DETERMINANTS OF MAXIMAL OXYGEN TRANSPORT AND UTILIZATION

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ABSTRACT

Maximal $\dot{V}O_2$ ($\dot{V}O_2$max) has mostly been the province of exercise physiologists wishing to provide a measure of athletic potential or to characterize subjects in exercise-related research. It is also used clinically to determine a patient’s exercise capacity. More recently, it has been recognized that the study of $\dot{V}O_2$max can provide fundamental insight into $O_2$ transport at all points between inspired air and muscle mitochondria. This review focuses on understanding how $\dot{V}O_2$max is set and concludes that the more athletic one is, the more $\dot{V}O_2$max is sensitive to $O_2$ transport conductances in the lungs, circulation, and skeletal muscle. These transport conductances form an integrated system, all components interacting to define $\dot{V}O_2$max. A particularly important component is diffusive conductance in muscle. This appears to be abnormal in chronic conditions such as obstructive pulmonary disease and heart and renal failure and may well explain why correction of central cardiovascular defects in $O_2$ transport in such patients fails to restore exercise capacity.

INTRODUCTION

Oxidative phosphorylation within mitochondria of mammalian cells is the fundamental energy-producing biochemical process that uses oxygen ($O_2$) and makes life possible. The basic reaction involved is as follows:

$$3 \text{ADP} + 3 \text{Pi} + \frac{1}{2} \text{O}_2 + \text{NADH} + \text{H}^+ \rightarrow 3 \text{ATP} + \text{NAD}^+ + \text{H}_2\text{O}.$$

In this reaction, ADP and ATP are adenosine di- and tri-phosphate, respectively (the latter containing the high energy bonds that are transduced into...
energy when the reaction is reversed). Pi is inorganic phosphate, and NADH and NAD\(^+\) are the reduced and oxidized forms of nicotinamide adenine dinucleotide. H\(_2\)O is water, and H\(^+\) is a hydrogen ion.

Understanding the determinants of maximal oxygen utilization, or \(\dot{V}O_2\)max, requires an understanding of the factors that limit the maximal forward rate of the above reaction. Basically they can be broken down into (a) those factors that determine the rate of O\(_2\) transport from the environment to the mitochondrial sites of O\(_2\) utilization and (b) those factors unrelated to O\(_2\) transport that can influence the above reaction. These factors include a large number of biochemical phenomena related to substrate availability for, and enzyme acceleration of, the many reactions that feed oxidative phosphorylation such as the Krebs cycle and glycolysis. This subdivision may appear arbitrary, but it has a practical basis: On moving from rest to heavy exercise, acceleration of O\(_2\) transport depends on physiological phenomena with a biophysical underpinning; enhancement of O\(_2\) utilization through the second set of factors is, at least for short-term exercise, essentially dependent on intracellular biochemical processes. These different but interacting groups of factors thus require somewhat different approaches to facilitate their understanding. It is the thesis of this review that under most normal conditions, O\(_2\) supply dictates \(\dot{V}O_2\)max rather than substrate or enzyme availability. Accordingly, the focus will be mostly on O\(_2\) transport, with evidence presented to support this underlying hypothesis.

Maximal O\(_2\) utilization occurs during sustained extreme physical exertion. Termination of such exercise due to perceived inability by an individual to continue merges at least three separate sets of occurrences. First, the individual ceases exercise because of unpleasant symptoms such as undue shortness of breath, severe discomfort in the working muscles, or exhaustion. Second, exercise may be in part terminated because of fatigue, which should be distinguished from exhaustion and be reserved for a neuromuscular phenomenon in which muscle force cannot be maintained in the face of continued neurological stimulation. Finally, further effort may be unachievable due to limitation of O\(_2\) supply to, and/or utilization of O\(_2\) by, the mitochondria. It is this last occurrence that is the focus of our review. Confusion over determinants of exercise capacity has arisen because of failure to separate these three kinds of phenomena, which generally occur at the same time.

This review deals only with determinants of \(\dot{V}O_2\)max, not with symptoms or with fatigue.

**DEFINITION OF MAXIMAL O\(_2\) UTILIZATION (\(\dot{V}O_2\)max)**

Even limiting oneself to a discussion of \(\dot{V}O_2\)max does not preclude confusion because \(\dot{V}O_2\)max is a somewhat elusive variable both conceptually and ex-
DETERMINANTS OF MAXIMAL $\dot{V}O_2$

Experimentally. Thus applying the law of mass action to the above equation for oxidative phosphorylation suggests that as long as each reactant can be supplied and each product removed without limit, the rate of $O_2$ utilization should be able to increase without limit. However, to be a useful concept, given that in vivo there is finite availability of all substrates and enzymes, we should be content to discuss maximal $O_2$ utilization in the context of realistic metabolism. The fundamental point is that a maximal rate of $O_2$ utilization can in fact be shown experimentally to exist in normal skeletal muscle.

Thus, in intact mammals, at very high exercise levels, it can generally be shown that even if external power is increased, there is no significant further rise in $\dot{V}O_2$ (3, 36, 91, 98). The positive linear relationship between external power and $\dot{V}O_2$ characteristic of submaximal exercise flattens out (or asymptotes) to define $\dot{V}O_2\max$ (Figure 1, upper panel). At the other end of the integrative spectrum, it is also known that $O_2$ availability determines $O_2$ utilization in simpler in vitro conditions such as in cell culture (111) (Figure 1, lower panel). In cell culture, below some $P_{O_2}$, respiration falls linearly, showing that under such conditions, $O_2$ availability is limiting the rate of $O_2$ use through oxidative phosphorylation. Above that $P_{O_2}$, $\dot{V}O_2$ is not dependent on $O_2$ availability but on enzyme or substrate levels. Has $\dot{V}O_2$ plateaued (Figure 1, upper panel) because of $O_2$ supply limitation or because of $O_2$-unrelated substrate/enzyme limitation as in Figure 1 (lower panel)?

The bulk of the evidence (reviewed below) points to $O_2$ supply limitation. A plethora of acute studies manipulating the $O_2$ transport pathway underlies this assertion, because it is reasonable to assume that acute studies (over a period of a few minutes) in intact humans or animals reflect constant structure and substrate/enzyme availability in the $O_2$ transport system components. Thus when $O_2$ availability is reduced acutely, $\dot{V}O_2\max$ falls. This is true no matter whether the loss of $O_2$ transport occurs because of inspiratory hypoxia (73), reduced muscle blood flow (4, 10, 40), or reduced Hb concentration (39, 48, 116).

Although such studies provide convincing evidence that at subnormal rates of $O_2$ supply, $\dot{V}O_2\max$ is indeed $O_2$ supply limited, the same conclusions are not reached concerning limits to $O_2$ utilization under normal baseline conditions. To evaluate this situation, which is probably the most important circumstance in which to understand how $\dot{V}O_2\max$ is achieved, one must provide a mechanism of increasing $O_2$ availability and ask whether $\dot{V}O_2\max$ is correspondingly higher. This is intrinsically difficult, particularly in intact animals or humans. Thus increasing $FI_{O_2}$ all the way to 1.0 increases inspired $P_{O_2}$ almost fivefold but increases the $O_2$ concentration of the arterial blood by only 8–10%, due to the flattening out of the $O_2$-Hb dissociation curve. Given that (a) the measurement of $V_O_2$ at the mouth is nearly impossible at $FI_{O_2}>0.5$ for technical reasons, (b) measurement of $\dot{V}O_2$ during extreme exercise is
Figure 1  Upper panel shows 20 s-averaged data for a typical trained subject exercising at increasing intensity until exhaustion. Oxygen uptake (VO\textsubscript{2}) increases linearly (open circles) until just before exhaustion, when VO\textsubscript{2} fails to further rise despite increasing effort (closed circles). Lower panel shows relationship between cultured kidney cell VO\textsubscript{2} and PO\textsubscript{2} in the culture medium. Above about 2 torr, VO\textsubscript{2} is PO\textsubscript{2} independent, but at lower values, VO\textsubscript{2} is dependent on available O\textsubscript{2}. Data from Wilson et al (111).

challenging at any FIO\textsubscript{2}, and (c) only a small increase in O\textsubscript{2} transport is expected as noted above, it is not surprising that the anticipated effect of increasing FIO\textsubscript{2} on VO\textsubscript{2max} has been difficult to verify (107, 108). However, acutely augmenting blood volume by transfusion has provided clear-cut and reproducible evidence of a higher VO\textsubscript{2max} (11, 29, 81, 94) in intact humans,
DETERMINANTS OF MAXIMAL $\dot{V}O_2$

and increasing muscle blood flow in human or animal models has provided equally good evidence that when $O_2$ supply is increased by this method, so too is maximal $\dot{V}O_2$ (76, 86, 96).

The overall conclusion from such studies of intact systems in which $O_2$ supply has been augmented acutely, and thus prior to any structural or biochemical adaptation, is that $O_2$ supply does indeed limit the maximal rate of oxidative phosphorylation in normal circumstances. In vivo estimates of cytochrome $a,a_3$ redox state by near infrared spectroscopy (18) further support this conclusion. However, it should be noted that this technology is difficult and is contaminated by larger signals from myoglobin and hemoglobin; thus it is not surprising that others have failed to find such cytochrome reduction (95) during exercise.

If one reexamines the conclusion that $\dot{V}O_2$max is generally limited by $O_2$ supply, it becomes necessary to refine one's definition of $\dot{V}O_2$max. This is because plateauing of $\dot{V}O_2$ will occur at different absolute values of $\dot{V}O_2$ as $O_2$ supply is acutely manipulated. Consequently, there is in practice no single, absolute $\dot{V}O_2$max for intact biological systems but rather the following: For any given set of circumstances determining maximal $O_2$ supply, a plateau in $\dot{V}O_2$ (i.e. $\dot{V}O_2$max) can potentially be observed and defined. The word potential is used because due to discomfort, many individuals will quit exercise before a clear plateauing tendency is visible. Again, such plasticity of $\dot{V}O_2$max is observed within the time it takes to manipulate $O_2$ supply, usually minutes. This must eliminate any structural or biochemical adaptation as the basis for the altered $\dot{V}O_2$max under such conditions. Of course, $\dot{V}O_2$max can be altered over a longer period by a combination of structural and biochemical changes induced by various stimuli, as is well known (reviewed in 7, 92).

The preceding presents a view that does not account for individual variability in maximal rates of $O_2$ transport and utilization. Such variability requires further modification of the above notions. Current evidence suggests that greater athletic ability for endurance activities is associated with greater vulnerability to limited $O_2$ supply. Thus augmenting $O_2$ supply improves $\dot{V}O_2$max little if at all in untrained humans or nonathletic mammalian species, but such individuals are also less susceptible to reduced exercise capacity when $O_2$ supply is reduced than their more athletic counterparts (82). Also, acute hypoxia results in proportionately more reduction in maximal $\dot{V}O_2$ in athletes than in sedentary subjects (56). There are at least two possible reasons for this. First, if untrained individuals possess less metabolic machinery to use $O_2$ due to fewer mitochondria, they are less likely to be dependent on an $O_2$ supply that may be in excess for the respiratory potential. Second, maximal cardiac output is well known to be less than in trained subjects (7). A low cardiac output naturally favors diffusive loading of $O_2$ in the lungs and $O_2$ unloading in the tissues by providing potentially longer capillary transit times for the red
cell. Consequently, natural or trained athletic ability must be taken into account in discussing the limits to exercise capacity to avoid needless confusion and pseudo-controversy over the importance of O₂ transport.

DETERMINANTS OF MAXIMAL O₂ SUPPLY

The above introduction serves to focus attention on the O₂ transport pathway. To avoid confusion, this transport pathway must be clearly defined. Many workers, especially in clinical fields, consider O₂ transport to be the sum total of all O₂ transport components down to the arteriolar blood supply of the tissue in question. They call this total O₂ transport or O₂ delivery, which is the product of the blood flow rate to the tissue and the arterial concentration of O₂. Arterial O₂ concentration is itself a product essentially of arterial O₂ saturation (SaO₂) and Hb concentration ([Hb]), (ignoring the usually but not always minor contribution of physically dissolved O₂). The same investigators generally consider that arterial O₂ saturation represents lung function, but as will be shown below, this is an unjustified assumption if taken literally. Although lung function is certainly a major determinant of arterial saturation, so too is blood flow rate (QT) through the lungs, especially at maximal exercise, and this is largely determined by cardiac function. The above definition of O₂ delivery or transport is

\[ \text{total O}_2 \text{ transport} = 1.39 \times [\text{Hb}] \times \text{SaO}_2 \times \dot{Q}_T \]  

for the body as a whole. For any tissue, QT (pulmonary blood flow or cardiac output) should be replaced by the corresponding tissue blood flow rate.

The above, however, ignores a critical component of the O₂ pathway—that between the tissue microcirculatory O₂ exchange vessels, which may include not only capillaries but also arterioles and venules (8, 20, 88) and the mitochondria. This is a physically short pathway and one in which O₂ is transported passively by diffusion (55). If all of the O₂ available as defined in Equation 2 were always completely transported to the mitochondria and consumed via Equation 1, Equation 2 would indeed suffice as a definition of O₂ transport. However, it is well known that blood flowing through exercising muscles is not depleted of O₂ even at \( \dot{V}_\text{O}_2\text{max} \) (68, 83). Consequently, the O₂ extraction process cannot be ignored. This is even more important in human disease states of compromised O₂ transport such as emphysema and bronchitis, lung fibrosis, chronic heart failure, and chronic renal failure with anemia, where recent evidence (see below) suggests that O₂ conductance from the tissue microcirculation to the mitochondria is particularly impaired.

Figures 2 and 3 lay out a standard conception of the O₂ transport pathway. Figure 2 shows all major steps, whereas Figure 3 magnifies the final component in the tissue of interest, generally, but not always, skeletal muscle.
If O₂ supply to mitochondria appears to be the normal determinant of \( \dot{VO}_2 \text{max} \), it is critical to develop a qualitative (and quantitative) construct accounting for the spectrum of experimental observations, each of which provides evidence for involvement of one or more, but usually not all, portions of the O₂ pathway in an integrative manner.

A simple construct for this simultaneously considers the two governing equations underlying O₂ transport: one that expresses the rate of O₂ transport by diffusion between the microcirculation and the mitochondria—Equation 3—and an expansion of Equation 2 that describes the rate of O₂ transport from the environment through the tissue microcirculation—Equation 4:

\[
\dot{VO}_2 = DO_2 \ [PCAPO_2 - PMITOO_2].
\]

Here, DO₂ is a lumped O₂ conductance coefficient embodying all impediments to O₂ movement from the red cells to the mitochondria. PCAPO₂ and
Figure 3  Simplified model of O₂ transport in a skeletal muscle. O₂ is convected through the microcirculation from arteriole to venule, mostly in the red cell (RBC), and simultaneously diffuses out of the red cell through the capillary fluids, capillary wall, and interstitium to the cell membrane of the muscle fiber. O₂ then further diffuses to the mitochondria, a process probably enhanced by the presence of myoglobin in the cytoplasm.

PMITO₂ are average microvascular and mitochondrial PO₂ values, respectively, and VO₂ is O₂ utilization.

The modification to Equation 2 acknowledges that not all O₂ is extracted from the arterial blood, such that

\[ \dot{V}O_2 = 1.39 \dot{Q} [Hb] [SaO_2 - SvO_2], \]

where SvO₂ is the O₂ saturation of venous blood from the tissue in question, whose blood flow is \( \dot{Q} \). Dissolved O₂ in the blood is ignored for simplicity.

Considering the limiting case where at \( \dot{V}O_2 \text{max} \), PMITO₂ is very close to zero (47), Equation 3 is simplified to

\[ \dot{V}O_2 \text{max} = \text{DO}_2 \cdot \text{PCAP}_O_2, \]

where the variables on the right hand side of Equations 4 and 5 are those at \( \dot{V}O_2 \text{max} \).

If one now regards \( \text{DO}_2 \), \( \dot{Q} \), [Hb], and SaO₂ as independent or input variables
DETERMINANTS OF MAXIMAL $\text{VO}_2$

to the system, then Equations 4 and 5 form a system of two simultaneous equations in the two unknowns, $\text{VO}_2\text{max}$ and $\text{SvO}_2$, because it can be shown that PCAPO$_2$ is dependent on SaO$_2$ and SvO$_2$ and thus can be calculated from their values. It then remains to solve this pair of equations for $\text{VO}_2\text{max}$ and $\text{SvO}_2$, which is a problem well-suited to computer analysis (100).

The construct afforded by Equations 4 and 5, while clearly a simplification of reality, fits well into the observations about how $\text{VO}_2\text{max}$ varies with a number of different interventions that individually alter blood flow, [Hb], or arterial O$_2$ saturation. Thus it is evident that variation of any of the four input variables (DO$_2$, Q, [Hb], and SaO$_2$) has the power to affect $\text{VO}_2\text{max}$. These variables underlie changes in muscle O$_2$ transport (DO$_2$), blood flow (Q), blood composition ([Hb]), and pulmonary function (SaO$_2$).

Numerous publications by Hogan and co-workers (38, 39, 41, 43, 45) and an analysis of these by Gainer (25) have explored how in a single animal model, these equations are borne out experimentally and explain the great majority of observations of effects of altering O$_2$ transport on $\text{VO}_2\text{max}$. A related approach based on Ohm's law, different in detail but similar in concept, has been described by di Prampero & Ferretti (17) and is in general agreement with the above, although not mechanistic in construct.

Although the simplicity of such an analysis should be kept in mind, a major overall conclusion is inescapable: The concept of "the" limiting factor to $\text{VO}_2\text{max}$ is no longer an appropriate concept. All parts of the O$_2$ transport pathway are involved in determining $\text{VO}_2\text{max}$. Thus a change in O$_2$ conductance of any one component will change $\text{VO}_2\text{max}$ in the same direction. The concept that must replace that of the limiting factor is reflected in the question: Quantitatively, what is the relative importance of each step of the O$_2$ transport pathway as a contributing determinant of $\text{VO}_2\text{max}$?

INFLUENCE OF INDIVIDUAL O$_2$ TRANSPORT PATHWAY STEPS ON $\text{VO}_2\text{max}$

**Inspired O$_2$ Concentration**

Whether studying intact individuals, isolated mitochondria, or preparations in between, altering the O$_2$ level to which muscle is exposed is both easy to do and of intrinsic interest. Consequently, much data exist on this topic, especially in intact animals and humans.

For instance, by changing barometric pressure (PB) (as in ascent to altitude or by diving) but not inspired O$_2$ concentration (FlO$_2$), inspired PO$_2$ (PIO$_2$) is altered; by changing FlO$_2$ at constant PB, similar changes in PIO$_2$ can be achieved (because PIO$_2$ is the product of PB and FlO$_2$). Comparison of these two strategies allows inferences on the role of PB to be made, and it appears
ALTITUDE AND VO2max

![Graph showing VO2max vs inspired PO2.

Figure 4 Dramatic reduction in VO2max with ascent to extreme altitude. The curve is increasingly steep as PI02 falls (see text). Maximal VO2 on the Everest summit is about 15 ml·kg⁻¹·min⁻¹, about equal to that of a patient with advanced cardiopulmonary disease at sea level.

that there is little evidence that PB itself acutely affects maximal O2 transport and utilization. However, some workers feel that acute changes in PB can affect other transport processes such as that of water across capillary surfaces (57). For the present, it is reasonable to propose that most evidence suggests that altering inspiratory O2 levels by either method is equivalent at the same PI02.

Classical studies of maximal exercise capacity in field and chamber ascents to extreme altitude (15, 73, 109) have shown how dramatically VO2max is reduced as one climbs higher. Typical data are shown in Figure 4. The nonlinearity of this relationship is explained by three factors. Firstly, the nonlinear shape of the O2-Hb dissociation curve protects against desaturation of arterial blood at modest altitudes until arterial PO2 begins to fall below about 60 torr, the knee of that curve. Secondly, and also because of the shape of the O2-Hb curve, diffusion limitation of O2 uptake in the lung is accentuated as PO2 falls on to the steep portion of the dissociation curve (67). Thirdly, maximal cardiac output, and hence muscle blood flow, falls with adaptation to high altitude, the more so the higher the ascent (72, 75). Thus total O2 transport (Equation 2) is reduced even further. There is a small counterbalancing factor that tends to oppose these negative effects—slightly increased extraction of O2 from the
muscle microcirculation, as the interaction between Equations 4 and 5 would require. This, however, is of little quantitative benefit.

Although such dramatic decreases in \( \dot{V}O_2 \text{max} \) with hypoxia are easily shown and well understood, the converse is problematic. Increased \( \text{PIO}_2 \) in normal average subjects has produced small and thus equivocal results. Reviewed by Welch (108), a majority of studies show that \( \dot{V}O_2 \text{max} \) is slightly increased by hyperoxia. Because of the flattening of the \( O_2 \)-Hb curve at high \( \text{PIO}_2 \), one cannot expect more than about a 10% increase in \( \dot{V}O_2 \text{max} \) from breathing pure \( O_2 \). This is because when room air is breathed, Hb is virtually fully saturated, even during heavy exercise, such that gains in arterial \( O_2 \) concentration reflect mostly added dissolved \( O_2 \). At the low solubility of \( O_2 \) (0.03 ml/liter•torr), a 500 torr increase in arterial \( P_O_2 \) from 100 to 600 torr (\( \text{FIO}_2 \) from 0.21 to 1.0) produces only a 15-ml/liter increase in arterial \([O_2]\), which is about 10% or less of the total room air value of arterial \([O_2]\). Coupled to the difficulty in measuring \( \dot{V}O_2 \) using conventional expired gas analysis at high \( \text{FIO}_2 \) values and the fact that measured whole body \( \dot{V}O_2 \) reflects more than just muscle \( O_2 \) utilization, it is not surprising that studies often have been inconclusive. Although the \( O_2 \) loading limitation is hard to overcome in human subjects, studies adding a fluorocarbon to plasma to increase \( O_2 \) solubility have shown an increased \( \dot{V}O_2 \text{max} \) in proportion to the increase in total \( O_2 \) transport (Equation 2) (45) in isolated dog muscle. In humans, the measurement problems and specificity of muscle \( O_2 \) use referred to above can be avoided if the arterial and venous circulations of the muscles are directly accessed. This can be done for the human quadriceps by means of arterial and femoral venous catheterization (1, 86). This also permits blood flow measurement and hence calculation of \( \dot{V}O_2 \) by Equation 4. When such studies are done, it is clear that \( \dot{V}O_2 \text{max} \) is indeed increased by hyperoxia, at least in trained subjects (54). In sedentary individuals, the same methodology reveals no significant benefit of hyperoxia (82), and thus some of the confusion over effects of hyperoxia may reflect differences in the athletic capability of subjects (see above).

The influence of athletic state on sensitivity to hyperoxia (56) is perhaps best illustrated by elite athletes in whom exercise-induced arterial \( O_2 \) saturation is well known (16, 110). Powers and co-workers (71) found a predictably small but nonetheless significant increase in \( \dot{V}O_2 \text{max} \) of elite athletes (70.1 to 74.7 ml•kg\(^{-1}\)•min\(^{-1}\)) as \( \text{FIO}_2 \) was increased from 0.21 to only 0.26, coincident with correction of modest exercise-induced arterial desaturation. The relative increase in saturation of 5.8% was similar to that of \( \dot{V}O_2 \text{max} \) (6.6%). Even more clear-cut is the effect of hyperoxia in the thoroughbred racehorse (52). Here, due to a combination of pulmonary diffusion limitation causing hypoxemia and extreme rightward shift of the \( O_2 \)-Hb curve due to hyperthermia, hypercapnia, and acidosis, arterial saturation at \( \dot{V}O_2 \text{max} \) is about 80%. Breathing 35% \( O_2 \) restores saturation to about 98%, and both maximal speed
and \( \dot{V}O_2 \) are increased by the same relative amount, i.e. by almost 20% (P Wagner, unpublished observations).

Clearly, \( VO_2 \text{max} \) varies acutely with \( PI_0_2 \), and the more athletic the individual, the greater the effect.

**Pulmonary Function**

Conceptually distinct from \( PI_0_2 \) (which mathematically affects \( PO_2 \) at every point in the \( O_2 \) transport pathway independently of organ function) is the issue of how pulmonary function affects maximal \( O_2 \) transport. The potential exists for exceeding pulmonary \( O_2 \) and \( CO_2 \) exchange capacity in several ways. First, ventilatory limits may be reached such that further increases in exercise workload are not accompanied by corresponding increases in ventilation. The same could happen to pulmonary blood flow (see section on cardiovascular function). Second, the gas exchange process could be impaired by the demands of exercise. Thus rapid breathing rates could impair mixing of inhaled gas with that in the alveoli; high rates of blood and gas flow could result in their nonuniform distribution within the lungs. This would cause ventilation/perfusion \( (VA/Q) \) mismatch and reduce arterial \( PO_2 \) as a result. High blood flow rates reduce average red cell transit time in gas exchange vessels (despite vascular volume recruitment in the lung), and this could result in diffusion limitation of pulmonary \( O_2 \) uptake. The high pulmonary vascular pressures associated with high blood flow rates could lead to transient extravascular fluid accumulation or even microvascular rupture and these could negatively affect both \( VA/Q \) matching and diffusion equilibration. Finally, because \( VO_2 \) is known to rise relatively more than cardiac output, mixed venous \( PO_2 \) must fall (Equation 4). To the extent there are any intrapulmonary or postpulmonary (bronchial, Thebesian) shunts, arterial \( PO_2 \) will be reduced more during exercise than at rest due to the lower (venous) \( PO_2 \) of the blood that is carried.

Do any of these deleterious phenomena occur in normal subjects? Unequivocally, yes. The extent varies considerably among individuals, and not all of the above factors are important. However, relatively few normal human subjects perform maximal exercise without evidence of some degree of pulmonary dysfunction. Thus the common denominator of any of the above effects, the alveolar-arterial \( PO_2 \) difference \( (AaPO_2) \), is almost uniformly increased and progressively so, the more intense the exercise (106). At \( VO_2 \text{max} \), values of \( AaPO_2 \) commonly reach 30 torr (corresponding values at rest are generally 5–10 torr).

Of the above potential factors, which appear to be important? In the average subject (neither sedentary nor elite), a combination of \( VA/Q \) inequality and diffusion limitation of \( O_2 \) uptake accounts for a majority of the \( AaPO_2 \) (26,
Determinants of maximal \( \dot{V}O_2 \)

30, 35, 103). Indirect evidence suggests that \( \dot{V}A/\dot{Q} \) inequality is more likely due to transient pulmonary interstitial fluid accumulation than to the dynamic effects of high ventilation or blood flow per se (90). Pulmonary and postpulmonary shunts are trivial, generally not measurable factors. Gas mixing imperfection is similarly not considered to be of quantitative significance (37, 103). Ventilatory limits are not generally reached because arterial PCO\(_2\) at \( \dot{V}O_2max \) is classically 30–35 torr, well below resting levels, which implies that ventilation increases relatively even more than does CO\(_2\) production (and thus \( \dot{O}_2 \) utilization). On average, diffusion limitation accounts for more than half of the AaP\( \dot{O}_2 \) at \( \dot{V}O_2max \) with \( \dot{V}A/\dot{Q} \) inequality contributing the remainder (26, 35, 103).

As with the effects of PIO\(_2\) on \( \dot{V}O_2max \), the effects of pulmonary dysfunction on \( \dot{O}_2 \) exchange are systematically related to athletic capacity. Thus the most sedentary individuals (human and other) are least demonstrably affected by pulmonary dysfunction (14, 56, 82). There may be no evidence of diffusion limitation and certainly adequate ventilatory reserves exist to allow arterial PCO\(_2\) to fall to between 30 and 35 torr. At the other extreme are elite athletes who usually show by several criteria quantitatively important effects of limited pulmonary function. Presumably due to their higher cardiac output (related to athletic prowess), there is a shorter red cell contact time in the lung, resulting in diffusion limitation and occasionally marked hypoxemia (71, 110). There can also be evidence of failure to maintain the typical hypocapnia of maximal exercise in elite athletes, with arterial PCO\(_2\) increasing toward (normal resting) values of 40 torr (56). Coincident with this is evidence of expiratory flow limitation (51). This evidence is based on maximal flow-volume loop values (obtained at rest) being reached in mid-expiration during maximal exercise. Johnson et al (50) found, as might be expected, that expiratory flow limitation is more likely with advancing age because lung compliance increases, favoring dynamic compression of airways. However, it should be pointed out that expiratory flow limitation per se does not imply that a mechanical limit has been reached to total minute ventilation, even if arterial PCO\(_2\) begins to rise. The control of breathing during exercise is complex and remains obscure. It may well be that the system accepts some compromise between the chemical drive to breathe (from PCO\(_2\) and H\(^+\)) and the cost of breathing (mechanical and hence metabolic), which allows PCO\(_2\) to rise even if there is still physical capacity to further ventilate (69). This is very difficult to resolve experimentally. Mechanical unloading studies replacing N\(_2\) (of room air) with helium show an increase in ventilation (60, 70), but this does not resolve the question precisely because the mechanical situation has been changed. McParland's (62) studies interposing a deadspace volume between the subject and a valve box have shown no effect on \( \dot{V}O_2max \) and a corresponding increase in minute ventilation to preserve alveolar ventilation. Although done only in moderately
fit subjects (\(\dot{V}O_2\)max of 40–50 ml min\(^{-1}\) kg\(^{-1}\)), this certainly argues against a mechanical limit to breathing in this type of person.

The thoroughbred equine is an example of an elite athlete that demonstrates pulmonary functional limits to a greater extent than even Olympic-level human athletes. Marked arterial hypoxemia from diffusion limitation is the norm (104). This is not surprising because maximal cardiac output per kg body weight is about double that of a fit human (0.7 vs 0.4 L min\(^{-1}\) kg\(^{-1}\)), which would contribute to reduced transit time of red cells in the pulmonary circulation. In vivo arterial PO\(_2\) (expressed at body temperature) is often in the 60–70 torr range; this is only occasionally seen in humans (16, 71, 110). In addition, arterial PCO\(_2\) rises, often markedly, to between 50 and 60 torr at VO\(_2\)max. Although this can be avoided with helium-O\(_2\) breathing (22, 24), the issue of mechanical ventilatory limitation is still unresolved. There is more likelihood of resolving this in horses than in humans because of the stride-respiratory rate entrainment known to occur in this species (9).

Clearly, the lungs are problematic to O\(_2\) transport, increasingly so with athletic capacity.

**Cardiovascular Function**

Cardiac output rises linearly with exercise load in normal subjects and does not show evidence of reaching a plateau (2). In accord with the Frank-Starling relationship, higher ventricular filling pressures are observed (74); ventricular function studies and echocardiographic and electrocardiographic variables are all consistent with adequate myocardial O\(_2\) supply for the cardiac workload imposed by the external power output (75). Evidence for ischemia in normal subjects does not exist clinically or physiologically, even at extreme altitudes equivalent to that of Mt. Everest (> 8,000 m, PB ~250 torr, P<sub>1</sub>O\(_2\) ~43 torr, arterial PO\(_2\) ~30 torr) (61, 75, 97).

Control of cardiac output and its distribution is complex and well described in classic texts (85) and is tied to exercise intensity through a variety of neuronal and hormonal factors mediated in large part by the autonomic nervous system, as well as by mechanical factors related to various muscle pumps that facilitate return of venous blood to the heart. This huge topic is not further addressed here.

Consequently, unlike the lungs, which show evidence of impaired function at VO\(_2\)max, increasingly so with increasing athletic ability, there is little to suggest impaired cardiac function. It is well known that cardiac output is higher in athletes. This can be inferred simply from Equation 4, because (a) arterial saturation is if anything lower in athletes despite a higher VO\(_2\)max, as discussed above, and (b) venous saturation is mostly low at all levels of athletic ability at VO\(_2\)max. The only factor left to permit a higher VO\(_2\) in athletes is
DETERMINANTS OF MAXIMAL $\dot{V}O_2$

a high cardiac output. Therefore, it should come as no surprise that there is a close correlation between $\dot{V}O_2\text{max}$ and maximal cardiac output over the range of athletic capacity (7). Elite athletes are marked by this attribute, perhaps above all others. Within an individual experimental preparation such as the isolated muscle, blood flow is similarly a key determinant of $\dot{V}O_2\text{max}$ because of its dominant influence on total $O_2$ transport (Equation 2).

It is worth stressing that this close relationship does not exclude other factors from affecting maximal $O_2$ transport and $\dot{V}O_2\text{max}$.

An interesting question is the balance between the positive effects of a high cardiac output on convective $O_2$ transport to muscle (i.e. via Equation 2) and the coincident negative effects of the same high cardiac output on diffusive loading of $O_2$ in the lung and unloading in the tissues. This can be modeled cleanly; actual in vivo experiments altering flow are technically difficult and more importantly are muddied by unwanted potential secondary effects of change in microvascular flow distribution and blood volume in the lungs and muscle. Calculations suggest that in average subjects at sea level, humans are positioned delicately at a point such that decreases in cardiac output would greatly reduce $O_2$ transport, whereas increases would have only a modest beneficial effect due to increasing diffusion limitation (Figure 5). This is even more evident at extreme altitude where diffusion limitation is more apparent (105). Here the relatively low maximal cardiac output (of $\sim 18 \text{ L\cdot min}^{-1}$ at Mt. Everest compared to $\geq 25 \text{ L\cdot min}^{-1}$ in the same subjects at sea level) (75) is not the limitation one might predict. Any gain in convective transport of $O_2$ that would result from a higher cardiac output is calculated to be completely offset by increased diffusion limitation in both the lungs and muscles (adapted from 101) (Figure 5).

The preceding discussion ties cardiac output to exercise load, implies no interference to cardiac function at $\dot{V}O_2\text{max}$, but suggests a counterbalancing effect on $O_2$ transport of a high cardiac output due to impaired $O_2$ diffusion equilibration in the lungs and muscles. Not addressed is whether cardiac output at $\dot{V}O_2\text{max}$ has reached some mechanical limit that could be imagined simply by decreased ventricular filling time as the heart rate rises with exercise intensity. Abundant data, however, show that as heart rate increases generally linearly (with exercise load) all the way to $\dot{V}O_2\text{max}$, stroke volume asymptotes toward a plateau but does not fall (32). This would argue (but not prove) that a mechanical limit has not been reached. Moreover, it is possible to augment maximal cardiac output experimentally in normal subjects and animals. Horwitz & Lindenfeld (49) showed how maximal cardiac output could be increased 20-30% by blood volume augmentation using dextran. Of great interest, Stray-Gundersen et al (96) showed that pericardiectomy increased both cardiac output and $\dot{V}O_2\text{max}$ by about 20% (compared to control sham-operated dogs). These data support the central theme of this review: $\dot{V}O_2\text{max}$ is determined by $O_2$
Figure 5  Modeling the effects of changes in cardiac output on VO\textsubscript{2max}. At sea level, maximal VO\textsubscript{2} is sensitive to cardiac output but increases provide lessening benefit due to concurrent pulmonary and muscle diffusion limitation as capillary transit time falls. However, at altitude (Everest summit), due to even greater effects of diffusion limitation, cardiac output has essentially no influence on VO\textsubscript{2max}.

supply (and thus is altered predictably by changes in O\textsubscript{2} transport) rather than by mitochondrial oxidation capacity of muscle. Second, they suggest that at least in the untrained dog, ventricular function can be limited by pericardial constraints, probably by limiting diastolic filling. Thus, indirectly, there is a mechanical limit shown by these studies but one that can be modified by hypervolemia, for example.

The thoroughbred equine is an excellent example of the importance of blood volume and cardiac filling in the cardiac output response to exercise. This species is well known to use its large splenic reservoir of red cells to bolster both circulating blood volume and hematocrit during exercise (66). Splenectomy (with several weeks allowed for recovery and retraining) reduces cardiac output by about 20% at VO\textsubscript{2max}, and this is rapidly restored to normal by blood transfusion (102). Corresponding changes in VO\textsubscript{2max} accompany these changes in blood flow, as do reductions in right atrial pressure after splenectomy and restoration with transfusion.

In summary, unlike the lungs, cardiac function is well preserved during maximal exercise. However, it is quite dependent on ventricular filling as shown by pericardiectomy or volume loading or splenectomy. Increases in
cardiac output are considerably offset by impaired diffusive \( \text{O}_2 \) transport both in the lungs and muscles such that in severe hypoxia, little or no increase in net \( \text{O}_2 \) transport is expected to result from increasing cardiac performance.

**\( \text{O}_2 \) Extraction from Blood**

The close correlation of \( \dot{\text{V}}\text{O}_2\text{max} \) to cardiac output under normal circumstances, combined with the technical difficulties in studying \( \text{O}_2 \) extraction from blood in the muscles, has left this area relatively underinvestigated. However, the development of new approaches to measure \( \text{O}_2 \) transport and related phenomena by magnetic resonance, near infrared, and phosphorescence quenching-based techniques has rekindled interest. Moreover, there is a groundswell of opinion that in human chronic diseases such as heart failure, chronic obstructive lung disease, and chronic renal failure there may well be an independent defect of intramuscular \( \text{O}_2 \) transport that compounds the well-known convective \( \text{O}_2 \) transport defects (of reduced cardiac output, arterial \( \text{O}_2 \) saturation and [Hb], respectively).

The \( \text{O}_2 \) pathway from muscle microvascular red cells (RBC) to the mitochondria is complex, as shown in Figure 3. Sequential steps begin with chemical dissociation of \( \text{O}_2 \) from Hb. \( \text{O}_2 \) must then diffuse out of the red cell and through the plasma to the capillary wall. Further diffusion occurs through the capillary wall, interstitium, and sarcolemma to reach the interior of the myocyte. Potentially long diffusion distances may then exist for \( \text{O}_2 \) to reach distant mitochondria (although a commonly found sub-sarcolemmal juxtagapillary accumulation of mitochondria reduces the distance many \( \text{O}_2 \) molecules must traverse). The intracellular presence of myoglobin (Mb) is thought to facilitate the transport of \( \text{O}_2 \) within the cell (113, 115). This may be the result of the mobility of Mb itself, as well as the result of Mb-\( \text{O}_2 \) binding, which reduces intracellular free \( [\text{O}_2] \), and thus \( \text{PO}_2 \) and enhances the \( \text{PO}_2 \) gradient responsible for \( \text{O}_2 \) diffusion. Note that if the mitochondrial system is a syncytial network, as three-dimensional images suggest, rather than a collection of separate organelles, this network might influence \( \text{O}_2 \) pathways and may imply less of a role for Mb in intracellular \( \text{O}_2 \) transport than currently thought. Another potential preferential pathway for intracellular movement of \( \text{O}_2 \) independent of myoglobin is through lipid (59, 93).

Given the complexity of the \( \text{O}_2 \) transport pathway from Hb to the mitochondria, is there evidence that this pathway significantly impairs maximal \( \text{O}_2 \) transport, and if so, what can be said about the relative contributions of the various components to this impedance?

The answer is that there must be a significant impedance to this pathway, if for no other reason than muscle venous blood contains a fair amount of \( \text{O}_2 \) even at \( \dot{\text{V}}\text{O}_2\text{max} \). Venous \( \text{PO}_2 \) is frequently 20 torr, with saturation of Hb in
the 15% range for average normal subjects (83). What prevents 100% extraction of $O_2$? That it is not limited mitochondrial oxidative capacity in most subjects has already been documented (see above), based on immediate increases in $V_02$ as $O_2$ supply is enhanced. What processes could be responsible for incomplete extraction on the basis of impaired transport? This situation is analogous to that of dissecting the causes of the alveolar-arterial $P_02$ difference in the process of pulmonary $O_2$ exchange. There are four possibilities:

1. A limited (finite) overall diffusional conductance for $O_2$ between Hb and the mitochondria (i.e. $D_02$ of Equation 3);
2. Heterogeneity of perfusion with respect to local $O_2$ demand (not necessarily with respect to muscle mass per se);
3. Functional or structural shunts of arterial blood into the venous system;
4. Direct diffusion of $O_2$ from pre-exchange arteries to post-exchange veins through muscle tissue.

Evidence for items 3 and 4 in maximally exercising mammalian skeletal muscle is weak to nonexistent. Honig et al (46), using cryospectroscopy, have found no elevation of Hb-$O_2$ saturation in venules closely juxtaposed to arterioles in exercising dog muscle, and in any event, the importance of this phenomenon would decrease as muscle blood flow increases with exercise. In such muscles, there is no evidence of anatomical shunts. Heterogeneity, however, is another matter. Different fiber types have different $O_2$ requirements and thus probably different flow requirements, which would be disclosed by microsphere measures of regional muscle blood flow (13), but these can only be referenced to muscle mass, not metabolic rate ($V_02$). However, it is possible that blood flow and $V_02$ would be matched as a function of fiber type. More randomly based flow heterogeneity may occur, and it is clear from video microscopy of resting muscle that such uneven flow is seen (19, 21). Whether uneven flow functionally impacts $O_2$ transport depends on the size of the functional unit of muscle. Perhaps the presence of myoglobin facilitates the even distribution of $O_2$ even in the face of uneven blood flow. Perhaps local production of metabolites regulates local blood flow in tune with local $V_02$. The data of Gayeski et al (27, 28) show broadly similar intracellular $P_02$ during exercise across a range of fibers, which suggests that this may be the case. Further evidence that the perfusion heterogeneity disclosed by microsphere measurements, with respect to mass, may not reflect perfusion/metabolism heterogeneity is in the studies of Hogan (38, 44). The same rate of $O_2$ supply into the muscle vasculature by perfusion of two bloods that differ only in Hb affinity produces a change in $V_02max$ exactly as predicted from a model of diffusion-limited $O_2$ transport. Heterogeneity does not lead to any effect of Hb-$O_2$ affinity on $V_02max$. However, the importance of heterogeneity during
exercise is not fully resolved and must await undiscovered technologies for direct assessment of the distribution of flow and metabolic rate.

Returning to the O₂ pathway of Figure 3, can one tease out parts of that pathway likely to be more important in impeding O₂ transport than others? Classical work by Krogh (55) at the start of this century led to the simple idea that distance from the capillary integrated with position relative to arterial and venous ends of the microcirculation would dictate local [O₂] within the cell on the basis of Fick’s law of diffusion (Equation 3). This produced the concept of the “Krogh cylinder” and the “lethal corner” for O₂ insufficiency. More recent studies have considerably altered our view of this pathway due to the fact that the pathway is functionally and structurally very non-uniform. Basically, distance is thought to be unimportant. This is not because the laws of diffusion are wrong, but because intracellular O₂ conductance is evidently very high, negating the effects of distance. Evidence for this is Gayeski’s (28) intracellular cryospectroscopic data showing intracellular PO₂ in working dog muscle of 1–3 torr when adjacent intravascular PO₂ lies between about 20 and 100 torr (with a mean value of ~40 torr). Thus most of the impedance is between the Hb molecule and the sarcolemma, a very short (2–3 μm) physical distance. Although Honig’s technique has been questioned and has more limited spatial resolution than previously thought, the basic conclusion likely is correct. Theoretical calculations by Groebe & Thews (33) support this as well. Very recently, nuclear magnetic resonance measurements of intracellular myoglobin saturation in intact human quadriceps muscle at maximum VO₂ further support this conclusion (77). Here, with Mb saturation averaging 60%, intracellular PO₂ averages only about 3 torr. Such agreement among three totally different approaches strengthens the general conclusions that O₂ transport is impeded mostly somewhere between the Hb molecule in the red cell and the muscle cell wall.

Slow chemical off-loading kinetics (34) and/or a large inter-red cell space reducing the effective red cell–capillary contact area for O₂ transport (23) could in theory be responsible for part of the impedance to O₂ transport. If relevant, both effects could change O₂ efflux rates in the same direction as changes in [Hb]. Hogan (39) found that [Hb] plays a large role in O₂ conductance in isolated canine muscle, and Schaffartzik (89) found similar effects in intact human as [Hb] was acutely varied. The original data of Cain (12) in dogs at rest, showing [Hb] dependance of VO₂ at a given reduced level of O₂ delivery, can also be interpreted as evidence of this impedance. Augmenting the inter-red cell space with fluorocarbons to enhance plasma O₂ solubility (45) or with free Hb solution (42) has provided evidence that the normally carrier-free plasma space between microvascular red cells does not offer significant impedance to O₂ transport despite theoretical predictions to the contrary (23). Perhaps, mixing is rapid enough within the microvessels that the expected defect is not
seen. Much more work needs to be done to resolve this issue. It is important to do so because the effect of [Hb] on O₂ conductance is substantial (39), because of interest in blood doping in sports medicine circles (29), and because of the development of manufactured soluble O₂ carriers (fluorocarbons, synthetic hemoglobins) in lieu of whole blood transfusion, carriers that will occupy the plasma space (6, 79, 112).

In most circumstances, [Hb] remains stable and within normal limits, yet there are very large differences in muscle O₂ conductance between different populations. Trained athletes have higher values than sedentary subjects (82, 83); training itself increases muscle O₂ conductance in the same person (82) by some 30%, without changes in [Hb]. However, in heart failure and chronic lung diseases, muscle O₂ conductance is very low, again in patients whose [Hb] is normal.

The remaining component to be addressed in the O₂ pathway in muscle, is the capillary wall itself. Intuitively, the richness of capillary supply is likely to be a key factor in determining O₂ conductance and in explaining the above differences between subject groups in O₂ transport within muscle. Bebout (5) compared genetically similar canine muscle that had undergone either endurance training or total immobilization and compared it to control, unexercised muscle. Maximal VO₂ of the three groups related closely to the number of capillaries per fiber but not to diffusion distance or capillary density (a factor that depends on both capillary numbers and fiber area). Calculated muscle O₂ conductance related equally well to capillary number but not to distance-related parameters. These controlled studies support the well-established observations that endurance training in mammalian species increases the number of capillaries along with VO₂max (87). They also suggest that Oelz’s (65) findings (that elite high-altitude climbers had pulmonary function no different from normal subjects but >20% capillary number per fiber in leg muscles) may account in part for ability to reach great altitudes without supplemental O₂. It is O₂ conductance in muscle that is predicted to be the most important factor capable of increasing VO₂max at great altitude (101).

In summary, it is clear that while much work remains to be done in muscle O₂ transport, the process of diffusion of O₂ between the red cell and the mitochondria encounters measurable impedance and explains in large part the way in which maximal VO₂ is limited by O₂ supply.

Relative Influence of Each Part of the O₂ Transport Pathway on Maximal O₂ Transport

To assess maximal O₂ transport conductance, experiments altering one pathway step at a time are necessary. Although this can be done, there are often one or more secondary effects in other parts of the O₂ transport pathway that
make it difficult to interpret the result as due only to the intended change of the primary variable. Theoretical calculations are useful in addressing such issues. Table 1 shows calculated sensitivity of $\dot{V}O_2_{\text{max}}$ to each of the primary $O_2$ transport conductances, at sea level and at extreme altitude (Everest summit), for a trained athlete (using a particular set of normal values). At sea level, $\dot{V}O_2_{\text{max}}$ is sensitive to all variables, at varying degrees. The effect of reducing $O_2$ conductance at any step is clearly much greater than that of increasing conductance by the same percent, consistent with the nonlinear behavior shown in Figure 5; but at altitude, pulmonary and intramuscular $O_2$ diffusional transport are relatively more important than blood flow. In most cases, the relative effect on $\dot{V}O_2_{\text{max}}$ is less than that of the altered conductance because for each, multiple opposing effects occur.

**Extrapolations to Disease**

The majority of research discussed above comes from studies of normal human or animal skeletal muscle; however, the hope is to use these principles in the understanding and evaluation of disease. Although the fundamental physical basis of $O_2$ transport must be the same as in health, disease may affect the quantitative aspects of one or more components of the $O_2$ transport and utilization system. Caution is needed in interpreting data from patients with disease on a paradigm of normal physiology. On the other hand, attempting to make
such interpretations would be an excellent way to create hypotheses. Perhaps the most instructive approach is to return to the two equations that describe O₂ transport in convective and diffusive terms (Equations 4 and 5, respectively). If one assumes that muscle venous PO₂ and mean capillary PO₂ rise and fall together (as conditions are altered) and proportionally, Equation 5 can be written as

\[ \dot{V}O_2 = DO_2 \cdot k \cdot PvO_2. \]  

6.

On a diagram where \( \dot{V}O_2 \) is on the Y axis and \( P_{vO_2} \) is on the X axis, Equation 6 is a simple straight line through the origin; the slope is a function of the overall O₂ muscle conductance, \( DO_2 \) (Figure 6, *upper panel*). On the same diagram, Equation 4 can be plotted, given values for blood flow, arterial O₂ saturation, and [Hb]. Implicit is the ability to interconvert between \( S_{vO_2} \) and \( P_{vO_2} \), which requires knowledge of the O₂-Hb dissociation curve. This gives rise to the curved, negatively sloped line of Figure 6, which in fact represents an inverted O₂-Hb dissociation curve. The Y intercept of this curve, when \( P_{vO_2} = 0 \), equals total O₂ transport (Equation 2). The X intercept of this curve, hypothetically when \( \dot{V}O_2 = 0 \), must occur when \( P_{vO_2} = \) arterial PO₂ and no O₂ is thus extracted from the blood. The key point is that the intersection of the two lines in Figure 6 gives the only point where the two transport processes yield the same \( \dot{V}O_2 \); this must be \( \dot{V}O_2 \) max, and the corresponding \( P_{vO_2} \) is the obligatory venous PO₂, consistent with that \( \dot{V}O_2 \) and the given variables: \( DO_2, QT, [Hb], \) and \( S_{aO_2} \).

If any component of Equation 4 is perturbed, the shape and position of the curved line in Figure 6 (*upper panel*) must be changed. For example, reducing \( S_{aO_2} \) by breathing an hypoxic gas will produce the indicated shift in the curved line (Figure 6, *lower panel*) and a new lower point of intersection, with the straight line describing diffusive transport. Thus a given degree of hypoxemia is expected to produce a predictable new and lower \( \dot{V}O_2 \) max that is not only proportional to the new, lower value of total O₂ transport (Equation 2) but also proportional to a new, lower venous PO₂ (Equation 6). Normal muscle has been shown to behave in this manner across several species [human (83), dog (43), rat (31), horse (102)] as arterial PO₂ is altered. Although this predictable behavior of \( \dot{V}O_2 \) max does not distinguish between heterogeneity and diffusion limitation as causes of residual O₂ in venous blood, it permits an overall measurement of functional O₂ conductance as the slope of the straight line.

Clearly, to apply this concept to diseases, one must first demonstrate that \( \dot{V}O_2 \) max is indeed dependent on O₂ supply. Thus proportional behavior among \( \dot{V}O_2 \) max, total O₂ transport, and muscle venous PO₂ must be present as O₂ supply is manipulated. If so, the concept of Figure 6 is usefully applied. If not, one must conclude that \( \dot{V}O_2 \) max is not limited by O₂ supply but rather by
Figure 6  Upper panel: a conceptual approach to understanding the interaction between diffusion and convection in the lungs, circulation, and muscles, which sets VO2max. The line of positive slope is the graphical equivalent of Equation 6; the curved line of negative slope is the corresponding equivalent of Equation 4. Their intersection defines maximal VO2. Lower panel: effect of reduction in inspired PO2 (from 100 to 40 torr) on VO2max predicted from Equations 4 and 6. VO2max and muscle venous PO2 are proportional due to dependence of O2 transport on intramuscular diffusion of O2.
limits to muscle $O_2$ oxidative capacity, and thus the analysis of Figure 6 becomes inapplicable. However, data obtained to date, although preliminary, are concordant with $O_2$ supply limitation of $\dot{V}O_2_{\text{max}}$ (78, 84).

Figure 7 shows mean data (99) of maximally exercising patients with chronic obstructive pulmonary disease (COPD) and similar data (82) from young healthy sedentary adults (about 35–40 mL•kg$^{-1}$•min$^{-1}$ $VO_2_{\text{max}}$). This is not a fair comparison, to be sure, because the COPD patients are considerably older: 50–70 years vs 20–30 years. Yet the comparisons are instructive. Convective $O_2$ transport is grossly reduced in COPD, which is shown by the curved line Y intercept (see above). However, the slope of the straight line is also much reduced from even normal sedentary subjects. This difference cannot be due to age alone: It is well known that $VO_2_{\text{max}}$ in the 50–70 age group is some 2–3 L•min$^{-1}$ for the average-sized person, not $<1$ L•min$^{-1}$ as shown for COPD. These data suggest a reduction in muscle $O_2$ conductance, and a good candidate mechanism would be a reduced muscle capillary bed. Although these data contain enough gaps to prevent a dogmatic conclusion, they suggest a testable hypothesis that COPD leads to an intrinsic myopathic interference to $O_2$ transport that reduces $\dot{V}O_2_{\text{max}}$ below that which would otherwise be expected, given the degree of convective $O_2$ supply reduction from lung disease per se. This hypothesis definitely deserves follow-up, and if substantiated, would have potential therapeutic implications for improving exercise tolerance (by training to induce muscle capillary growth, for example). Conversely, a lung transplant that fully restored convective $O_2$ supply to normal, but left muscle $O_2$ conductance untouched, would provide little increase in $\dot{V}O_2_{\text{max}}$ as Figure 7 implies.

Similar predictions might be made in other chronic diseases such as chronic heart failure and chronic renal failure. Indeed, renal failure patients have been shown to have a very disappointing exercise response to erythropoietin therapy despite returning [Hb] to near-normal values (63, 80). Thus the relative gain in $\dot{V}O_2_{\text{max}}$ is much less than that of [Hb] itself. The analysis of Figure 6 lends itself to understanding this outcome. After first showing that $\dot{V}O_2_{\text{max}}$ post-erythropoietin was $O_2$ supply dependent, Roca (84) found that the disappointingly small increase in $\dot{V}O_2_{\text{max}}$ was due mostly to an $O_2$ conductance value 30% lower than that found in well-matched sedentary volunteers. Also contributing to the small improvement was a significant reduction in muscle blood flow accompanying and offsetting the $O_2$ transport benefit of the higher [Hb]. The basis for the low $O_2$ conductance is not known with certainty, but a low capillary number has been found by muscle biopsy in patients with chronic renal failure (64).

While much work needs to be done to better understand the physiological basis of impaired $O_2$ transport in muscle in chronic diseases. Disappointing degrees of exercise recovery following cardiac transplantation (53), lung transplantation (58), and erythropoietin therapy (63, 80) point to an intrinsic muscle
DEFINMENTS OF MAXIMAL $\dot{V}O_2$

Figure 7 Based on Figure 6, analysis of maximal exercise in a typical patient with chronic obstructive lung disease. Not only is convective O$_2$ supply into the muscle circulation greatly impaired (downward displacement of the curved line), but O$_2$ conductance from the circulation to the mitochondria is significantly reduced (reduced slope of the straight line). Note that even if heart and lung function could be restored to control levels, VO$_2$max would remain very low if muscle O$_2$ conductance were to remain the same.

SUMMARY

This review has focused on the hypothesis that maximal O$_2$ utilization during exercise (VO$_2$max) is by and large the result of mitochondrial O$_2$ supply limitation rather than limited cellular oxidative capacity to use O$_2$, and much evidence has been presented to defend this position. On this basis, the major conclusions are

1. VO$_2$max is not limited by just one component of the O$_2$ transport pathway. Rather VO$_2$max is set by the quantitative interaction among all O$_2$ transport processes between the environment and the mitochondria.
2. Interference to conductance of any step in the pathway will predictably reduce VO$_2$max; Figure 6 represents a useful paradigm for analyzing the
effects of one or more such changes on overall system performance. So too do corresponding if slightly different approaches (17).

3. What is the importance any one step in the pathway for VO₂max? This can be deduced from the paradigm of Figure 6 under any given conditions, and calculated effects are shown in Table 1.

4. There is convincing evidence that the part of the O₂ transport pathway, from muscle microvascular red cells to the mitochondria, considerably hinders O₂ transport and thus contributes significantly to the setting of maximal VO₂.

5. Some of this impedance occurs within the microvasculature related to the concentration of Hb, but the majority appears closely related the number of capillaries associated with each muscle fiber.

6. Preliminary evaluation of patients with chronic diseases such as heart failure, renal failure, and lung disease suggests that, in addition to obvious interference to convective O₂ transport to muscle (produced by low blood flow, [Hb], or arterial O₂ saturation, respectively), there is an intrinsic myopathic effect impeding O₂ transport within muscle. This may be due to capillary rarefaction, and if present, will require much work to elucidate. Success in this area could be of great clinical significance.

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CONTENTS

A Personal View of Muscle and Motility Mechanisms, H E Huxley 1
Determinants of Maximal Oxygen Transport and Utilization, P D Wagner 21

Mechanisms of Gene Expression and Cell Fate Determination in the Developing Pulmonary Epithelium, B P Hacket, C D Bingle, J D Gitlin 51
Formation of Pulmonary Alveoli and Gas-Exchange Surface Area: Quantitation and Regulation, G D Massaro, D Massaro 73
Morphogenesis of the Lung: Control of Embryonic and Fetal Branching, S R Hilfer 93
Molecular Mechanisms of Beta-Adrenergic Relaxation of Airway Smooth Muscle, M I Kotlikoff, K E Kamm 115
Defects in G Protein-Coupled Signal Transduction in Human Disease, A M Spiegel 143
Glucokinase Mutations, Insulin Secretion, and Diabetes Mellitus, G I Bell, S J Piklis, I T Weber, K S Polonsky 171

Molecular Mechanism of Growth Hormone Action, C Carter-Su, J Schwartz, L J Smit 187
Transgenic Approaches to Salivary Gland Research, L C Samuelson 209
Molecular Genetics of Early Liver Development, K S Zaret 231
The Trefoil Peptide Family, B E Sands, D K Podolsky 253
Intestine-Specific Gene Transcription, P G Traber, D G Silberg 275

Queer Current and Pacemaker: The Hyperpolarization-Activated Cation Current in Neurons, H-C Pape 299
Low-Threshold Calcium Currents in Central Nervous System Neurons, J R Huguenard 329
Persistent Sodium Current in Mammalian Central Neurons, W E Crill 349
Myocardial Potassium Channels: Electrophysiological and Molecular Diversity, D M Barry, J M Nerbonne 363
Cyclic Nucleotide-Gated Ion Channels: An Extended Family with Diverse Functions, J T Finn, M E Grunwald, K-W Yau 395

Physiology and Biochemistry of the Kidney Vacuolar H+-ATPase, S L Gluck, D M Underhill, M Iyori, L S Holliday, T Y Kostrominova, B S Lee 427
Thin Filament-Mediated Regulation of Cardiac Contraction, L S Tobacman 447
Inherited Diseases of the Vasculature, C L Shovlin, J Scott 483

The Polyclonal Origin of Myocyte Lineages, T Mikawa, D A Fischman 509
Multiple Roles of Carbonic Anhydrase in Cellular Transport and Metabolism, R P Henry 523
Downregulation of Cellular Metabolism During Environmental Stress: Mechanisms and Implications, S C Hand, I Hardewig 539
Post-Exercise Lactate Metabolism: A Comparative Review of Sites, Pathways, and Regulation, T T Gleeson 565
Upper Limits to Mass-Specific Metabolic Rates, R K Suarez 583
Molecular Mechanisms of Renal Apical Na/Phosphate Cotransport, H Murer, J Biber 607

Pathophysiology of the Aquaporin Water Channels, L S King, P Agre 619
Molecular Mechanisms of NaCl Cotransport, M R Kaplan, D B Mount, E Delpire, G Gamba, S C Hebert

Special Topic: Molecular Motors of Eukaryotic Cells, H L Sweeney

The Active Site of Myosin, I Rayment, C Smith, R G Yount

The Movement of Kinesin Along Microtubules, J Howard

The Kinetic Cycles of Myosin, Kinesin, and Dynein, D D Hackney

Mutational Analysis of Motor Proteins, H L Sweeney, E L F Holzbaur