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Limiting Factors of Exercise Performance

Limitierende Faktoren der körperlichen Leistungsfähigkeit

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SUMMARY

Endurance exercise performance depends on several interacting factors, some physiological and some psychological. Important among these is achieving a high rate of O_2 transport from the air to the muscle mitochondria and at the same a high capacity to metabolize O_2 for ATP generation. O_2 transport occurs via an integrated, in series, system of conductances reflecting the lungs (involving ventilation and alveolar-capillary diffusion); the heart and cardiovascular system (involving circulatory transport from lungs to muscle and also affecting O_2 diffusion equilibration in the lungs and muscle); the blood (via the concentration of hemoglobin and also the shape and position of the O_2 dissociation curve); and the muscles themselves (involving diffusive O_2 transport from the microcirculation to the mitochondria). The present analysis combines all of these steps and processes into a single, integrated system to explain how maximal O_2 transport depends on each and every step of the transport pathway. It further shows how each step individually affects maximal transport similarly in a non-linear fashion - controlling overall O_2 flow when its conductance is low but having little overall effect when high. Finally, how maximal mitochondrial metabolic capacity to use O_2 can be considered together with maximal O_2 transport to set the limits to maximal VO_{2max} is shown. Experimental data are presented to confirm this integrated, conceptual approach.

Key words: exercise performance, O_2 -transport, endurance, cellular metabolic capacity

INTRODUCTION

While the assigned title refers to exercise performance, this brief review focuses on one aspect of performance: attainment of maximal oxygen consumption (VO_{2max}). Endurance exercise performance depends on several factors in addition to VO_{2max} itself, such as motivation, tolerance for pain and dyspnea, development of neuromuscular fatigue, and the intensity of exercise that can be attained before lactate levels rise significantly. It would be beyond the scope of this review to attempt discussing and integrating all of these factors.

Oxygen consumption requires two interacting systems: the O_2 transport system that delivers O_2 from the air to the muscle mitochondria, and the cellular metabolic processing system that uses the O_2 to generate energy in the form of ATP through the mitochondrial respiratory chain. Individual components of both systems are very well known. What remains incompletely understood is how maximal O_2 transport itself depends on several

ZUSAMMENFASSUNG

Die Ausdauerleistungsfähigkeit wird von diversen miteinander in Wechselwirkung stehenden physiologischen und psychologischen Faktoren beeinflusst. Diese sind sowohl eine hohe O_2 -Transportrate zwischen der Atemluft und den Mitochondrien als auch eine hohe Kapazität des O_2 -Metabolismus für die ATP-Synthese. Der O_2 -Transport stellt ein Weiterleitungssystem dar, das aus den Lungen (Ventilation und alveolar-kapillare Diffusion), dem Herz-Kreislauf-System (O_2 -Transport von den Lungen zum Muskel und dem O_2 -Diffusionsgleichgewicht in den Lungen und Muskel), dem Blut (Hämoglobin-Konzentration sowie Form und Position der O_2 -Dissoziationskurve) sowie den Muskeln selbst (O_2 -Transport aus der Mikrozirkulation in die Mitochondrien) besteht. Die vorliegende Arbeit fasst diese einzelnen Prozesse in einem Modell-System zusammen, anhand dessen die Abhängigkeit der maximalen O_2 -Transportrate von jedem systemimmanentem Prozess auf dem Transportweg gezeigt werden kann. Weiter zeigt dieses Modell, dass jeder Schritt im System die maximale Transportkapazität auf ähnlich nicht-lineare Weise beeinflusst. Ist der O_2 -Transport niedrig, so ist der Kontrolleinfluss auf die Gesamtsauerstoff-Flussrate hoch; bei hohem O_2 -Transport hingegen ist der Einfluss der einzelnen Prozesse auf die Gesamtsauerstoff-Flussrate niedrig. Die VO_{2max} wird somit über die maximale mitochondriale metabolische Kapazität und damit über die Sauerstoffnutzung und über die maximale Sauerstofftransport limitiert. Die integrierte konzeptionelle Herangehensweise des vorgestellten Modell-Systems kann mit experimentell ermittelten Daten bestätigt werden.

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tissues and organs in an integrated manner, and how O_2 transport integrates with O_2 metabolic utilization to set VO_{2max} .

The purpose of this review is to explain how these systems in fact integrate and set VO_{2max} under any set of circumstances.

O_2 TRANSPORT

Transport of O_2 from the air to the muscle mitochondria involves the lungs and chest wall, the heart and cardiovascular system, the blood, and the muscle itself (9). In the lungs, ventilation first brings fresh O_2 from the air to the alveoli. Diffusion then transports the O_2 from alveolar gas across the alveolar-capillary membrane into the pulmonary capillary blood. The next step is perfusion-transport of the O_2 in the blood through the pulmonary capillaries, back to the left heart and then to the muscles via the systemic arterial tree.

The final step is the unloading of O_2 from Hb within the

muscle microvascular red cells, and diffusion from there out of the microvessels, into the myocytes, and to the mitochondria. It is critical to appreciate that this system is an in series, or “bucket brigade” system:

A given O₂ molecule must pass through each of the above steps in sequence. An important property of such an in series system is that every step affects maximal throughput (5,8). A second important property of such an in series system is that each step can affect the performance of all other steps. One clear example is that when blood flow is increased, it may inherently limit O₂ transfer at the diffusion-based steps in the lungs and muscle. This risk occurs simply because high blood flow may reduce gas exchange transit time.

Figure 1 brings together the several steps in the O₂ transport pathway, showing blood flow bringing O₂ to the muscle vascular bed (a convective process), and subsequently, diffusion allowing O₂ to move from the red blood cells to the mitochondria, as shown in panel A. In panel B, the amount of O₂ given up by the blood per unit time as it flows through the muscle bed is formulated according to the well known Fick principle of mass conservation: The amount of O₂ lost from the blood per minute is the product of muscle blood flow rate (Q_l) and the O₂ concentration difference between arterial and muscle venous blood. Arterial O₂ concentration is denoted CaO₂; that for venous blood CvO₂; Note that CaO₂ (arterial O₂ concentration), already reflects the influence of ventilation, alveolar-capillary diffusion in the lungs and blood flow through the pulmonary vascular bed. In panel C, the diffusive process for O₂ moving from the muscle microvascular red cells to the mitochondria is defined by the laws of diffusion, also an expression of mass conservation: The amount of O₂ transferred by diffusion per minute is the product of the diffusing capacity of the muscle for O₂ (D in Figure 1) and the difference between the red cell PO₂ (PcapO₂) and the mitochondrial PO₂ (PmitO₂). Here P_{CAP}O₂ is the mean capillary PO₂, averaged along the capillary length.

To simplify the concepts, we will assume that mitochondrial PO₂ during maximal exercise is so low it can be ignored compared to PcapO₂. This is reasonable as the former is no greater than 3-4 mm Hg (2) while the latter is 40-50 mm Hg (4). For purposes of presentation, we will also assume that mean capillary PO₂ is proportional to PO₂ in the muscle venous blood. That is, as muscle venous PO₂ (PvO₂) rises or falls, so too does mean capillary PO₂.

This assumption allows us to replace PcapO₂ in panel C of Figure 1 by k x PvO₂ where k is a constant (that happens to be about 2.0). The reason we make this reasonable (4) assumption becomes clear if we compare the equation in Figure 1 panel B with that in Figure 1 panel C:

Panel B: $VO_2 = Q \times [CaO_2 - CvO_2]$ (1)

Panel C: $VO_2 = D \times [P_{cap}O_2 - P_{mit}O_2] = D \times k \times PvO_2$ (2)

The key concept is that while equation 1 reflects the convective transport process based on blood flow and while equation 2 reflects the diffusive transport process, both equations must describe the same quantitative flow rate of O₂. Thus, VO₂ in both equations must be the same. What is more, both equations contain PvO₂ (or its equivalent, CvO₂, which is defined by PvO₂ and the Hb dissociation curve) and PvO₂ must also be the same in both equations.

This is better discussed in the framework of a figure that shows both equations (7). This is done in Figure 2, Panel A where VO₂ is

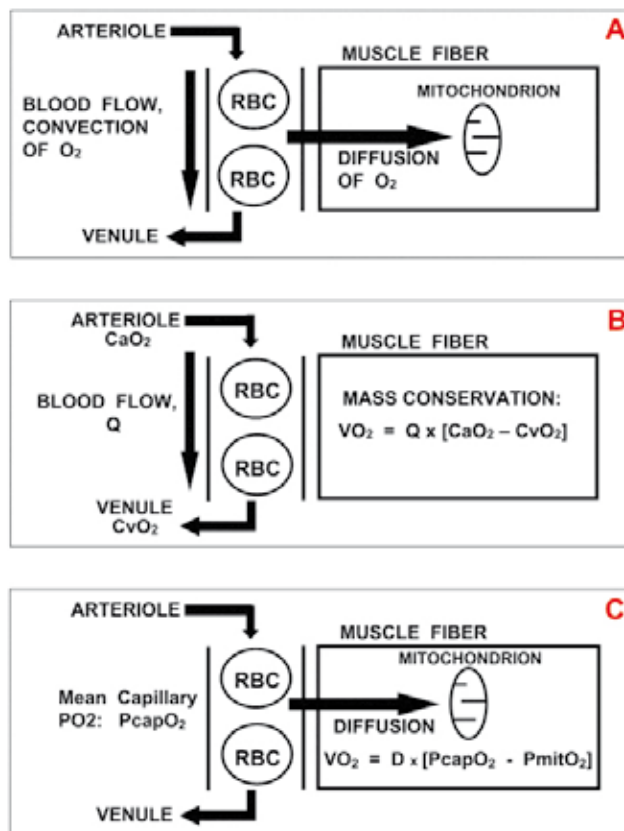


Figure 1: Model of O₂ transport consisting of convective blood flow from the lungs to the muscle and subsequent diffusion from the muscle microvasculature to the mitochondria (A). In B and C, equations are given describing the convective and diffusive components respectively.

plotted against PvO₂. The curved line of negative slope traces equation 1. The open square represents the amount of O₂ delivered to the muscle (product of blood flow and arterial O₂ concentration) and would be the VO₂ if all O₂ delivered to the muscle vasculature could be made available by diffusion to the mitochondria, such that none was left in the venous blood. The closed square represents both VO₂ and muscle venous PO₂ if no O₂ at all was taken out of the muscle blood flow: zero VO₂ and a venous PO₂ equal to that in the inflowing arterial blood. Neither of these extremes occurs in live muscle, but the curved line between them shows the only combinations of VO₂ and PvO₂ that satisfy mass conservation (equation 1).

The straight line of positive slope traces equation 2, and shows the only combinations of VO₂ and PvO₂ that satisfy equation 2. The critical concept is that the point of intersection of the two lines, marked by the closed circle, is the only point on the entire figure where both equations are simultaneously satisfied, and thus marks the actual VO₂ and PvO₂ that must be present.

It should be evident that as the slope of the line for equation 2 (i.e., the muscle O₂ diffusing capacity) changes, so too will the point of intersection of the two lines even if the other line remains unchanged. Symmetrically, as the determinants of the curved line for equation 1 change, this line (and thus point of intersection of the two lines) will also shift. The determinants of the line for equation 1 are arterial PO₂ (and concentration, which reflects mostly arterial PO₂ and [Hb]) and muscle blood flow, as equation 1 shows. In turn, arterial PO₂ depends on ventilation, and alveolar-capillary

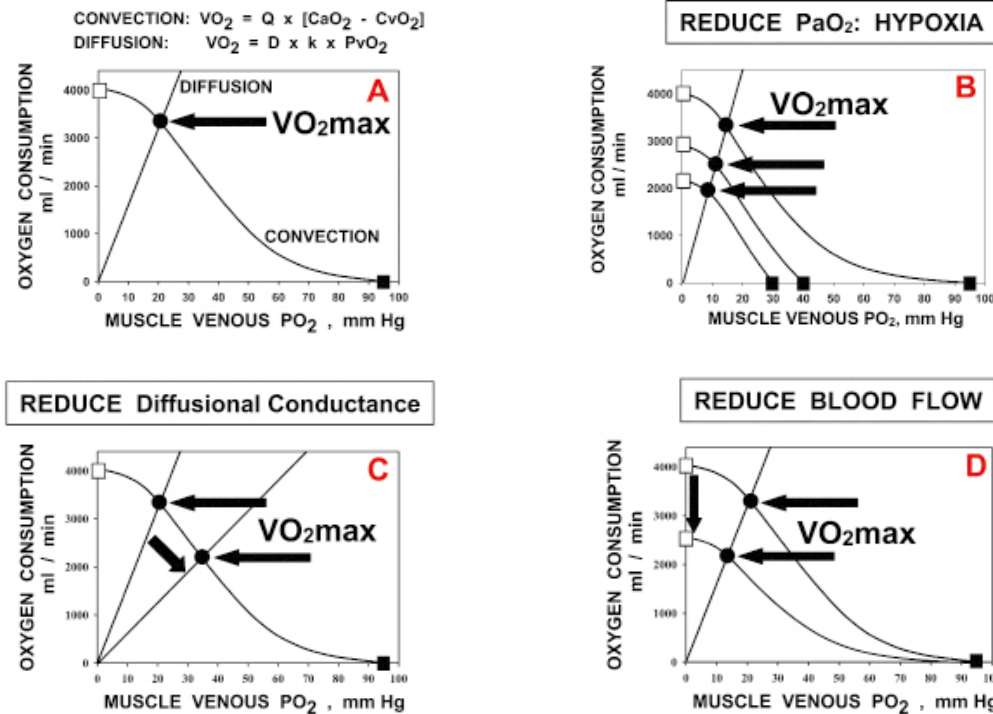


Figure 2: How the components of O₂ transport interact to determine VO_{2max}: A: simultaneous solution to the two transport equations shown in Figure 1 (convection equation is depicted in panel 1B, diffusion equation is described in panel 1c) shows how VO_{2max} is a function of pulmonary, cardiovascular, blood and muscle function (since the position of the intersection point defining VO_{2max} depends on these tissues and organs. In panels B, C and D, how changes in arterial PO₂ (B), muscle diffusing capacity (C) and muscle blood flow (D) would independently affect VO_{2max} are shown.

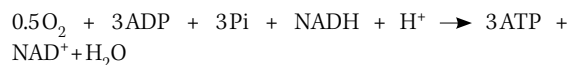
diffusion. Taken together, it should now be clear that the point of intersection depends on lung, cardiovascular, blood, and muscle function. If the values for blood flow, [Hb], arterial PO₂ and muscle diffusing capacity are those at maximal exercise, the VO₂ defined by the intersection of equations 1 and 2 must be VO_{2max}.

How changes in the key determining variables – arterial PO₂ (and O₂ concentration), muscle diffusing capacity, and muscle blood flow – individually affect VO_{2max} is shown in Figure 2, panels B, C and D respectively. In panel B, progressive hypoxia reduces arterial PO₂ (closed squares) from normal (~95 mm Hg) to (in these particular examples) 40 and then 30 mm Hg, simultaneously decreasing arterial O₂ saturation and thus [O₂] as indicated by the open squares. Maximal VO₂ must fall linearly with PvO₂ as arterial PO₂ is reduced. In panel C, reduction in diffusing capacity means a decrease in the slope of the diffusing capacity line as shown. VO_{2max} must fall, while PvO₂ must rise. In contrast, when muscle blood flow is reduced, VO_{2max} again falls, but so too does PvO₂, and along the same line as in panel B. These predictions are borne out by many different studies, reviewed in (6).

CELLULAR METABOLIC CAPACITY

The preceding discussion has made another important assumption: That the mitochondria have the capacity to use all of the O₂ that can be transported according to Figure 2. However, it can be imagined that oxidative enzyme levels in, for example, very inactive subjects, may be low enough that the O₂ transport system can deliver more O₂ to the mitochondria than they can use. This potential metabolic limitation on VO_{2max} can be incorporated into the scheme of Figure 2, and this is done in Figure 3. In Panel A, the concept of maximal mitochondrial oxidative capacity is shown on a plot of Wilson et al's data (10) relating VO₂ of a mitochondrial suspension

to PO₂ in the medium. At PO₂ values below about 2 mm Hg, there is an essentially proportional relationship where VO₂ depends on PO₂, but at higher PO₂ values, VO₂ plateaus at a maximal value that cannot be increased by further raising PO₂. This behavior is predictable, based on the equation for oxidative phosphorylation:



Because O₂ is a reactant on the left side of the equation, the velocity of the forward reaction will be particularly affected by [O₂] when [O₂] is low, but essentially not at all when [O₂] is high, and the other reactants now become limiting.

The maximal value of metabolic capacity to use O₂ is shown in Figure 3 as a horizontal line depicting that maximal possible VO₂ for two hypothetical scenarios (panel B, where maximal metabolic capacity exceeds maximal O₂ transport capacity at all three arterial PO₂ values shown by the three negatively sloped lines taken from Figure 2, panel B), and panel C, where maximal metabolic capacity is much lower and is less than maximal O₂ transport capacity at the two higher arterial PO₂ values.

In both panels, actual VO_{2max} must be the lesser of maximal O₂ transport capacity and maximal metabolic capacity. Thus, in panel B, where transport < metabolic capacity, the VO_{2max}/PvO₂ relationship follows the linear, proportional line of Figure 2; in panel C, the relationship remains proportional to PvO₂ below maximal metabolic capacity (i.e., in hypoxia) but, as hyperoxia is imposed, becomes completely independent of PvO₂ at the VO₂ equal to metabolic capacity. Panel D shows, with data from trained normal subjects (3) and untrained, sedentary subjects (1), that training appears to change the relationship from one limited mostly by metabolic capacity to one limited entirely by O₂ transport capacity.

In summary, maximal VO₂ is one (but not the only) important

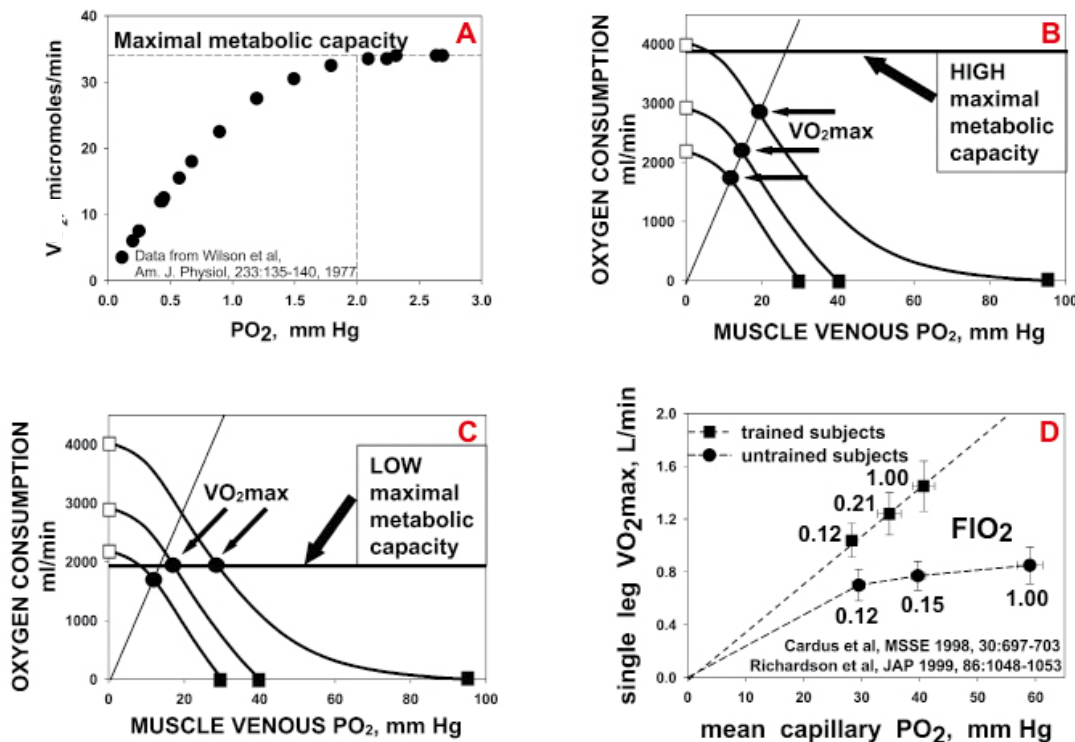


Figure 3: Incorporation of maximal mitochondrial oxidative capacity (MMOC) to use O₂ into the transport diagram of Figure 2. A: MMOC defined by the asymptotic value of V_{O₂} at high P_{O₂} in isolated mitochondria. B: O₂ transport determines V_{O₂}max when MMOC is higher than transport capacity. C: O₂ transport capacity or MMOC determine V_{O₂}max when MMOC is low, depending on arterial P_{O₂}. D: Data from normal subjects showing that trained subjects recapitulate the pattern in B while untrained subjects show the pattern in C.

determinant of maximal endurance exercise capacity. Maximal V_{O₂} is set by the interplay between two systems: 1) that for O₂ transport from the air to the mitochondria, involving the lungs, heart, blood and muscle, and 2) that for mitochondrial metabolic use of delivered O₂. The way in which all of these factors come together to determine V_{O₂}max is conveniently understood from a diagram that combines the mass conservation principles of both convection and diffusion of O₂ with that of oxidative phosphorylation. This analysis shows that there is no single determinant of V_{O₂}max – it depends on conditions and the values of the above variables. In particular, all involved variables contribute to setting V_{O₂}max through their interactions as a system.

Competing interests: None.

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