A theoretical model for oxygen transport in skeletal muscle under conditions of high oxygen demand

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McGuire, B. J., and T. W. Secomb. A theoretical model for oxygen transport in skeletal muscle under conditions of high oxygen demand. J Appl Physiol 91: 2255–2265, 2001.—Oxygen transport from capillaries to exercising skeletal muscle is studied by use of a Krogh-type cylinder model. The goal is to predict oxygen consumption under conditions of high demand, on the basis of a consideration of transport processes occurring at the microvascular level. Effects of the decline in oxygen content of blood flowing along capillaries, intravascular resistance to oxygen diffusion, and myoglobin-facilitated diffusion are included. Parameter values are based on human skeletal muscle. The dependence of oxygen consumption on oxygen demand, perfusion, and capillary density are examined. When demand is moderate, the tissue is well oxygenated and consumption is slightly less than demand. When demand is high, capillary oxygen content declines rapidly with axial distance and radial oxygen transport is limited by diffusion resistance within the capillary and the tissue. Under these conditions, much of the tissue is hypoxic, consumption is substantially less than demand, and consumption is strongly dependent on capillary density. Predicted consumption rates are comparable with experimentally observed maximal rates of oxygen consumption.

Oxygen transport from blood into tissue occurs by passive diffusion. The maximum distance that oxygen can diffuse from a blood microvessel into surrounding tissue decreases with increasing oxygen consumption rate and is a few tens of micrometers in tissues with high oxygen demand, such as heavily working skeletal muscle. For a tissue with a given capillary density, the diffusion of oxygen to the mitochondria where it is consumed is one of the factors limiting the maximal rate of oxygen consumption (VO2 max). Observations of maximally working single muscles in humans have shown a substantial oxygen saturation in the venous blood, in the range 15–30% (1, 28, 24, 25), showing that oxygen extraction is incomplete, reflecting diffusive limitation of oxygen transport (33). More complete extraction of the oxygen available in the blood would result in very low values for the partial pressure of oxygen (PO2) at the venous end of capillaries, which would not provide a sufficient PO2 gradient for oxygen diffusion. Clearly, both convective and diffusive limitations of oxygen transport are important in determining VO2 max.

A further factor that may limit the oxygen consumption of strongly stimulated muscle is the maximal rate of turnover of mitochondrial enzymes in the Krebs cycle, which limits oxygen demand. Blomstrand et al. (3) showed a correlation between the oxygen consumption rate of a maximally working human leg muscle and the maximal activity of the enzyme oxoglutarate dehydrogenase. Thus limited oxygen demand, perfusion limitation, and diffusion limitation may all play a part in determining VO2 max in skeletal muscle.

At the microvascular level, the distribution of PO2 in tissue surrounding microvessels in heavily working muscle has been debated. In some analyses of oxygen diffusion from blood to tissue (see below), it has been assumed that the decline in PO2 occurs mainly in the tissue. However, studies of dog gracilis muscle at VO2 max (11) showed low values and small gradients of PO2 throughout most of the tissue. The results were attributed to effects of the particulate nature of blood on oxygen transport within capillaries and to the facilitation of oxygen transport by myoglobin. Richardson et al. (26) used magnetic resonance spectroscopy to measure average myoglobin saturation in exercising human skeletal muscle and concluded that average tissue PO2 is low during maximal exercise. These studies suggested that PO2 declines steeply in the radial direction inside capillaries and within the first few micrometers outside capillaries, with small gradients in the bulk of the tissue.

Since the classical work of Krogh (19), many investigations of oxygen transport to skeletal muscle have used theoretical models (22). Krogh’s model is based on the following assumptions: each capillary is the sole oxygen supply for a surrounding cylindrical region of tissue, the PO2 at the vessel wall is assumed to equal that of the blood, the decline of PO2 along a capillary is neglected, oxygen diffuses radially from the capillary, and consumption is uniform in the tissue. In subsequent models (21), several of these assumptions were
relaxed. For example, Blum (4) included axial decline in blood Po2 and considered both constant and linear oxygen uptake kinetics. The importance of intravascular resistance to oxygen transport from blood to tissue was shown by Hellums (14) and Hellums et al. (15). Theoretical estimates of the minimum Po2 required to achieve complete tissue oxygenation at maximal consumption in a variety of muscles and species were obtained by Roy and Popel (29).

Federspiel (9) developed a two-dimensional model of oxygen delivery to a muscle fiber with a prescribed distribution of Po2 at its surface. Groebe and Thews (12) considered a single cylindrical muscle fiber with several adjacent capillaries in an effort to evaluate the effects of model geometry on predicted Po2 profiles in heavily working muscle. Both studies predicted relatively shallow gradients of Po2 within muscle fibers, as observed by Gayeski and Honig (11). Secomb and Hsu (30) computed the Po2 at each point in a finite tissue domain, taking into account the effects of all microvessels within the domain. Their model showed that Po2 levels in capillaries in resting skeletal muscle can be strongly influenced by oxygen diffusion from arterioles at distances of 100 μm or more. As oxygen consumption rate increases, such relatively long-range effects become less important, and when consumption is very high, the assumption of the Krogh model, that each point in the tissue receives oxygen only from the nearest capillary, becomes increasingly justified. Under such conditions, the use of a model based on the Krogh cylinder concept is appropriate.

The goal of the present study is to use a theoretical model for oxygen transport from capillaries to exercising skeletal muscle to predict the dependence of oxygen consumption rate on oxygen demand, on the basis of a consideration of transport processes occurring at the microvascular level. A wide range of oxygen demand is considered, including conditions of high oxygen demand in which a significant fraction of the tissue becomes hypoxic (Po2 < 1 Torr). None of the previous models cited above has analyzed the dependence of oxygen consumption on demand under such conditions. Oxygen consumption is assumed to depend on Po2 according to Michaelis-Menten kinetics, and results are compared with those obtained when zero-order consumption kinetics is assumed. Nonuniform oxygen consumption due to mitochondrial clustering around the capillary is considered. Effects of the decline of oxygen content in blood flowing through capillaries, intravascular resistance to oxygen diffusion, and myoglobin-facilitated diffusion are included. As in the Krogh cylinder model, the capillaries are assumed to be parallel and evenly spaced, so that each capillary supplies oxygen to a surrounding uniform cylindrical region of tissue. A range of capillary densities is considered.

This model is used to investigate the roles played by oxygen demand, perfusion limitation, and diffusion limitation in determining VO2max of skeletal muscle. Profiles of Po2 in the tissue surrounding the capillary are determined and are compared with measurements of tissue Po2 in maximally stimulated skeletal muscle. The overall average oxygen consumption rate as a function of demand is calculated and compared with experimental VO2max values in human skeletal muscle. Previous studies (29) have explored the relationship between oxygen transport at the capillary level and VO2max. However, no theoretical results including all the factors considered here have previously been compared with experimentally determined oxygen consumption rates. The results are used to test the hypothesis that oxygen consumption rates in maximally stimulated skeletal muscle can be predicted on the basis of observed values of capillary density, blood perfusion, and oxygen transport parameters in blood and in tissue.

**METHODS**

**Governing equations.** The tissue is represented as an array of uniformly spaced cylinders with capillaries along the axes. Each tissue cylinder is assumed to be supplied with oxygen exclusively by the capillary within it (Fig. 1). Oxygen diffusion in the axial direction is neglected, as evidenced by the fact that the Po2 gradients are much steeper in the radial direction than in the axial direction. Then Fick’s law of diffusion and conservation of mass lead to the following equation for oxygen diffusion in muscle tissue

\[ K \left( \frac{1}{r} \frac{d}{dr} \left( r \frac{dP}{dr} \right) \right) = M(P) \]  

where P is the partial pressure of oxygen at a radial distance of r within the tissue cylinder, K (the Krogh diffusion coefficient) is the product of the diffusivity and solubility of oxygen in tissue, and M(P) is the oxygen consumption rate per unit volume of the tissue cylinder. With Michaelis-Menten kinetics, \( M(P) = M_0 \frac{P}{P_0 + P} \), where \( M_0 \) is the oxygen demand, i.e., the consumption when the oxygen supply is not limiting, and \( P_0 \) is the Po2 at which consumption is half of the demand. With zero-order kinetics, \( M = M_0 \) when \( P > 0 \) and \( M = 0 \) when \( P = 0 \).

At the blood-tissue interface, both Po2 and oxygen flux must be continuous. Because of intravascular resistance to oxygen diffusion, the Po2 at the blood-tissue interface may be less than the average Po2 within the blood. This effect can be represented approximately (15) by \( \frac{q}{v} = M \left( \frac{P_b - P(R_c)}{R_c} \right) \) where q is the rate of oxygen diffusion from the capillary per unit length, \( M \) is a mass transfer coefficient, \( P_b \) is the average partial pressure of oxygen within the blood, and \( P(R_c) \) is the

![Fig. 1. Geometry of the Krogh cylinder-type model. Inner cylinder represents the capillary. Outer cylinder corresponds to tissue cylinder. Shaded area: example of hypoxic region under conditions of high demand. \( R_t \), tissue cylinder radius; \( R_c \), capillary radius; z, distance along the capillary.](http://jap.physiology.org/)
partial pressure of oxygen at the capillary wall, \( r = R_c \). Equating this to the diffusive flux into the tissue gives the following boundary condition at the capillary wall
\[
2\pi R_c \frac{dP}{dr}
\bigg|_{r=R_c} = -M_n [P_b - P(R_c)]
\]
(2)

The capillary walls are considered to be part of the tissue region. It is assumed that no oxygen is exchanged across the outer boundary of the tissue cylinder, so that
\[
\frac{dP}{dr}
\bigg|_{r=R} = 0
\]
(3)

where \( R \) is the tissue cylinder radius.

The effects of myoglobin-facilitated diffusion of oxygen within the tissue are included mathematically by defining the myoglobin-facilitated PO2 (10) as
\[
P^* = P + (D_{Mb}C_{Mb}V_m/K)S_{Mb}(P)
\]
(4)

where \( D_{Mb} \) is the diffusion coefficient for myoglobin, \( C_{Mb} \) is the total concentration of myoglobin, \( S_{Mb}(P) \) is its oxygen saturation, and \( V_m \) is the molar volume, and by replacing \( P \) with \( P^* \) where it refers to tissue PO2, i.e., in Eqs. 1 and 3 and the left-hand side of Eq. 2.

Clustering of mitochondria around capillaries has been observed (16). Because oxygen consumption takes place almost entirely within the mitochondria, such clustering would lead to increased oxygen demand where the mitochondria are dense and very low demand where they are sparse. Mitochondrial clustering is represented in the model as increased oxygen demand with Michaelis-Menten kinetics in an inner cylindrical region around the capillary and no oxygen consumption in the outer region. To show the effects of clustering independent of changes in overall demand, the average demand in the entire cylinder is held at a fixed level in these calculations.

As blood flows along the capillary, oxygen is extracted and the average PO2 in the blood (\( P_b \)) declines. By conservation of mass, the decline of convective oxygen flux must equal \( \dot{q} \), i.e.,
\[
\frac{d}{dz}(\dot{Q}C) = -\dot{q}
\]
(5)

where \( \dot{Q} \) is blood flow rate and \( z \) is distance along the capillary. The oxygen content of blood is given by \( C = C_B S_{Hb}(P) \), where \( C_B \) is the carrying capacity of blood at 100% saturation and the oxyhemoglobin saturation is described using the Hill equation (22)
\[
S_{Hb}(P) = \frac{(P/P_{50})^n}{1 + (P/P_{50})^n}
\]
(6)

where \( P_{50} \) is the Po2 at which hemoglobin is 50% saturated and \( n \) is a constant. This is a good approximation, except in cases of extremely rapid unloading of oxygen by red blood cells. The red cell transit time assumed here is much larger than the time constant for oxyhemoglobin dissociation, and so the Hill equation is appropriate.

Parameter values. Parameter values are chosen to represent blood flow in human skeletal muscle under physiological conditions and are summarized in Table 1. At high flow rates, such as assumed here, the decline in PO2 in arterioles is small, and the Po2 entering the capillary is assumed to equal that of the arterial blood, i.e., \( P_b = 100 \) Torr when \( z = 0 \). Experimentally determined values for \( K \) in skeletal muscle range from \( 5 \times 10^{-10} \) to \( 10 \times 10^{-10} \) (cm²/s)(cm³ O₂/cm³). Here, \( K = 9.4 \times 10^{-10} \) (cm²/s)(cm³ O₂/cm³) is assumed (2). To model the effects of myoglobin, the following parameter values are assumed:
\[
D_{Mb} = 1.73 \times 10^{-7} \text{ cm}^2/\text{s} \quad (18) \quad C_{Mb} = 3.83 \times 10^{-7} \text{ mol/cm}^3 \quad (20) \quad V_m = 2.24 \times 10^4 \text{ cm}^3
\]

The oxygen-myoglobin saturation \( S_{Mb}(P) \) is represented by a Michaelis-Menten equation, with half-saturation at a PO2 of \( P_{Mb50} = 3.2 \) Torr (26).

The oxygen content of blood depends on the oxyhemoglobin saturation and the oxygen carrying capacity of the blood at full saturation. The PO2 at which hemoglobin is 50% saturated, \( P_{50} \), indicates hemoglobin’s oxygen affinity. Under standard conditions, \( P_{50} \) is ~26 Torr for human blood (22). Numerous studies have shown that \( P_{50} \) increases during

Table 1. Summary of parameter values used in model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_b )</td>
<td>Average blood PO2 at capillary entrance</td>
<td>100 Torr</td>
</tr>
<tr>
<td>( P_{50} )</td>
<td>Half-maximal hemoglobin saturation</td>
<td>26, 39 Torr</td>
</tr>
<tr>
<td>( n )</td>
<td>Hill equation exponent</td>
<td>2.7</td>
</tr>
<tr>
<td>( C_r )</td>
<td>Oxygen carrying capacity of blood</td>
<td>0.2 cm³ O₂/cm³ blood</td>
</tr>
<tr>
<td>( Sh )</td>
<td>Sherwood number</td>
<td>1.5–2.5</td>
</tr>
<tr>
<td>( K_{pl} )</td>
<td>Krogh diffusion constant in plasma</td>
<td>( 8.3 \times 10^{-10} ) (cm²/s)(cm³ O₂/cm³·Torr⁻¹)</td>
</tr>
<tr>
<td><strong>Tissue parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \dot{V} )</td>
<td>Average blood flow</td>
<td>2.25, 3.49 mm/s</td>
</tr>
<tr>
<td>( K )</td>
<td>Krogh diffusion constant in tissue</td>
<td>( 9.4 \times 10^{-10} ) (cm²/s)(cm³ O₂/cm³·Torr⁻¹)</td>
</tr>
<tr>
<td>( M_0 )</td>
<td>Oxygen demand</td>
<td>0–80 cm³ O₂·100 cm²·min⁻¹</td>
</tr>
<tr>
<td>( P_6 )</td>
<td>Half-maximal oxygen consumption</td>
<td>1 Torr</td>
</tr>
<tr>
<td>( D_{Mb} )</td>
<td>Myoglobin diffusion coefficient</td>
<td>( 1.73 \times 10^{-7} ) cm²/s</td>
</tr>
<tr>
<td>( C_{Mb} )</td>
<td>Concentration of myoglobin</td>
<td>( 3.83 \times 10^{-7} ) mol/cm³</td>
</tr>
<tr>
<td>( P_{50Mb} )</td>
<td>Half-maximal myoglobin saturation</td>
<td>3.2 Torr</td>
</tr>
<tr>
<td>( N )</td>
<td>Capillary density</td>
<td>468–1,000 capillaries/mm²</td>
</tr>
<tr>
<td><strong>Geometric parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( R_c )</td>
<td>Capillary radius</td>
<td>2.5 μm</td>
</tr>
<tr>
<td>( L )</td>
<td>Capillary length</td>
<td>0.5 mm</td>
</tr>
<tr>
<td>( R_t )</td>
<td>Tissue cylinder radius</td>
<td>18–26 μm</td>
</tr>
</tbody>
</table>

Where multiple values of a parameter are considered, bold values represent the standard case.
exercise, a “right shift” of the oxyhemoglobin dissociation curve, enhancing oxygen unloading. Endurance training has also been shown to cause an increase in P_{50} in trained muscle. Thomson et al. (31) observed a P_{50} of 38.8 Torr in a range of capillary densities from 468 to 1,000 capillaries/mm².

To show the effects of demand on consumption, a muscle. Thomson et al. (31) observed a P_{50} of 38.8 Torr in a range of capillary densities from 468 to 1,000 capillaries/mm². The dependence of oxygen consumption on P_{O2} is not considered, and a reference value of 40 cm³ O₂ from 1.5 to 3 are consistent with available data. Here, Sh = 2.5 is assumed, except where noted, and K_{pl} = 8.3 × 10^{-10} (cm²/s) (cm³ O₂·cm⁻³·Torr⁻¹), giving M = 6.52 × 10^{-9} (cm²/s) (cm³ O₂·cm⁻³·Torr⁻¹).

Numerical procedures. The capillary is discretized into 100 points along its length. At each point, Eqs. 1, 3, and 4 are solved numerically to determine the radial profile of P_{O2}. The total consumption per unit length is found by numerically integrating the consumption per unit volume over the cross section of the tissue cylinder, i.e.

\[ q = \int_{V_c}^{p_0} M(P) 2\pi r dr \quad (8) \]

The decline in blood oxygen content to the next nodal point is then computed using Eq. 5, and the corresponding P_{0} at that point is obtained by solving Eq. 6. This procedure is repeated along the length of the capillary. For each value of M, the consumption rate averaged over the entire tissue cylinder, \( M(P) \), is computed. In hypoxic regions, consumption falls below demand according to Michaelis-Menten consumption kinetics, so average consumption may be less than M_{0}.

RESULTS

Figure 2 shows the predicted variation of P_{O2} with position in the tissue cylinder, including effects of intravascular resistance and myoglobin-facilitated diffusion. The decline in the average blood P_{O2} as it flows down the length of the capillary is shown in Fig. 2A.

Radial P_{O2} profiles at three distances along the capillary are shown in Fig. 2B. At each location along the cylinder, P_{O2} declines with increasing distance from the capillary. The P_{O2} in the tissue adjacent to the capillary is substantially lower than the mean P_{O2} within the capillary as a result of intravascular resistance to radial oxygen transport. In reality, intracapillary P_{O2} is continuous with the tissue P_{O2} but varies with both position and time as red blood cells traverse the capillary. For simplicity, only the average intracapillary level is shown in Fig. 2B. At the upstream end of the capillary (\( z = 0 \)), the P_{O2} remains relatively high throughout the tissue, dropping from 78.9 Torr at the capillary wall to 35.5 Torr at the outer boundary of the cylinder. However, P_{O2} declines rapidly along the cylinder. At the midpoint (\( z = L/2 \)), the mean intravascular P_{O2} is 34.7 Torr, and the tissue P_{O2} drops to 0.5 Torr at the outer edge of the cylinder. At this point, much of the tissue is hypoxic, leading to a reduced rate of oxygen consumption, according to Michaelis-Menten kinetics. Beyond this point, intravascular P_{O2} declines more slowly, because less oxygen is being consumed per unit capillary length.

Figure 3 shows cumulative frequency distributions of tissue P_{O2} and myoglobin saturation, when demand is 40 cm³ O₂·100 cm⁻³·min⁻¹. Figure 3A indicates that...
a large fraction of tissue has low tissue PO2. With 468 capillaries/mm² and P50 = 26 Torr, 37% of the tissue is hypoxic (PO2 < 1 Torr) and more than 90% of the tissue has a PO2 less than 12.5 Torr. Increasing capillary density to 600 capillaries/mm² reduces the fraction of tissue that is hypoxic to 20%. If a right shift in the oxyhemoglobin dissociation curve is considered (by linearly increasing P50 from 26 Torr at the arterial end to 39 Torr at the venous end of the capillary) in addition to an increased capillary density of 600 capillaries/mm², 1.4% of the tissue is hypoxic. The corresponding distributions of myoglobin saturation are shown in Fig. 3B, indicating that saturation is fairly evenly distributed over a wide range.

The relationship between oxygen supply, demand, and consumption is shown in Fig. 4. The rate of convective oxygen supply to the tissue cylinder is 49.2 cm³ O₂•100 cm⁻²•min⁻¹, and this represents an upper limit to consumption. The demand is the rate at which oxygen would be consumed if all the tissue was well oxygenated. At low levels of demand (M₀ < 10 cm³ O₂•100 cm⁻³•min⁻¹), the consumption is equal to the demand, but at higher levels, consumption falls short of demand. The limited ability of oxygen to diffuse into the tissue restricts the consumption that is achieved. Predicted consumption decreases with increasing intravascular resistance, i.e., with decreasing Sh. In the absence of intravascular resistance to oxygen diffusion, a demand of 40 cm³ O₂•100 cm⁻³•min⁻¹ results in a predicted consumption rate of 30.3 cm³ O₂•100 cm⁻²•min⁻¹.
Inclusion of the effects of intravascular resistance to oxygen transport further reduces the predicted rate of consumption. For example, when the demand is 40 cm$^3$ O$_2$·cm$^{-3}$·min$^{-1}$, the predicted consumption is 24.7 cm$^3$ O$_2$·cm$^{-3}$·min$^{-1}$ for the standard value of intravascular resistance ($Sh = 2.5$). The effect of varying the intravascular resistance is also shown in Fig. 4. The limit $Sh \to \infty$ corresponds to the case of no intravascular resistance.

To assess the sensitivity of the results to the assumed Michaelis-Menten oxygen uptake kinetics, further calculations were carried out with the assumption that local consumption equals demand until the PO$_2$ falls to zero (zero-order kinetics). The region of tissue that receives oxygen is smaller with zero-order kinetics than with Michaelis-Menten, but the consumption rate is higher. Overall, zero-order kinetics increase oxygen consumption by 3% (from 24.7 to 25.5 cm$^3$ O$_2$·cm$^{-3}$·min$^{-1}$) relative to Michaelis-Menten kinetics when $M_0 = 40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$.

The diffusive resistance to oxygen transport depends on the capillary density, $N$. For a given level of oxygen demand, increasing $N$ decreases the amount of oxygen that each capillary must deliver, and so a smaller PO$_2$ gradient is needed to produce the necessary flux. Furthermore, higher $N$ corresponds to a smaller $R_t$ and therefore a shorter distance over which oxygen must diffuse. Consequently, predicted oxygen consumption increases substantially with increasing $N$, as shown in Fig. 5. Increasing $N$ from 468 to 800 capillaries/mm$^2$ increases predicted consumption by 33%, to 32.8 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ when $M_0 = 40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$.

A conceptual model has previously been proposed (33) in which $V\dot{O}_2$ max is determined by the condition that the PO$_2$ at the venous end of each capillary equals the minimum PO$_2$ required for complete oxygenation of the adjacent tissue. This concept is explored in Fig. 6, which shows the variation of predicted mean intravascular PO$_2$ at the venous end of capillaries with oxygen consumption rate (solid line). Because the perfusion rate is assumed to be fixed, venous PO$_2$ drops with increasing consumption rate. The shape of this curve is dictated by conservation of mass and does not depend on the distribution of tissue PO$_2$. The predicted consumption that can be achieved when demand is 40 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ corresponds to a venous PO$_2$ of 25.5 Torr (or 24.2 Torr if mitochondrial clustering is assumed). The dashed curve in Fig. 6 shows the minimum blood PO$_2$ that is required to supply oxygen to the outer boundary of the tissue cylinder ($r = R_t$) if a uniform consumption rate is assumed. The intersection of the dashed curve and the zero-order kinetics curve corresponds to a venous PO$_2$ of 25.5 Torr (or 24.2 Torr if mitochondrial clustering is assumed).
of the two curves represents the point at which the blood $P_O_2$ at the downstream end of the capillary is equal to the minimum $P_O_2$ required to meet $M_O$. This implies that the maximum consumption rate that could be achieved assuming a uniform consumption rate with no hypoxia throughout the tissue cylinder is 19.0 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$. According to the present model, significantly higher overall consumption rates can be achieved if demand is increased and a portion of the tissue is permitted to become hypoxic.

Predicted rates of oxygen consumption, under several different sets of assumptions, are compared in Fig. 7 with experimentally measured $V_{O_2 \text{max}}$ values. Experimental results are indicated by solid bars, and the other bars represent theoretical predictions. For each, the shaded region shows consumption when $M_0 = 40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, the hatched region shows the additional consumption when mitochondrial clustering near the capillary is assumed, and the white region shows the additional consumption when $M_0$ is increased to 80 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ throughout the tissue. The leftmost bars correspond to the case in which effects of intravascular resistance and myoglobin-facilitated diffusion are neglected. Subsequent bars show the cumulative results of successively including intravascular resistance, myoglobin-facilitated diffusion, a right shift in the oxyhemoglobin dissociation curve ($P_{50}$ increasing linearly from 26 Torr at the entrance to 39 Torr at the venous end of the capillary), and increased capillary density (as discussed below).

The predictions shown in Fig. 7A correspond to the results of Andersen and Saltin (1) for the human quadriceps muscle, with a perfusion rate of 0.041 cm$^3$ blood·cm$^{-3}$·s$^{-1}$, corresponding to an oxygen supply of 49.2 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$. The third bar (+Myo) in Fig. 7A, including effects of intravascular resistance and myoglobin-facilitated diffusion, corresponds to the standard case shown in Figs. 2, 4, and 5. Inclusion of intravascular resistance reduces predicted consumption significantly, from 29.9 to 24.3 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$. Myoglobin-facilitated diffusion leads to only a small (<2%) increase in consumption to 24.7 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ for $M_0 = 40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ (model and +IVR bars). Myoglobin-facilitated diffusion is then 13% less than the observed $V_{O_2 \text{max}}$ value of 35.0 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ (1). A right shift in the oxyhemoglobin dissociation curve (+RS bar) increases consumption by almost 14%. Predicted consumption with $M_0 = 80$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ is then 13% less than the observed $V_{O_2 \text{max}}$. To obtain consumption levels close to the observed $V_{O_2 \text{max}}$, a capillary density higher than 468 capillaries/mm$^2$ must be assumed. For example, increasing capillary density to 600 capillaries/mm$^2$ (+HD bar) leads to predicted consumption rates of 32.1 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ for $M_0 = 40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, 33.8 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ with mitochondrial clustering, and 36.1 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ when $M_0 = 80$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, which are close to the observed level.

In the study by Richardson et al. (25), the perfusion in the quadriceps muscle was 0.0642 cm$^3$ blood·cm$^{-3}$·s$^{-1}$, corresponding to an oxygen supply of 75.7 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$. Predictions for this higher perfusion level are shown in Fig. 7B. Relative to Fig. 7A, oxygen supply is increased by ~54%, but the increase in consumption is less, ~12% for the case including effects of intravascular resistance and myoglobin (gray +Myo bar). Inclusion of intravascular resistance, myoglobin-facilitated diffusion, and right shifting the oxyhemoglobin dissociation curve lead to
similar effects to those seen in Fig. 7A. In this case, even when a right shift is included, the predicted consumption rates (31.4 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ when $M_0 = 40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, 33.4 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ with clustering, and 34.9 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ when $M_0 = 80$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$) fall far short of the reported $V_{O2_{max}}$, which is 60.2 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ (25). According to the model, such high oxygen consumption can only be achieved by a combination of high demand and high $N$. Clearly, this reported consumption rate cannot be achieved with a demand of 40 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, as seen in the +HD bar, under these conditions, mitochondrial clustering has practically no effect on oxygen consumption, and predicted consumption still falls short of the reported $V_{O2_{max}}$ value. However, if an increased $N$ is coupled with a demand of 40 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, the resulting consumption is 57.4 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, close to the observed $V_{O2_{max}}$.

**DISCUSSION**

*Factors determining oxygen consumption rate.* When $M_0$ is high in skeletal muscle, the rate of oxygen consumption depends not only on the demand, but also on the rate of convective delivery and on the diffusive processes occurring within capillaries and in the surrounding tissue. The present analysis shows that all these factors have significant effects on the consumption rate that is achieved. Clearly, consumption cannot exceed either the demand of the muscle or the convective supply (Fig. 4). When demand is low, all tissue has sufficient oxygen, and predicted consumption equals demand. As demand increases, the limited rate of oxygen diffusion leads to low oxygen levels in the outer regions of the tissue cylinder, as shown schematically in Fig. 1. This oxygen deficiency causes the average consumption within the cylinder to fall below the demand. Further increases in demand, beyond $\sim40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, lead to only slight increases in consumption (Fig. 4).

As shown previously (14), inclusion of intravascular resistance to oxygen diffusion significantly lowers the predicted consumption rate (Figs. 4 and 7, +IVR). Thus both intravascular resistance and resistance to diffusion within the tissue are important factors in determining consumption. With increased capillary density, the size of each tissue cylinder is reduced, reducing the diffusion resistance. Furthermore, for a given consumption rate, each capillary has to deliver less oxygen, reducing the effect of diffusion resistance on oxygen delivery. This leads to marked increases in predicted consumption (Figs. 5 and 7, +HD). At higher $N$s, consumption increases with demand beyond 40 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ before leveling off (Fig. 5).

The role of myoglobin in oxygen delivery has been controversial. Gayeski and Honig (11) considered that myoglobin was an important factor in oxygen transport within muscle fibers. Conley et al. (5) used measurements of myoglobin saturation in vivo made with magnetic resonance spectroscopy to support the opinion that myoglobin may play a role in facilitating oxygen transport in skeletal muscle but did not quantify the effects of myoglobin on oxygen transport. In a recent review, Jürgens et al. (17) concluded that myoglobin plays at most a minor role in oxygen transport under physiological conditions. A similar conclusion was reached by Roy and Popel (29). According to the present analysis, inclusion of myoglobin-facilitated diffusion has relatively small effects on overall oxygen transport. It leads to shallower $P_{O2}$ gradients, lower intravascular $P_{O2}$ values, higher $P_{O2}$ levels in the outer part of the cylinder where tissue is hypoxic, and a slight (<2%) net increase in consumption (Fig. 7, +Myo). To understand this result, it is helpful to consider the facilitation pressure ($P_F = D_{mb}C_{mb}V_m/K$, which represents the contribution of myoglobin to oxygen transport in terms of an effective additional partial pressure of oxygen available to drive diffusive transport (10). For the parameter values used here ($D_{mb} = 1.73 \times 10^{-7}$ cm$^2$/s), $P_F = 1.6$ Torr, which is much less than the capillary $P_{O2}$ even at the venous end. This result reflects the fact that the diffusivity of myoglobin in muscle is two orders of magnitude less than the diffusivity of oxygen. Therefore, myoglobin-facilitated oxygen transport would not be expected to have much effect. Some earlier models were based on the diffusivity of myoglobin measured in protein solutions (18), $D_{mb} = 8 \times 10^{-7}$ cm$^2$/s. Assuming this value gives $P_F = 7.3$ Torr and leads to a 5% increase in the oxygen consumption rate when $M_0 = 40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$.

The effects of a right shift of the oxyhemoglobin dissociation curve and mitochondrial clustering can also increase consumption, as indicated in Fig. 7. A right shift of the oxyhemoglobin dissociation curve increases blood $P_{O2}$ at a given saturation and therefore increases the $P_{O2}$ gradient for oxygen diffusion into tissue. Simulating a right shift by linearly increasing $P_{50}$ from 26 to 39 Torr along the length of the capillary leads to a significantly increased consumption (Fig. 7, +RS). Additional simulations in which $P_{50}$ varied smoothly from 26 to 39 Torr, but with nonlinear dependence on distance traveled, showed very similar results. Effects of mitochondrial clustering are represented here by assuming that consumption occurs only in a region surrounding each capillary representing half of the tissue volume. For an average consumption rate 40 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, clustering leads to a significant increase in consumption (Fig. 7, +HD), virtually all the tissue is well oxygenated at a uniform demand of 40 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ and clustering has almost no effect.
Model predictions are sensitive to \( N \), which is equal to the capillary-to-fiber ratio divided by the average fiber cross-sectional area. Changes in \( N \) can be caused by changes in the number of capillaries per fiber or in fiber size. Because the model assumes that each capillary supplies oxygen exclusively to the surrounding cylinder of tissue, regardless of the number of fibers intersected by that cylinder, the results are not sensitive to the capillary-to-fiber ratio or the fiber size per se, but only to \( N \) (i.e., capillaries/mm\(^2\)).

Some effects that are not considered in this model may also influence consumption rates. Only oxygen diffusion from capillaries is considered. In resting muscle, a significant fraction of the \( M_0 \) can be met by oxygen diffusion from arterioles. However, this fraction decreases with increasing \( M_0 \) (30). In the model, the contribution of oxygen dissolved in the plasma to convective delivery is neglected. Additional calculations including this component were carried out, showing that predicted consumption increased by \(<1.1\%\). Capillaries are lined with a glycocalyx or endothelial surface layer 0.5–1 \( \mu \)m thick that can exclude flowing red blood cells (23). This layer may increase intravascular resistance to oxygen diffusion, but its effects are unknown. The assumed Sherwood number, \( Sh = 2.5 \), was based on theoretical estimates that neglect such effects (15).

**Effects of nonuniform capillary spacing and flow.**

The Krogh-type model assumes that all capillaries in the tissue are identical, with the same flow in each and uniform spacing between them. In reality, capillaries are not evenly spaced, and this heterogeneity may lead to reduced oxygen delivery, because capillaries in more densely perfused regions may flow through regions of higher \( P_{O_2} \) where less oxygen is extracted. Under conditions of very high demand, however, even relatively densely perfused areas can be assumed to contain a significant amount of hypoxic tissue, particularly near the downstream end of each capillary, so that extraction from each capillary is not greatly affected by the presence of near neighbors. According to this argument, the effect of nonuniform spacing on average consumption is expected to be small when demand is very high. Heterogeneity in capillary length or flow rate could also affect the results. To estimate the effects of variations in capillary lengths, two cylinders were considered, one \( 1/2 \) longer than the standard case and the other \( 1/2 \) shorter, and both with the same flow as in the standard case. The consumption rate was averaged over the two cylinders and compared with the standard single-cylinder case. Similarly, to investigate the effects of uneven flow distribution, two cylinders of the same length were considered, one with \( 1/2 \) higher flow than the standard case and the other with \( 1/2 \) lower flow. In both cases the result was a slight decrease in overall average consumption, \(<2.1\%\).

**Relationship to venous \( P_{O_2} \).**

According to the conceptual model of Wagner (33), for a given perfusion rate, the \( P_{O_2} \) at the venous end of capillaries declines with increasing consumption, whereas the \( P_{O_2} \) required to achieve tissue oxygenation increases. Wagner suggested that \( V_{O_2 \text{max}} \) is reached when venous \( P_{O_2} \) falls to the minimum needed for complete tissue oxygenation. This condition is indicated graphically in Fig. 6 by the intersection of the two curves. Wagner defines \( V_{O_2 \text{max}} \) as the point at which venous blood \( P_{O_2} \) is equal to the \( P_{O_2} \) required to fully meet the \( M_0 \) of the tissue, i.e., no hypoxic regions are present. However, as shown in Fig. 6, significantly higher overall oxygen consumption rates can be achieved if oxygen demand increases beyond the level at which hypoxia first appears. With further increases in demand, consumption in the well-oxygenated regions increases, whereas the hypoxic regions spread and consumption decreases there according to Michaelis-Menten kinetics. The decrease in consumption in hypoxic regions is more than compensated for by the increased consumption in well-oxygenated regions, and the net effect is an increase in consumption. For example, the curves in Fig. 6 intersect when demand is 19 cm\(^3\) \( O_2 \cdot 100 \text{ cm}^{-3} \cdot \text{min}^{-1} \) and consumption is 17.9 cm\(^3\) \( O_2 \cdot 100 \text{ cm}^{-3} \cdot \text{min}^{-1} \). Increasing demand to 40 cm\(^3\) \( O_2 \cdot 100 \text{ cm}^{-3} \cdot \text{min}^{-1} \) results in a significantly higher consumption rate, 24.7 cm\(^3\) \( O_2 \cdot 100 \text{ cm}^{-3} \cdot \text{min}^{-1} \). Therefore, Wagner’s conceptual model, if applied quantitatively, may underestimate the maximal oxygen consumption rate. Similarly, the predictions of end-capillary \( P_{O_2} \) at \( V_{O_2 \text{max}} \) by Roy and Popel (29), which were mainly in the range 20–30 Torr, were based on the assumption that no hypoxia is present and correspond to the intersection of the two curves in Fig. 6. According to the present model, their approach may overestimate end-capillary \( P_{O_2} \) at \( V_{O_2 \text{max}} \) by several millimeters of mercury.

**Comparison with observations of tissue oxygen levels.**

Gayeski and Honig (11) used cryospectrophotometry to measure myoglobin saturation of dog gracilis muscle rapidly frozen at \( V_{O_2 \text{max}} \). Measured myoglobin saturation levels were between 8% and 40%, corresponding to \( P_{O_2} \) values of 0.5 Torr and 3.5 Torr, based on \( P_{Mb50} = 5.3 \) Torr for dog muscle. They reported shallow \( P_{O_2} \) gradients of \(<0.1 \text{Torr/} \mu \text{m} \) and low, nonzero \( P_{O_2} \) values throughout the tissue at distances greater than 3 \( \mu \text{m} \) from the nearest capillary. They concluded that most of the drop in \( P_{O_2} \) between red blood cells in a capillary and an adjacent muscle fiber occurs outside the fiber or within a few micrometers inside the fiber. These results were stated to contradict classical theories of oxygen transport to tissue such as the Krogh model and were attributed to the effects of intravascular resistance and myoglobin facilitation. In subsequent studies, Voter and Gayeski (32) showed that the sampling region of the earlier studies was larger than assumed by Gayeski and Honig (11), implying that the oxygen gradients may have been larger than originally estimated. However, these studies supported the previous conclusion that oxygen gradients are shallow with low \( P_{O_2} \) throughout the tissue at maximal consumption.

The present model shares some significant features with these observations. It predicts that a substantial fraction of the tissue is hypoxic, with low nonzero \( P_{O_2} \) and shallow gradients. With the standard assump-
tions, 68% of the tissue has a PO$_2$ of <3.5 Torr and 37% has a PO$_2$ of <1 Torr, as shown in Fig. 3A. PO$_2$ gradients are <1 Torr/$\mu$m in 84% of the tissue and <0.1 Torr/$\mu$m in 32% of the tissue. Although a wide range of myoglobin saturation is predicted, as shown in Fig. 3B, much of the tissue is in the approximate range that was found by Honig and Gayeski (11). The main factors contributing to these behaviors are evident in Fig. 2. Intravascular resistance to oxygen diffusion leads to a significant radial decline in PO$_2$ within capillaries, PO$_2$ declines rapidly with distance traveled along the capillary, and PO$_2$ declines with radial distance within 5–10 $\mu$m of the capillaries. Low gradients occur in hypoxic regions, because consumption is low in those regions. As already pointed out, myoglobin-facilitated diffusion is not an important factor.

Comparison with measured values of $\dot{V}O_2_{\text{max}}$. Oxygen consumption depends on $M_0$. On the basis of the experimental work of Blomstrand et al. (3) and Richardson et al. (25), a range of $M_0$ from 0–80 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ was considered. In the absence of a measured value for $M_0$, no unique prediction of $\dot{V}O_2_{\text{max}}$ can be made. However, predicted consumption increases slowly with $M_0$ in the range from 40 to 80 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ (Fig. 4). Therefore, consumption rates for $M_0$ values in this range can be considered as approximate predictions of $\dot{V}O_2_{\text{max}}$.

In experiments using knee extensor exercise, oxygen consumption can be measured in a single quadriceps muscle to determine $\dot{V}O_2_{\text{max}}$, independent of systemic limitations on oxygen delivery. Results using this approach (1, 25) are compared in Fig. 7 with model predictions. With standard parameter values ($N = 468$ capillaries/mm$^2$, $P_{50} = 26$ Torr, including intravascular resistance and myoglobin), the model underestimates the measured $\dot{V}O_2_{\text{max}}$ values. However, the values of some key parameters were not measured in the experimental studies, and it is of interest to examine what values of these parameters would lead to consumption rates close to measured $\dot{V}O_2_{\text{max}}$ values.

Andersen and Saltin (1) observed an average $\dot{V}O_2_{\text{max}}$ of 35 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ in subjects who ranged in training from sedentary to endurance trained. In the corresponding model results (Fig. 7A), when a right shift in the oxyhemoglobin dissociation curve is included by linearly increasing $P_{50}$ from 26 Torr at the arterial end to 39 Torr at the venous end of the capillary, consumption with $M_0 = 40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ increases from 24.7 to 28.0 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ but is still less than the measured value. With mitochondrial clustering and a right shift, the consumption is 29.9 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, and when $M_0 = 80$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ the consumption with the right shift is 30.6 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$. Assuming a higher capillary density, $N = 600$ capillaries/mm$^2$, leads to a predicted consumption of 32.1 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ when $M_0 = 40$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, close to the measured value. Therefore, the observed $\dot{V}O_2_{\text{max}}$ can be accounted for by modifying the standard model to include a right shift of the oxyhemoglobin dissociation curve and a slightly higher capillary density.

The subjects in the experiments of Richardson et al. (25) were competitive endurance bicyclists, and $\dot{V}O_2_{\text{max}}$ values with a mean of 60.2 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ were obtained, much higher than any model predictions with a capillary density of 468 capillaries/mm$^2$. However, if capillary density is increased to 1,000 capillaries/mm$^2$ and a right shift is included, with $M_0 = 80$ cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$, a consumption rate of 57.4 cm$^3$ O$_2$·100 cm$^{-3}$·min$^{-1}$ is predicted, close to the measured value. Endurance training has been shown to have many effects on skeletal muscle, including increasing $N$ and mitochondrial number and causing an even more pronounced right shift in the oxyhemoglobin dissociation curve during exercise when compared with untrained subjects. The highest $N$ in human skeletal muscle found in the literature was 810 capillaries/mm$^2$ (8). $N$ estimated by staining methods may substantially underestimate the true $N$ (13). According to the model results, a combination of these effects, including a marked increase in $N$, must be present in the muscles of the subjects studied by Richardson et al. (25) to account for the very high muscle-specific $\dot{V}O_2_{\text{max}}$ levels observed.

In conclusion, a theoretical model for oxygen transport to tissue has been developed on the basis of the tissue cylinder concept of Krogh (19) but incorporating recent information on oxygen transport mechanisms and parameters. According to the model, oxygen consumption rates under conditions of high demand depend on both convective and diffusive limitations on oxygen delivery. Intravascular resistance to oxygen diffusion significantly restricts delivery, whereas myoglobin-facilitated diffusion in tissue plays a negligible role. A right shift of the oxyhemoglobin dissociation curve can significantly enhance delivery, and consumption rates are sensitively dependent on $N$. When demand is high, much of the tissue is predicted to be hypoxic, with low PO$_2$ gradients, as observed experimentally.

Predicted $\dot{V}O_2_{\text{max}}$ are comparable in magnitude to experimentally observed $\dot{V}O_2_{\text{max}}$ values. Andersen and Saltin (1) considered subjects whose level of physical activity ranged from sedentary to endurance trained. The average value determined for these subjects can be predicted with this model using capillary densities found in the literature. Richardson et al. (25) reported a much higher average $\dot{V}O_2_{\text{max}}$ value for endurance trained athletes. This value can only be explained with the model by assuming $N$s near 1,000 capillaries/mm$^2$.

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