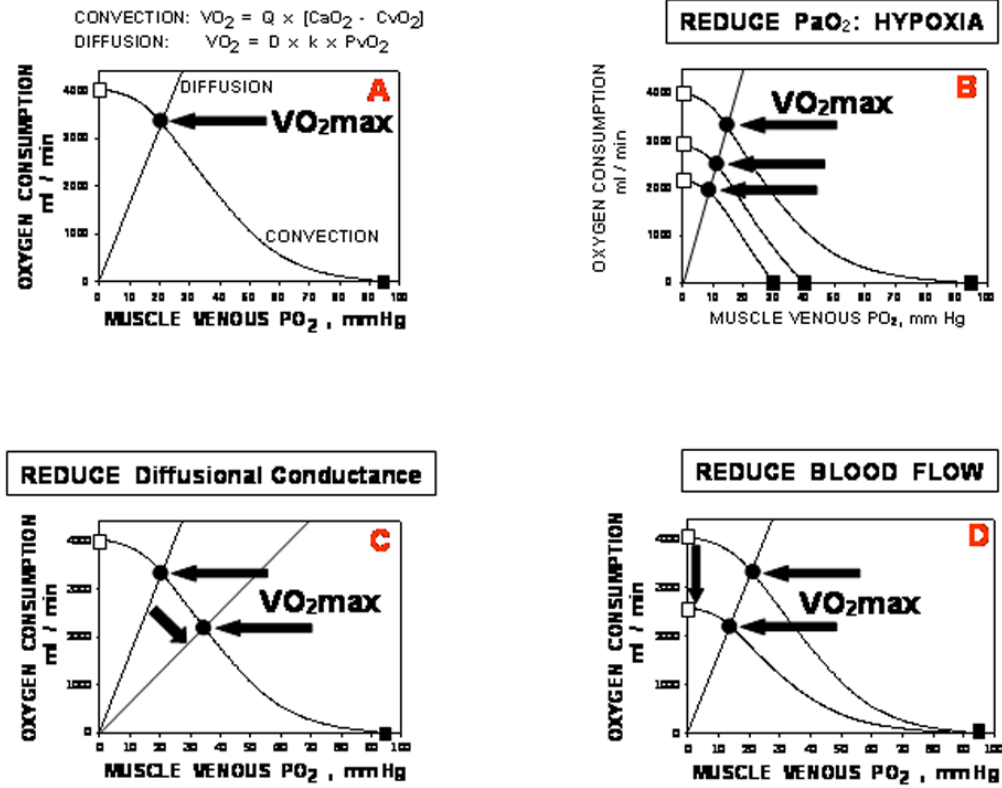


Figure 5. Panel A: Bringing the circulatory convective and muscle diffusive components together on a diagram relating VO_2 to PvO_2 . Panel B: Effects of progressive arterial hypoxemia on VO_2MAX ; Panel C: Effects of reduced muscle diffusing capacity on VO_2MAX ; Panel D: Effects of reduced muscle blood flow on VO_2MAX . See text for details. The key point is that each factor involved in O_2 transport plays a role in setting VO_2MAX .

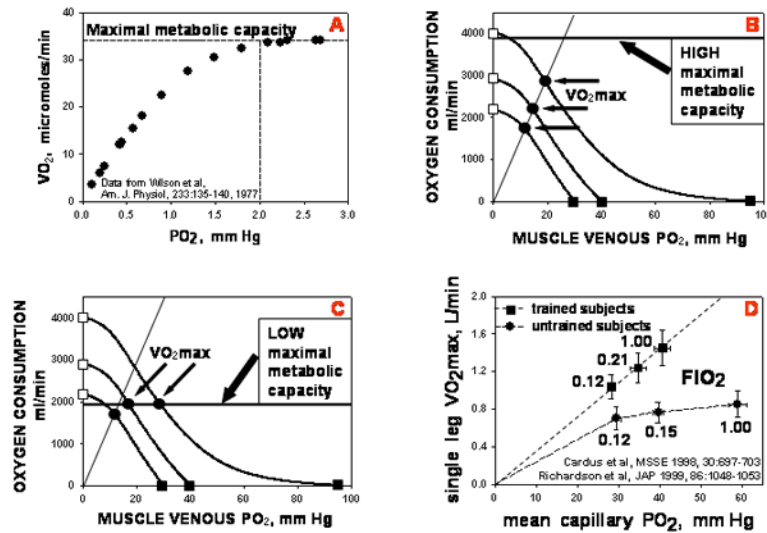


Figure 6.

Adding maximal mitochondrial oxidative capacity (MMOC) to the transport diagram of Figure 5. Panel A: MMOC is the highest, plateau value of $\dot{V}O_2$ when PO_2 no longer affects $\dot{V}O_2$ [13]. Panel B: When MMOC exceeds maximal O_2 transport capacity, the latter determines $\dot{V}O_2$ MAX just as in Figure 5. Panel C: When MMOC is less than maximal O_2 transport capacity at any FIO_2 , MMOC and not transport limits $\dot{V}O_2$ MAX. Panel D: Experimental data showing that fit subjects are limited by O_2 transport while unfit subjects are essentially limited by MMOC (until FIO_2 is reduced substantially).