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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_2 is shown. Experimental data are presented to confirm this integrated, conceptual approach.

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

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.

Schlüsselwörter: Leistungsfähigkeit, O_2-Transport, Ausdauer, zelluläre Stoffwechselkapazität

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 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 $V O_{2max}$ 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 O_2 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 O_2 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 O_2 transport pathway, showing blood flow bringing O_2 to the muscle vascular bed (a convective process), and subsequently, diffusion allowing O_2 to move from the red blood cells to the mitochondria, as shown in panel A. In panel B, the amount of O_2 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 O_2 lost from the blood per minute is the product of muscle blood flow rate (Q.) and the O_2 concentration difference between arterial and muscle venous blood. Arterial O_2 concentration is denoted CaO_2; that for venous blood CvO_2: Note that CaO_2 (arterial O_2 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 O_2 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 O_2 transferred by diffusion per minute is the product of the diffusing capacity of the muscle for O_2 (D in Figure 1) and the difference between the red cell PO_2 ($PcapO_2$) and the mitochondrial PO_2 ($PmitoO_2$). Here $P_{CAP}O_2$ is the mean capillary PO_2, averaged along the capillary length.

To simplify the concepts, we will assume that mitochondrial PO_2 during maximal exercise is so low it can be ignored compared to $PcapO_2$. 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 PO_2 is proportional to PO_2 in the muscle venous blood. That is, as muscle venous PO_2 (PvO_2) rises or falls, so too does mean capillary PO_2.

This assumption allows us to replace $PcapO_2$ in panel C of Figure 1 by k x PVO_2 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: $VO_2 = D \times [PcapO_2 - PmitoO_2] = D \times k \times PvO_2$ (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 O_2. Thus, VO_2 in both equations must be the same. What is more, both equations contain PvO_2 (or its equivalent, CvO_2, which is defined by PVO_2 and the Hb dissociation curve) and PvO_2 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 VO_2 is

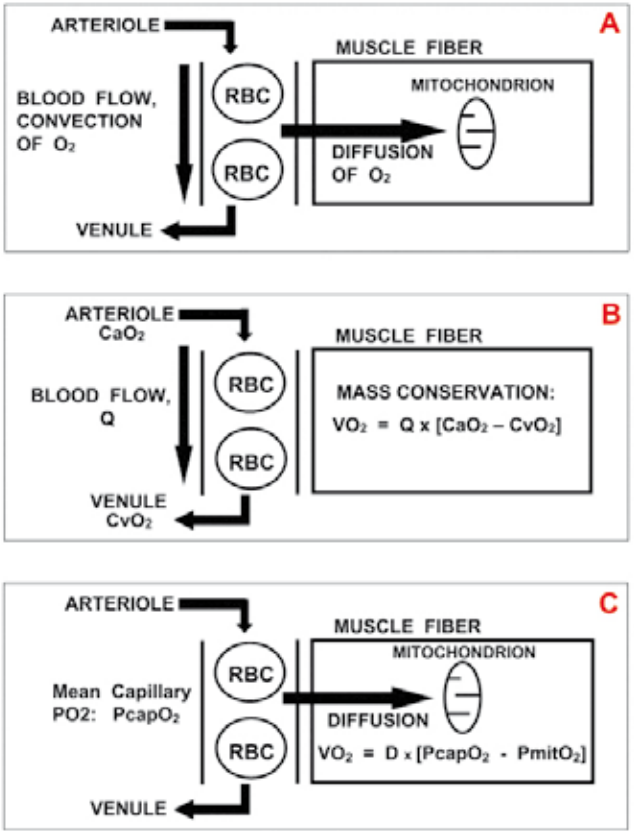

Figure 1: Model of O_2 transport consisting of convective blood flow from the lungs to the muscle and subsequent diffusion from the muscle microvasculature to the mitochondria (A). In B and C, equations are given describing the convective and diffusive components respectively.

plotted against PvO_2. The curved line of negative slope traces equation 1. The open square represents the amount of O_2 delivered to the muscle (product of blood flow and arterial O_2 concentration) and would be the VO_2 if all O_2 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 VO_2 and muscle venous PO_2 if no O_2 at all was taken out of the muscle blood flow: zero VO_2 and a venous PO_2 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 VO_2 and PvO_2 that satisfy mass conservation (equation 1).

The straight line of positive slope traces equation 2, and shows the only combinations of VO_2 and PvO_2 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 VO_2 and PvO_2 that must be present.

It should be evident that as the slope of the line for equation 2 (i.e., the muscle O_2 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 PO_2 (and concentration, which reflects mostly arterial PO_2 and [Hb]) and muscle blood flow, as equation 1 shows. In turn, arterial PO_2 depends on ventilation, and alveolar-capillary

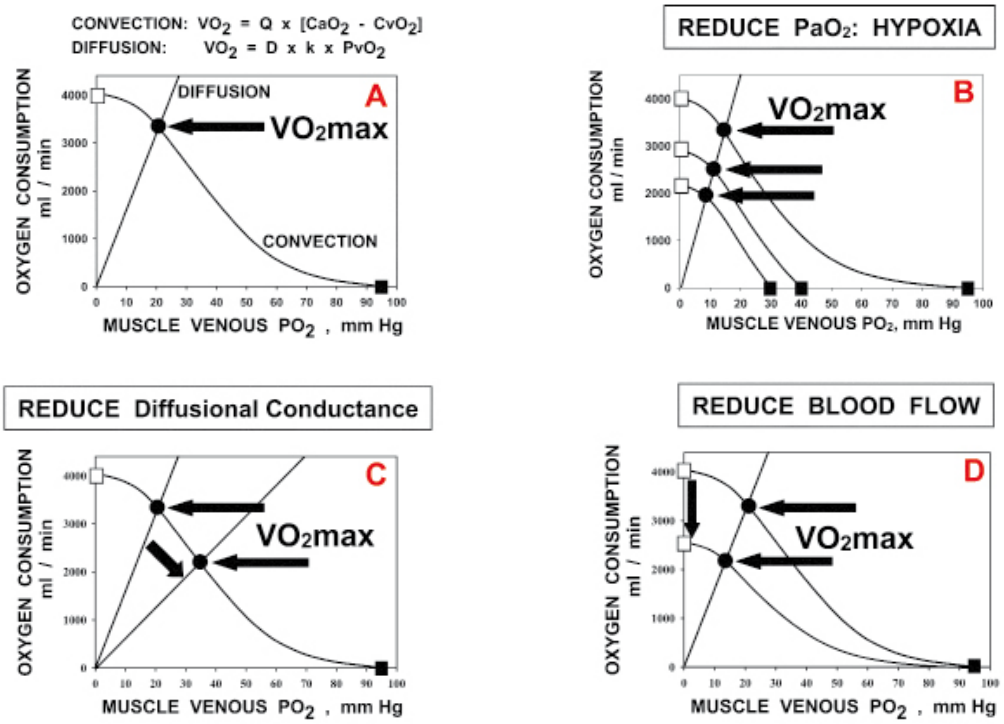

Figure 2: How the components of O_2 transport interact to determine VO_{2max}. A: simultaneous solution to the two transport equations shown in Figure 1 (convection equation is depicted in panel 1B, division equation is described in panel 1c) shows how VO_{2max} is a function of pulmonary, cardiovascular, 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 PO_2 (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 PO_2 and muscle diffusing capacity are those at maximal exercise, the VO_2 defined by the intersection of equations 1 and 2 must be VO_{2max}.

How changes in the key determining variables – arterial PO_2 (and O_2 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 PO_2 (closed squares) from normal (~95 mm Hg) to (in these particular examples) 40 and then 30 mm Hg, simultaneously decreasing arterial O_2 saturation and thus $[O_2]$ as indicated by the open squares. Maximal VO_2 must fall linearly with PvO_2 as arterial PO_2 is reduced. In panel C, reduction in diffusing capacity means a decrease in the slope of the diffusing capacity line as shown. V O_{2max} must fall, while PvO_2 must rise. In contrast, when muscle blood flow is reduced, VO_{2max} again falls, but so too does PvO_2, 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 O_2 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 O_2 transport system can deliver more O_2 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 VO_2 of a mitochondrial suspension to PO_2 in the medium. At PO_2 values below about 2 mm Hg, there is an essentially proportional relationship where VO_2 depends on PO_2, but at higher PO_2 values, VO_2 plateaus at a maximal value that cannot be increased by further raising PO_2. This behavior is predictable, based on the equation for oxidative phosphorylation:

$$0.5O_2 + 3ADP + 3Pi + NADH + H^+ \rightarrow 3ATP + NAD^+ + H_2O$$

Because O_2 is a reactant on the left side of the equation, the velocity of the forward reaction will be particularly affected by $[O_2]$ when $[O_2]$ is low, but essentially not at all when $[O_2]$ is high, and the other reactants now become limiting.

The maximal value of metabolic capacity to use O_2 is shown in Figure 3 as a horizontal line depicting that maximal possible VO_2 for two hypothetical scenarios (panel B, where maximal metabolic capacity exceeds maximal O_2 transport capacity at all three arterial PO_2 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 O_2 transport capacity at the two higher arterial PO_2 values.

In both panels, actual VO_{2max} must be the lesser of maximal O_2 transport capacity and maximal metabolic capacity. Thus, in panel B, where transport < metabolic capacity, the VO_{2max}/PvO_2 relationship follows the linear, proportional line of Figure 2; in panel C, the relationship remains proportional to PvO_2 below maximal metabolic capacity (i.e., in hypoxia) but, as hyperoxia is imposed, becomes completely independent of PvO_2 at the VO_2 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 O_2 transport capacity.

In summary, maximal VO_2 is one (but not the only) important

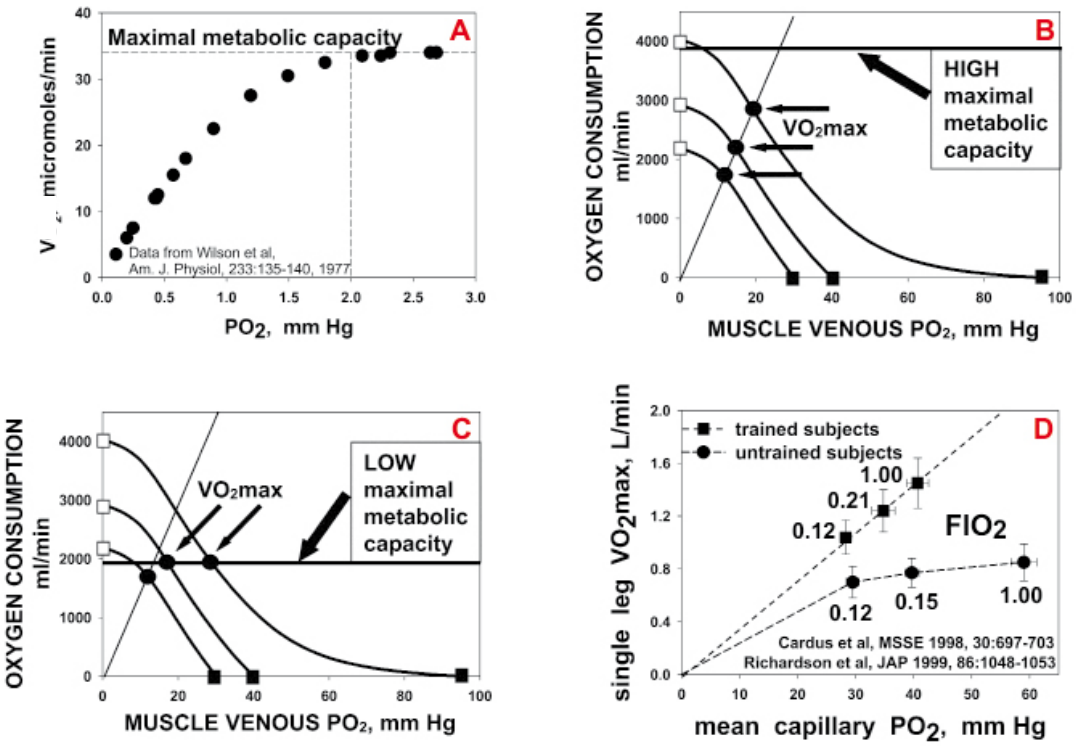

Figure 3: Incorporation of maximal mitochondrial oxidative capacity (MMOC) to use O_2 into the transport diagram of Figure 2. A: MMOC defined by the asymptotic value of VO_2 at high PO_2 in isolated mitochondria. B: O_2 transport determines VO_{2max} when MMOC is higher than transport capacity. C: O_2 transport capacity or MMOC determine VO_{2max} when MMOC is low, depending on arterial PO_2. 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 VO_2 is set by the interplay between two systems: 1) that for O_2 transport from the air to the mitochondria, involving the lungs, heart, blood and muscle, and 2) that for mitochondrial metabolic use of delivered O_2. The way in which all of these factors come together to determine VO_{2max} is conveniently understood from a diagram that combines the mass conservation principles of both convection and diffusion of O_2 with that of oxidative phosphorylation. This analysis shows that there is no single determinant of VO_{2max} – it depends on conditions and the values of the above variables. In particular, all involved variables contribute to setting VO_{2max} through their interactions as a system.

Competing interests: None.

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