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EVIDENCE FOR PERIPHERAL TISSUE DIFFUSION LIMITATION OF MAXIMUM O₂ UPTAKE

Peter D. Wagner, Jack Reeves, Bertron M. Groves, John Sutton, Allen Cymerman and Mark Malconian.

Department of Medicine, Section of Physiology
University of California, San Diego
La Jolla, CA 92093

and

Altitude Research Division
Department of the Army
U.S. Army Research Institute of Environmental Medicine
Natick, Mass. 01760

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Send correspondence to: Peter D. Wagner, M.D.
Department of Medicine, M-023A
University of California, San Diego
La Jolla, CA 92093
Evidence for Peripheral Tissue Diffusion Limitation of Maximal O2 Uptake

Maximum O2 consumption (VO2 max) is often said to be limited by blood O2 transport at sea level and by pulmonary diffusion disequilibrium at altitude. Neither of these mechanisms directly addresses the role of peripheral tissue O2 extraction. A retrospective analysis of directly measured mixed venous PO2 (PVO2) during exercise at both sea level and simulated altitude in 15 normal subjects revealed that PVO2 at VO2 max was very different at sea level compared to altitude. While even at submaximal workloads PVO2 at altitude readily fell below 20 torr, even at maximal workloads it remained at or above 20 torr at sea level in spite of a much higher VO2 max at sea level. Moreover, the relationship between VO2 max and PVO2 was linear through the origin in all subjects. On the assumption that at VO2 max, average effluent muscle capillary PO2 is proportional to PVO2, these data are compatible with the notion of tissue diffusion limitation of VO2 max. This argument is based on Fick's 1st law of diffusion further assuming that at VO2 max, mitochondrial PO2 is sufficiently close to zero to be negligible. Thus, one would predict that VO2 max is linearly dependent on the head of pre-
sure (P02) in the muscle capillary and by altering this P02 during altitude simulation, such linearity was demonstrated. Perhaps surprisingly, we found no difference in the PVO2/VO2 max relationship at altitude according to whether altitude exposure was acute or chronic. We suggest that: 1) VO2 max at any altitude is limited by peripheral tissue O2 diffusion between the capillary and the mitochondrion, 2) at any particular altitude, O2 delivery will set the actual VO2 max depending on the diffusing capacity of the tissues, with O2 delivery depending in turn on cardiac output, hemoglobin concentration and arterial O2 saturation.
Maximum oxygen uptake ($\dot{V}O_{2\text{max}}$) is often said to be limited by blood $O_2$ transport at sea level and by pulmonary diffusion disequilibrium at altitude. Neither of these mechanisms directly addresses the role of peripheral tissue $O_2$ extraction. A retrospective analysis of directly measured mixed venous $PO_2$ ($\dot{V}O_2$) during exercise at both sea level and simulated altitude in 15 normal subjects revealed that $\dot{V}O_2$ at $\dot{V}O_{2\text{max}}$ was very different at sea level compared to altitude. While even at submaximal workloads $\dot{V}O_2$ at altitude readily fell below 20 torr, even at maximal workloads it remained at or above 20 torr at sea level in spite of a much higher $\dot{V}O_{2\text{max}}$ at sea level.

Moreover, the relationship between $\dot{V}O_{2\text{max}}$ and $\dot{V}O_2$ was linear through the origin in all subjects. On the assumption that at $\dot{V}O_{2\text{max}}$, average effluent muscle capillary $PO_2$ is proportional to $\dot{V}O_2$, these data are compatible with the notion of tissue diffusion limitation of $\dot{V}O_{2\text{max}}$. This argument is based on Fick's 1st law of diffusion further assuming that at $\dot{V}O_{2\text{max}}$, mitochondrial $PO_2$ is sufficiently close to zero to be negligible. Thus, one would predict that $\dot{V}O_{2\text{max}}$ is linearly dependent on the head of pressure ($PO_2$) in the muscle capillary and by altering this $PO_2$ during altitude simulation, such linearity was demonstrated. Perhaps surprisingly, we found no difference in the $\dot{V}O_2/\dot{V}O_{2\text{max}}$ relationship at altitude according to whether altitude exposure was acute or chronic. We suggest that: 1) $\dot{V}O_{2\text{max}}$ at any altitude is limited by peripheral tissue $O_2$ diffusion between the capillary and the mitochondrion, 2) at any particular altitude, $O_2$ delivery will set the actual $\dot{V}O_{2\text{max}}$ depending on the diffusing capacity of the tissues, with $O_2$ delivery depending in turn on cardiac output, hemoglobin concentration and arterial $O_2$.
saturation.

Key words: maximum O\textsubscript{2} consumption
exercise
tissue diffusion
O\textsubscript{2} delivery
pulmonary diffusion
altitude
mixed venous P\textsubscript{O\textsubscript{2}}
INTRODUCTION

The steps that result in delivery of environmental O₂ to the mitochondria for energy generation are well-known. Alveolar ventilation delivers O₂ to the alveolar blood-gas barrier across which O₂ then diffuses and combines with hemoglobin. Blood containing O₂ is convected to the tissues where diffusional processes transport O₂ from the red cell to the intracellular sites of utilization. For many years there has been interest in how these linked processes function at maximum O₂ consumption (VO₂max), and especially which component might be the rate-limiting step that sets the upper limit on VO₂. There seems to be a general consensus that convective transport to the tissues by blood is the rate-limiting step in man at sea level (4, 11). However, others have suggested that it is not any component of the delivery system but rather that VO₂max is the result of maximal biochemical function of the mitochondrial energy generation system: Even if more O₂ could be supplied, it could not be used (9, 10). Still others have suggested a role for the central nervous system, especially at altitude. This is based on observations that at altitude (unlike sea level), muscle biopsies show little glycogen depletion at VO₂max (3).

The concept of a single rate-limiting process in determining VO₂max seems dissatisfying, however, at any metabolic rate less than that associated with true maximum biochemical utilization of O₂. It seems entirely possible that at less than full mitochondrial function, measured VO₂max could be raised by increasing the number of O₂ molecules delivered to the muscle per unit time. This in turn could be achieved by any factors that augment the
value of muscle $O_2$ delivery defined as the product of muscle bloodflow and arterial $O_2$ content. Potential factors include increases in bloodflow, hemoglobin concentration, arterial $O_2$ saturation and $O_2$ partial pressure.

Another phenomenon that seems to have received relatively little attention is the inability to completely extract $O_2$ from blood, even at $\dot{V}O_{2max}$. Only a few measurements of femoral venous or mixed venous $P_O_2$ have been made at $\dot{V}O_{2max}$, and while such $P_O_2$'s are low, they are not zero, and may be substantial. Thus, Pirnay et al. (10) noted that femoral venous $P_O_2$ did not fall below 17 torr while Andersen and Saltin (1) found femoral venous $P_O_2$ did not fall below 24 torr (sea level measurements); we found mixed venous $P_O_2$ measured at 80-90% of $\dot{V}O_{2max}$ and extrapolated to $\dot{V}O_{2max}$ was about 20 torr at sea level.

The key observation that led to the analysis in this paper is shown in figure 1 and pertains to mixed venous $P_O_2$ at several values of $\dot{V}O_{2max}$. This figure illustrates for one normal subject, mixed venous $P_O_2$ at several values of $\dot{V}O_2$, both at sea level and at simulated altitude (PB=347 torr). Equivalent altitude was 20,000 feet or 6096 m. Note that $PvO_2$ is much higher at sea level than at altitude and simultaneously $\dot{V}O_{2max}$ is also much higher at sea level. In fact, $PvO_2$ and $\dot{V}O_{2max}$ are essentially linearly related to one another by a line through the origin. In addition, $\dot{V}O_{2max}$ results in extraction of $O_2$ to different degrees at sea level compared to altitude. Importantly, extraction is not complete at either altitude. Based on those observations (confirmed in a total of 15 subjects), we offer the following analysis of how $\dot{V}O_{2max}$ may be determined.
ANALYSIS

Consider a vessel supplying a small region of skeletal muscle. For purposes of simplicity we ignore metabolism; bloodflow inequality throughout the muscle, and further consider all of the \( \text{O}_2 \) leaves the capillary at a single point spatially. It seems logical that these simplifications, used only for presentation purposes, can be removed later without altering the hypothesis.

The analysis is based on the concept of mass balance between capillary \( \text{O}_2 \) unloading (Fick principle), and tissue diffusion of \( \text{O}_2 \) from the capillary to the mitochondrion, (Fick's first law of diffusion). \( \text{O}_2 \) uptake by Fick principle is stated by the well-known relation:

\[
\dot{\text{V}}_{\text{O}_2} = \dot{\text{Q}}[\text{CaO}_2 - \text{CvO}_2]
\]  

(1)

where \( \dot{\text{Q}} \) is muscle bloodflow and \( \text{CaO}_2 \) and \( \text{CvO}_2 \) are \( \text{O}_2 \) contents of inflowing and effluent muscle capillary blood respectively.

Subsequent diffusion from the capillary to the mitochondrion can simply be expressed as

\[
\dot{\text{V}}_{\text{O}_2} = D_{\text{O}_2} [P_{\text{V}O_2} - P_{\text{mitO}_2}]
\]  

(2)

where \( D_{\text{O}_2} \) is some lumped parameter value of total conductance ("diffusing capacity") for \( \text{O}_2 \) over the complex pathway from the hemoglobin molecule in the red cell all the way to the mitochondrial site of utilization.

We will further assume that at \( \dot{\text{V}}_{\text{O}_2\text{max}} \), mitochondrial \( \text{P}_{\text{O}_2} \) is sufficiently low that it can be neglected, an assumption that appears reasonable (8).
Equation (2) then becomes

\[ \dot{V}O_2 = DO_2 \cdot PV_{O_2} \]  

(3)

Under steady state conditions, equations (1) and (3) must reflect the same quantities of \( O_2 \) being delivered per unit time. This mass conservation principle then leads to:

\[ \dot{V}O_2 = Q[CaO_2 - CvO_2] = DO_2 \cdot PV_{O_2} \]

Figure 2 plots \( \dot{V}O_2 \) both from equation (1) and equation (3) as a function of effluent venous \( PO_2 \). For equation (1), as \( PV_{O_2} \) increases from 0 to its hypothetical maximum value of inflowing arterial \( PO_2 \), \( \dot{V}O_2 \) will progressively fall towards zero. The relationship will be approximately linear because in the normal range of \( PV_{O_2} \) at \( \dot{V}O_{2\text{max}} \), \( PO_2 \) is on the steep, almost linear part of the \( O_2 \) Hb dissociation curve. For equation (3), the relationship between \( \dot{V}O_2 \) and \( PV_{O_2} \) is quite the opposite of that in equation (1): It is a straight line through the origin whose slope is the numerical value of the tissue \( O_2 \) conductance term \( DO_2 \) in equation (3). In words, the higher the effluent venous \( PO_2 \) (for a given bloodflow and arterial \( O_2 \) content), the lower will be \( \dot{V}O_2 \) calculated by Fick principle and the higher will be \( \dot{V}O_2 \) calculated by Fick's law of diffusion.

The point of intersection gives \( \dot{V}O_{2\text{max}} \). Thus, at any lower \( PV_{O_2} \), the Fick principle would allow a greater \( \dot{V}O_2 \) through greater extraction, but this could not in fact be realized because any lower \( PV_{O_2} \) could not support transport of \( O_2 \) by diffusion from the capillary to the mitochondrion. Any higher \( PV_{O_2} \) (than at the point of intersection of the two lines of figure 2)
could support a higher \( \dot{V}O_2 \) in terms of tissue diffusion but such a higher \( \dot{V}O_2 \) would not occur because the higher \( P_{V0_2} \) must per se be associated (equation (1)) with a lower actual \( \dot{V}O_2 \).

Figure 2 lends itself to further analysis. At any other muscle bloodflow, similar geometric expressions of equations (1) and (3) could be drawn, or alternatively for a given muscle bloodflow and arterial \( O_2 \) content, the relationships can be constructed for a muscle whose \( O_2 \) diffusive conductance (\( DO_2 \)) is different.

For a different bloodflow (but unchanged arterial \( O_2 \) content and \( DO_2 \)), effluent muscle \( PO_2 \) and \( \dot{V}O_{2\text{max}} \) would both change in the same direction as muscle bloodflow. Furthermore, the relationship between \( P_{V0_2} \) and \( \dot{V}O_{2\text{max}} \) will remain constrained by the same equation (equation (3)) as long as \( DO_2 \) is not altered by bloodflow. It is also easy to see how a change in arterial \( O_2 \) content will have qualitatively the same effect on \( P_{V0_2} \) and \( \dot{V}O_{2\text{max}} \) as will a change in muscle bloodflow (equation (3)).

The relationship between \( P_{V0_2} \) and \( \dot{V}O_{2\text{max}} \) would be altered differently if \( DO_2 \) were to increase. An increase in \( \dot{V}O_{2\text{max}} \) would be possible (at constant cardiac output and arterial \( O_2 \) content) while at the same time, \( P_{V0_2} \) would fall.

Figure 3 shows an extension of figure 2 to include a consideration of the effects of high altitude exposure causing a reduction in \( CaO_2 \). In particular, it shows the linear relationship to be expected between \( \dot{V}O_{2\text{max}} \) and \( P_{V0_2} \) at different altitudes. The major assumption of figure 3 is lack of change in \( DO_2 \) with altitude.
Examination of experimental data. The hypothesis of tissue diffusion limitation of $\dot{V}O_{2\text{max}}$ was developed in retrospect after examining data from two studies in which $P\dot{V}O_2$ at or near $\dot{V}O_{2\text{max}}$ was measured in 15 normal subjects (15,16). The purpose of these two studies was to examine pulmonary gas exchange rather than peripheral tissue events, and so the experimental design was not specifically formulated to test the hypothesis of peripheral tissue diffusion limitation. These studies have been described in detail and all that is needed from them are the values of mixed venous $PO_2$ and $\dot{V}O_{2\text{max}}$ in each subject at each exercise level. In both studies, simultaneous measurements of $\dot{V}O_2$ and $P\dot{V}O_2$ were made at rest and at several levels of steady state exercise up to 80-90% of $\dot{V}O_{2\text{max}}$, both at sea level and several simulated altitudes.

The first study (8 subjects) was an acute 1-day exposure to altitude (PB=429 torr and 523 torr or 15,000 feet and 10,000 feet equivalent altitudes respectively). It was done at Duke University in late 1983 (16). The second (7 subjects), referred to as Operation Everest II (OE II) (15), involved gradual simulated ascent to PB=240 torr equivalent in $P\dot{V}O_2$ to the summit of Mount Everest. In that study, data pertinent to the current paper were obtained at sea level and pressures of 347, 282 and 240 torr equivalent to 20,000, 25,000 and 29,000 feet above sea level (6096, 7620 and 8840 meters respectively). The relevant data appear in Tables I and II.

In both cases, mixed venous $PO_2$ was measured in blood samples drawn from an indwelling pulmonary artery catheter using conventional blood:gas electrodes. Oxygen uptake was measured by expired gas analysis using either a dry gas meter (15) or a Tissot spirometer (16) for ventilation and a mass
spectrometer (15) or gas chromatograph (16) for mixed expired O₂ and CO₂ concentrations. Close attention was paid to ensuring steady state conditions at all exercise loads which were set to achieve \( \dot{V}O_2 \) values of 80-90\% of \( \dot{V}O_{2\text{max}} \) (15) or a heart rate of about 175 min\(^{-1} \) (16). Only in OE II was true \( \dot{V}O_{2\text{max}} \) measured (15), and mixed venous PO₂ could thus be extrapolated to that value. \( \dot{V}O_{2\text{max}} \) was obtained on a separate occasion from when \( \overline{P}O_2 \) was measured (but at each altitude in which the studies measuring \( \overline{P}O_2 \) were conducted). In the acute altitude exposure study, given the high heart rates and lack of formal \( \dot{V}O_{2\text{max}} \) measurement, we have used the data assuming that at each altitude, the actual greatest \( \dot{V}O_2 \) achieved was a constant fraction of true \( \dot{V}O_{2\text{max}} \). Except for two specific occasions (Table I), we suggest that this is reasonable based on heart rate data and that any deviation from this assumption is probably a small random factor. If this assumption is true, linearity of the relationship between \( \overline{P}O_2 \) and greatest \( \dot{V}O_{2\text{max}} \) would still be expected although the slope of that relationship would not reflect the true value of DO₂: this estimate of tissue DO₂ would be systematically low, close to the same percentage as was the actual highest \( \dot{V}O_2 \) to \( \dot{V}O_{2\text{max}} \) (different by about 8\%, Table I). Two specific measurements were not used (Table I) because of clear-cut evidence of failure to achieve near-maximal heart rates. These were the PB=429 torr studies in subjects ML and DM.

RESULTS

Figures 4 and 5 present the entire set of relationships between measured mixed venous PO₂ and measured \( \dot{V}O_2 \) for both studies. Figure 4 represents acute altitude exposure while figure 5 refers to OE II. In figure 5 the
measured relationships are extrapolated to the independently measured values of $\dot{V}O_2_{\text{max}}$. Such extrapolations were done by hand and are seen to be generally of minor proportions.

It is remarkable that in all subjects the data lie close to a straight line through the origin. While all data in figure 4 fit the hypothesis well, figure 5 shows a curious systematic difference. The data at sea level, $PB=347$ torr and $PB=282$ torr fit extremely well, but this is not the case at the "summit" ($PB=240$ torr) in all 4 subjects in whom measurements were possible.

Figures 4 and 5 also show that the slopes of the $P\dot{V}O_2/\dot{V}O_2_{\text{max}}$ relationships vary considerably amongst the subjects of both studies. It is evident that those subjects with the lowest slopes (highest "$DO_2$") also have the highest $\dot{V}O_2_{\text{max}}$ values. Even though "$DO_2$" is determined by the ratio of $\dot{V}O_2_{\text{max}}$ to minimum $P\dot{V}O_2$, figures 4 and 5 indicate that there need not be any a priori relationship between "$DO_2$" and $\dot{V}O_2_{\text{max}}$. Thus it might have transpired, for example, that because of a lower cardiac output, $\dot{V}O_2_{\text{max}}$ may have been lower but $DO_2$ could still have remained high. Figure 6 shows the relationship between "$DO_2$" and $\dot{V}O_2_{\text{max}}$ (or greatest $\dot{V}O_2$ reached for the subjects of figure 4) and while $\dot{V}O_2_{\text{max}}$ does appear on both axes, there need not be such a clear relationship as figure 6 shows, as was argued above.

A more independent pair of variables is plotted in figure 7 to show the relationship between mixed venous $P_{O_2}$ (at $\dot{V}O_2_{\text{max}}$) and $\dot{V}O_2_{\text{max}}$ amongst all subjects at sea level. There is a clear correlation ($r=0.62$) between the two, such that a higher $\dot{V}O_2_{\text{max}}$ for any given subject is associated with a lower mixed venous $P_{O_2}$.
DISCUSSION

Assumptions. In considering the merits of this paper and its central hypothesis of tissue diffusion limitation of $\dot{V}O_2^{\text{max}}$, it should be remembered that the reported data were obtained before the hypothesis was ever conceived. Consequently, there are many assumptions and implications that, if not acceptable, may well refute the concept, and these should be presented to provide a foundation for any future work in this area. Perhaps the most important assumption is that of proportionality between mixed venous and effluent muscle capillary $P_O_2$. Note that equivalence is not necessary (because of Fick's law requiring that the $\dot{V}O_2^{\text{max}}/P_VO_2$ relationship pass through the origin). Further, proportionality is required only at $\dot{V}O_2^{\text{max}}$, at which $\dot{V}O_2$ the hypothesis is directed. We feel that the assumption is reasonable because of the extremely high cardiac output under most of the conditions that provided data for figures 4 and 5. Thus, cardiac output at $\dot{V}O_2^{\text{max}}$ was about 24 L/min throughout the acute altitude project (16) and at sea level, $PB=347$ and 282 torr, also in excess of 20 L/min in OE II. In fact, one possible explanation of the anomalous result at the summit (PB=240 torr) in OE II may be that because $\dot{V}O_2^{\text{max}}$ is low, so is cardiac output. While about 80-90% of the cardiac output of >20 L/min at sea level and intermediate altitudes must be perfusing exercising muscle, a considerably lower fraction will be devoted to muscle at the lower cardiac output on the "summit". Thus the blood returning from all tissues other than muscle contaminates returning muscle blood only to approximately 10-20%, except on the summit where the contamination was probably greater (assuming 4 L/min perfusing non-exercising tissues).
Perhaps the most direct and feasible approach to testing the assumption of proportionality between mixed venous and effluent muscle venous PO$_2$ would be to sample femoral venous and mixed venous blood simultaneously under all of the conditions of our studies. The literature was surprisingly found not to contain data of this type, and future evaluation of the diffusion limitation hypothesis must clearly examine femoral venous PO$_2$, even if some of that blood is derived from skin perfusion.

A second assumption is that in the acute altitude studies (figure 4) subjects reached a more or less constant fraction of $\dot{VO}_{2\text{max}}$ at the highest workload during which data were obtained at each altitude. Again, because of Fick's law of diffusion, a constant fraction of rather than equivalence to $\dot{VO}_{2\text{max}}$ is sufficient. Evidence supporting this assumption and also indicating how close each subject was to $\dot{VO}_{2\text{max}}$ (at sea level) came from heart rate data (Table 1) where the mean was 177±7 SD. $\dot{VO}_{2\text{max}}$ was estimated for each subject at sea level (Table 1) and the highest measured $\dot{VO}_2$ values expressed as a percentage of this estimate average 93±7 SD. Finally, heart rates at sea level, 10,000 feet and 15,000 feet averaged 177, 177 and 174 min$^{-1}$ respectively (excluding at 15,000 feet 2 subjects (ML and DM) who clearly did not reach heart rates close to their prior values at sea level or 10,000 feet). Taken together, these data support the use of these values as being very close to those expected at $\dot{VO}_{2\text{max}}$.

A third assumption pertains to steady state conditions necessary for equivalence of equations (1) and (3) in expressing $\dot{VO}_2$. In all subjects from both studies the data for this analysis were collected between the 3rd and 6th minutes of exercise at the heaviest workloads and between 5 and 10
minutes of exercise at lighter loads. Over these time periods, respiratory frequency, minute ventilation and heart rate were all constant to ±5%, and thus for the purposes of this analysis, a sufficiently steady state existed. Twenty second averages of VO₂ obtained from expired gas analysis by computer in OE II (12) showed no systematic variation in VO₂ during these time periods. End-tidal PO₂ and PCO₂ signals were constant to ±5% in the subjects from the acute altitude exposure study (16), but not measured in OE II.

A fourth assumption is that mitochondrial PO₂ is sufficiently close to zero that it can be neglected in equation (3). This is supported by data in the literature (8).

Finally, an implicit assumption of the foregoing analysis (but certainly not necessary for the hypothesis of tissue diffusion limitation itself) is that the effective diffusive conductance, DØ₂ of equation (3), is constant for any one subject amongst the various altitudes. It is certainly conceivable that acute altitude exposure (hypoxia) could alter vascular tone and thus potentially alter intercapillary distances and hence result in different "DØ₂" values from those at sea level. While this can probably be examined only by direct morphometric measurement at various altitudes, it is unlikely to be a factor at VO₂max. We feel it more reasonable that at VO₂max, irrespective of ambient PO₂, all working muscle vessels are fully dilated. An interesting issue does arise, however, for the subjects in OE II where extreme altitude was attained gradually over 40 days (15). It is possible that structural tissue adaptations such as reduction in muscle fiber size (2) and/or increased capillarity (13) occur to reduce intercapillary distances. The experiments performed in OE II do not directly address this
issue in a form pertinent to the current analysis: the best way to examine this possibility would be to study the same subjects (along the lines of this analysis) both after acute and after chronic altitude exposure. Tissue adaptation would be expected to result in an increased value for "DO₂" (i.e. a higher VO₂max at a lower capillary PO₂), and this could be directly tested by such an experiment. Until then, such considerations must remain speculative.

Alternative hypotheses. The observation that at VO₂max mixed venous PO₂ (and presumably effluent muscle venous PO₂) is considerably lower at altitude than at sea level (Tables I and II) despite much higher values of VO₂max at sea level is difficult to explain other than by the hypothesis of this paper. One possible alternative is that biochemical utilization of O₂ is truly at its maximum at sea level, and that additional O₂, even if available could not be used. Evidence against this explanation comes from reported increases in VO₂max while breathing elevated O₂ concentrations. This controversial area was reviewed by Welch (17) and despite difficulties of a technical nature in measuring VO₂ breathing high O₂ concentrations, 14 of 15 published studies reported an increase in VO₂max of 2-19% breathing gases of F1O₂ of 0.33 to 1.00 at sea level and also in hyperbaric studies. Further evidence against a biochemical limit to sea level VO₂max comes from studies in which hemoglobin concentration is acutely altered (4,7,14,20), whereby VO₂max increases and decreases in the same direction as hemoglobin levels.

The possibility that effluent muscle venous PO₂ is higher at sea level because of O₂ diffusion disequilibrium in the muscle capillary during unloading appears to require a reduced transit time as its basis. That
cardiac output was no higher at $\dot{V}O_{2\text{max}}$ at sea level compared to altitude in our subjects with acute altitude exposure (16) argues against this hypothesis.

**Data at the simulated summit of Mount Everest.** Figures 4 and 5 are remarkable for their consistency with the diffusion limitation hypothesis, except at PB=240 (Everest summit $P1O_2$) in the OE II experiment. It is difficult to explain the discrepancy. Maximum mean measured cardiac output in subjects 1,3 and 4 was 17.3 L/min at PB=282 and 18.0 L/min at PB=240. $\dot{V}O_{2\text{max}}$ for those three subjects at these altitudes were 1.86 L/min and 1.07 L/min respectively. One explanation could be that the subjects were not truly at $\dot{V}O_{2\text{max}}$ on the summit. The conditions were rather hectic and ensuring as good quality of measurement as at lower altitudes had to come second to concerns for the subjects' safety and comfort. Another possibility is some other dominant factor limiting performance at the summit (e.g. central nervous system influences unrelated to metabolic variables such as $PO_2$). While no clear answer can presently be given, the bulk of the measurements in the 15 subjects of both studies still fit the diffusion limitation hypothesis and further measurements under extreme hypoxia will be required to resolve the discrepancy on the summit.

**Limitation of $\dot{V}O_{2\text{max}}$ at sea level and simulated altitude.** As stated in the introduction, most physiologists appear to have concluded that $O_2$ delivery is the principal factor limiting $\dot{V}O_{2\text{max}}$ at sea level (4,11), while at altitude, pulmonary diffusion limitation becomes the critical factor (6,18).
This paper proposes a somewhat different view of what limits $\dot{V}O_{2\text{max}}$.

The central factor at any altitude is the capacity to transport O$_2$ by diffusion from the muscle capillary to the mitochondrion. The secondary factor is O$_2$ delivery (which is itself the product of the three principal terms: cardiac output, hemoglobin concentration and arterial O$_2$ saturation (ignoring dissolved O$_2$)). We propose that at any value of O$_2$ delivery, $\dot{V}O_{2\text{max}}$ is limited by tissue diffusion of O$_2$ from the red cell to the mitochondrial site of utilization. Specifically (as shown in figure 2), $\dot{V}O_{2\text{max}}$ is determined by the balance between what can be unloaded from blood as described by the Fick principle, and what can subsequently be transported to the mitochondrion by diffusion.

Any event that increases O$_2$ delivery (increased cardiac output, hemoglobin concentration or arterial O$_2$ saturation/PO$_2$) will increase $\dot{V}O_{2\text{max}}$. Equations (1) and (3) can be equated and solved to predict just how much increase in $\dot{V}O_{2\text{max}}$ is to be expected from a given change in O$_2$ delivery.

Finally, the relationship between O$_2$ delivery, $\dot{V}O_{2\text{max}}$ and effluent venous PO$_2$ can be altered by functional and/or structural tissue adaptations to, for example, exercise or chronic altitude exposure. Such alterations in "DO" would alter $\dot{V}O_{2\text{max}}$ for a given O$_2$ delivery in ways predictable from equations (1) and (3).

**Extension to the concept of critical PO$_2$.** In concept, the hypothesis of this paper fits the observation of a critical PO$_2$ (in the resting state) above which $\dot{V}O_2$ is independent of O$_2$ delivery and below which $\dot{V}O_2$ is proportional to O$_2$ delivery (5) as shown in figure 8. Suppose in reference to figure 8 a particular value of tissue DO$_2$ exists, thus leading to the line
through the origin having positive slope and describing Fick's law of
diffusion (compare figure 2). Also in figure 8, a number of lines of
negative slopes are drawn expressing \( \dot{V}O_2 \) by the Fick principle as a function
of venous \( P_O_2 \). Each line represents the allocation of a different cardiac
output but constant \( CaO_2 \). Assume resting \( \dot{V}O_2 \) is as marked by the dashed
horizontal line. Where that dashed line intersects the \( DO_2 \times P\dot{V}O_2 \) line,
yields the critical \( P\dot{V}O_2 \): at higher \( P\dot{V}O_2 \) values (occurring with higher
cardiac output values) diffusional transport is more than sufficient to
accommodate resting \( \dot{V}O_2 \). However, below critical \( P\dot{V}O_2 \), diffusional transport
capability is less than resting \( \dot{V}O_2 \) and so actual \( \dot{V}O_2 \) (solid circles) must
fall (and lie along the \( DO_2 \times P\dot{V}O_2 \) line) as \( P\dot{V}O_2 \) falls due to further
reductions in cardiac output. This analysis is compatible with the work of
Willford et al. (19) and extends the hypothesis from \( \dot{V}O_2\max \) down to resting
conditions.

**Future applications.** Should the tissue diffusion limitation hypothesis
be borne out by future work, diagrams such as figures 1, 4 and 5 might be
useful in analyzing adaptation to exercise or altitude. One could envisage
determining the \( \dot{V}O_2\max/P\dot{V}O_2 \) relationship prior to, and several weeks after an
exercise training program, or a sojourn at altitude. In each case, this
relationship requires measuring mixed venous or femoral \( P_O_2 \) at \( \dot{V}O_2\max \) at sea
level and at perhaps two values of reduced inspired \( P_O_2 \). Possible outcomes
and their interpretation are given in figure 9. One possible response of a
subject after exercise training might be to move further up the original
\( \dot{V}O_2\max/P\dot{V}O_2 \) relationship (to point A, figure 9 from the starting point 0),
which would be interpreted as an improvement in $\dot{V}O_{2\text{max}}$ produced by augmented $O_2$ delivery but without change in effective diffusing conductance for $O_2$ at the tissues. Another alternative might be to move from point O to point B on a new $DO_2/P\dot{V}O_2$ line. The necessary inference is that $\dot{V}O_{2\text{max}}$ was enhanced by a combination of increased $O_2$ delivery and increased tissue conductance. Yet another possibility is movement from O to C, and this would reflect an increase in tissue conductance with no augmentation of $O_2$ delivery. In all three cases in this specific illustration, $\dot{V}O_{2\text{max}}$ has been increased by the same amount, and it becomes possible to determine the individual contributions of $O_2$ delivery and of tissue conductance to such increases.
ACKNOWLEDGEMENTS

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REFERENCES


1986.


TABLE I. Acute altitude exposure. (Duke University study)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sea level, n=8</th>
<th>Pb=523, torr n=8</th>
<th>Pb=429, torr n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted $\dot{V}O_2_{max}$ L/min</td>
<td>Highest $\dot{V}O_2$ L/min</td>
<td>Lowest $PVO_2$ torr</td>
</tr>
<tr>
<td>ML</td>
<td>4.88</td>
<td>3.91</td>
<td>21</td>
</tr>
<tr>
<td>JG</td>
<td>3.17</td>
<td>2.89</td>
<td>24</td>
</tr>
<tr>
<td>BS</td>
<td>4.55</td>
<td>4.59</td>
<td>20</td>
</tr>
<tr>
<td>DM</td>
<td>2.54</td>
<td>2.20</td>
<td>27</td>
</tr>
<tr>
<td>RR</td>
<td>3.62</td>
<td>3.44</td>
<td>20</td>
</tr>
<tr>
<td>LM</td>
<td>2.08</td>
<td>2.08</td>
<td>21</td>
</tr>
<tr>
<td>TR</td>
<td>3.51</td>
<td>3.49</td>
<td>23</td>
</tr>
<tr>
<td>KS</td>
<td>3.60</td>
<td>3.16</td>
<td>15</td>
</tr>
<tr>
<td>Mean</td>
<td>3.49</td>
<td>3.22</td>
<td>21.4</td>
</tr>
<tr>
<td>SD</td>
<td>0.93</td>
<td>0.84</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*Data not used because of low heart rates suggesting failure to achieve $\dot{V}O_2_{max}$. 
TABLE II. Chronic altitude exposure (OE II).

<table>
<thead>
<tr>
<th>SL (n=7)</th>
<th>PB=347 (n=6)</th>
<th>PB=282 (n=5)</th>
<th>PB=240 (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>Measured VO$_{2}^{\text{max}}$</td>
<td>Extrapolated PVO$<em>{2}$ at VO$</em>{2}^{\text{max}}$</td>
<td>Measured VO$_{2}^{\text{max}}$</td>
</tr>
<tr>
<td>1</td>
<td>4.22</td>
<td>21</td>
<td>2.19</td>
</tr>
<tr>
<td>3</td>
<td>3.37</td>
<td>22</td>
<td>2.05</td>
</tr>
<tr>
<td>4</td>
<td>4.37</td>
<td>18</td>
<td>(2.23)</td>
</tr>
<tr>
<td>5</td>
<td>3.55</td>
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<td>1.77</td>
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<tr>
<td>8</td>
<td>4.48</td>
<td>19</td>
<td>2.12</td>
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<tr>
<td>9</td>
<td>3.06</td>
<td>26</td>
<td>1.60</td>
</tr>
<tr>
<td>$\bar{x}$</td>
<td>3.89</td>
<td>20.7</td>
<td>2.03</td>
</tr>
<tr>
<td>SD</td>
<td>0.56</td>
<td>3.0</td>
<td>0.30</td>
</tr>
</tbody>
</table>

* Swan-Ganz catheter could not be inserted.

** Subject removed from chamber prior to measurement at PB=282 and 240 torr. + subjects declined catheterization.

VO$_{2}^{\text{max}}$ in L/min; PVO$_{2}$ in torr.
FIGURE LEGENDS

Figure 1. Relationship between measured mixed venous $P_O^2$ and measured oxygen uptake at sea level and altitude ($P_B^2=347$ torr). Closed circles represent submaximal data and open circles extrapolations to measured maximum $\dot{V}O_2$. At maximum $\dot{V}O_2$, mixed venous $P_O^2$ is much less at altitude than at sea level, and both points lie on a straight line through the origin, the significance of which is explained in the text.

Figure 2. Graphical analysis of the relationship between convective unloading of oxygen from the muscle capillary (Fick principle) and diffusional transport of oxygen from the red cell to the mitochondrion (expressed by Fick's law of diffusion). These two expressions for oxygen transport can be represented by essentially straight lines on a diagram relating oxygen uptake to effluent muscle capillary $P_O^2$. The line with a negative slope expresses the Fick principle, while that with a positive slope, Fick's law. The point of intersection determines maximum $\dot{V}O_2$ as explained in the text. At $\dot{V}O_{2\text{max}}$, mitochondrial $P_O^2$ is assumed to be sufficiently close to zero as to be negligible for the purposes of this analysis.

Figure 3. Extension of the relationship between the Fick principle and Fick's law to conditions of altitude as well as sea level. The principle effect of altitude is to reduce arterial oxygen concentration which reduces the ordinate intercept of the Fick principle line as shown. For the same $\dot{D}O_2$, the point of intersection of the Fick principle and Fick law lines is
lower at altitude than at sea level. It is evident that one would expect a linear relationship through the origin between maximum oxygen uptake and effluent muscle capillary PO$_2$.

**Figure 4.** Data for 8 subjects showing the relationship between measured mixed venous PO$_2$ and measured oxygen uptake obtained during acute altitude exposure in the Duke University study referred to in the text. Data reflect sea level conditions (SL) and barometric pressures of 523 and 428 torr. Small solid circles are data at submaximal work rates, while the large symbols reflect the highest work rates and lowest mixed venous PO$_2$ values achieved. As shown in Table I, these reflect greater than 90% of predicted VO$_2$max on average. Notice that for each subject the data lie close to a line through the origin. Notice also that the slope of this line varies greatly amongst different subjects, reflecting different values of apparent tissue diffusing capacity.

**Figure 5.** Similar plots to those in figure 4 for chronic altitude exposure as observed in Operation Everest II (OE II). Data are shown for sea level, and barometric pressures of 347, 282 and 240 torr. Except at 240 torr, the relationship between mixed venous PO$_2$ and oxygen uptake at maximum VO$_2$ is linear as in figure 4. Again, the slopes of the linear relationship vary amongst the 7 subjects, indicating different levels of tissue diffusing capacity.
Figure 6. Relationship between maximum \( \dot{V}_O_2 \) and the calculated tissue diffusing capacity for both the acute (Duke) and chronic (OE II) altitude exposure studies. A good correlation is seen, and there is no difference between acute and chronic exposure apparent. This figure shows that subjects with a higher maximum oxygen consumption also have a higher tissue diffusing capacity.

Figure 7. Relationship between maximum \( V_O_2 \) at sea level and mixed venous \( P_O_2 \) at maximum \( \dot{V}_O_2 \) for the subjects from OE II (solid circles). Open circles reflect the Duke data which were obtained at an average of 93% of \( \dot{V}_O_2_{max} \). Although the relationship is not strong, those subjects with a higher \( \dot{V}_O_2_{max} \) had a lower mixed venous \( P_O_2 \). There was no apparent difference in this relationship between the two studies.

Figure 8. Theoretical explanation for the concept of the critical \( P_O_2 \), based on the same hypothesis as used to explain maximum oxygen consumption. As explained more fully in the text, at venous \( P_O_2 \)'s (and thus oxygen deliveries) above the critical \( P_O_2 \), tissue diffusing capacity is more than sufficient to meet the demands of resting \( \dot{V}_O_2 \). Below the critical \( P_O_2 \), tissue diffusing capacity is insufficient to deliver the oxygen required by resting metabolism (horizontal dashed line) and thus actual oxygen uptake must fall along the diffusing capacity line. The sequence of solid circles shows the relationship between actual \( \dot{V}_O_2 \) and venous \( P_O_2 \) as oxygen delivery is progressively reduced from right to left. Thus, the diffusion limitation hypothesis of \( \dot{V}_O_2_{max} \) can also be used to explain the development
of a critical $P_O_2$ when oxygen delivery is reduced at rest.

Figure 9. Hypothetical analysis of the effects of exercise training. The diagram relating oxygen uptake and venous $P_O_2$ used throughout this paper is again shown, and it is suggested that it can be used to analyze the improvement in maximum $\dot{V}O_2$ afforded by training. If a subject prior to training has a maximum oxygen uptake and mixed venous $P_O_2$ indicated by point 0, points A, B and C show three different ways in which a given increment in maximum oxygen uptake could be achieved.

Point A comes about with no change in tissue diffusing capacity, and only an augmentation in oxygen delivery. Point C represents the converse, namely, an increase in tissue diffusing capacity and no increase in oxygen delivery. Point B represents necessarily a combination of an increase in both tissue diffusing capacity and oxygen delivery. By assessing maximum oxygen uptake and mixed venous $P_O_2$ before and after training, it should be possible to partition the improvement in oxygen uptake quantitatively into that component due to improvement in tissue diffusion capability and that due to augmented oxygen delivery.
Relationship between measured mixed venous PO$_2$ and measured oxygen uptake at sea level and altitude (P_B=347 torr). Closed circles represent submaximal data and open circles extrapolations to measured maximum VO$_2$. At maximum VO$_2$, mixed venous PO$_2$ is much less at altitude than at sea level, and both points lie on a straight line through the origin, the significance of which is explained in the text.
\[ \dot{V}O_2 = \dot{Q} [CaO_2 - CvO_2] \]
\[ \dot{V}O_2 = DO_2 \left( PvO_2 - PmitO_2 \right) = DO_2 \times PvO_2 \]

**FIGURE 2.**

Graphical analysis of the relationship between convective unloading of oxygen from the muscle capillary (Fick principle) and diffusional transport of oxygen from the red cell to the mitochondrion (expressed by Fick's law of diffusion). These two expressions for oxygen transport can be represented by essentially straight lines on a diagram relating oxygen uptake to effluent muscle capillary PO\(_2\). The line with a negative slope expresses the Fick principle, while that with a positive slope, Fick's law. The point of intersection determines maximum \( \dot{VO}_2 \) as explained in the text. At \( \dot{VO}_2\) max, mitochondrial PO\(_2\) is assumed to be sufficiently close to zero as to be negligible for the purposes of this analysis.
Figure 3.

Extension of the relationship between the Fick principle and Fick's law to conditions of altitude as well as sea level. The principle effect of altitude is to reduce arterial oxygen concentration which reduces the ordinate intercept of the Fick principle line as shown. For the same $DO_2$, the point of intersection of the Fick principle and Fick law lines is lower at altitude than at sea level. It is evident that one would expect a linear relationship through the origin between maximum oxygen uptake and effluent muscle capillary $PO_2$. 

\[ \dot{Q} [CaO_2 - CvO_2] \]

**MUSCLE VENOUS $PO_2$ ($PvO_2$)**

$DO_2 \times PvO_2$

$VO_2$ MAX

0 arterial

OXYGEN UPTAKE
Data for 8 subjects showing the relationship between measured mixed venous PO$_2$ and measured oxygen uptake obtained during acute altitude exposure in the Duke University study referred to in the text. Data reflect sea level conditions (SL) and barometric pressures of 523 and 428 torr. Small solid circles are data at submaximal work rates, while the large symbols reflect the highest work rates and lowest mixed venous PO$_2$ values achieved. As shown in Table I, these reflect greater than 90% of predicted VO$_2$max on average. Notice that for each subject the data lie close to a line through the origin. Notice also that the slope of this line varies greatly amongst different subjects, reflecting different values of apparent tissue diffusing capacity.
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Similar plots to those of figure 4 for chronic altitude exposure as observed in Operation Everest II (OE II). Data are shown for sea level, and barometric pressures of 347, 282 and 240 torr. Except at 240 torr, the relationship between mixed venous PO2 and oxygen uptake at maximum VO2 is linear as in figure 4. Again, the slopes of the linear relationship vary amongst the 7 subjects, indicating different levels of tissue diffusing capacity.
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Relationship between maximum \( \dot{V}O_2 \) at sea level and mixed venous \( PO_2 \) at maximum \( \dot{V}O_2 \) for the subjects from OE II (solid circles). Open circles reflect the Duke data which were obtained at an average of 93% of \( \dot{V}O_2_{max} \). Although the relationship is not strong, those subjects with a higher \( \dot{V}O_2_{max} \) had a lower mixed venous \( PO_2 \). There was no apparent difference in this relationship between the two studies.
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