Predictions of capillary oxygen transport in the presence of fluorocarbon additives

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The high solubility of O2 in perfluorocarbon (PFC) compared to blood plasma has led to the development of fluorocarbon-based additives designed to enhance the O2-carrying capacity and delivery characteristics of blood. These fluorocarbon emulsions are designed to enhance O2 transport in critically ill patients and patients who have been hemodiluted after acute blood loss or during an operative procedure (29). One technique for improving O2 transport in patients undergoing surgery is intraoperative hemodilution, in which the patient's hematocrit is intentionally reduced by removing blood that will be transfused to the patient postoperatively. The lost volume is replenished with a crystalloid solution. Hemodilution also occurs as a result of volume repletion after acute blood loss. In either case, this has the effect of reducing total peripheral (vascular) resistance because the blood viscosity is decreased, which may improve O2 delivery in spite of decreased O2 content (19). If PFC is found to be a useful intravascular additive, transient infusion of fluorocarbon emulsions during hemodilution may further supplement O2 transport (16). Other applications of PFC include cardioplegia, O2 delivery distal to the balloon in coronary angioplasty (17), and liquid ventilation (10), to name a few.

The amount of O2 carried by the PFC is linearly related to the local Po2, unlike the sigmoidal O2 dissociation curve of hemoglobin. When PFC was added to the blood, an increase in tissue Po2 was observed (4). It has been shown theoretically that low O2 solubility in plasma is a major determinant of the intracapillary transport resistance to oxygen (8, 9). The increase in tissue Po2 with addition of PFC to the plasma may be the result of decreasing intracapillary resistance.

Hogan et al. (12) specifically investigated the use of PFC emulsions to decrease intracapillary transport resistance. To test the hypothesis that an increased O2 content in the plasma region is responsible for enhancing O2 transport, they performed experiments on electrically stimulated isolated dog gastrocnemius muscle preparations under control conditions [with plasma solubility (αp) = 3 × 10⁻⁵ ml O₂·ml⁻¹·torr⁻¹] and with 6 g/70 ml blood perfluorooctylbromide (αp = 5 × 10⁻⁵ ml O₂·ml⁻¹·torr⁻¹); the hemoglobin concentration was reduced to 8.7 g/dl (corresponding to systemic hematocrit (Hsys) = 0.26) in these experiments to increase the effect of this PFC. Increasing αp from 0.003 to 0.005 ml O₂·ml⁻¹·torr⁻¹ did not affect whole muscle diffusivity (Dm). Dm is defined by analogy to Fick's law of diffusion

\[ V_{O2} = D_{O2} \cdot (P_{cap} - P_{mt}) \]  

where \( V_{O2} \) is O2 uptake, \( P_{cap} \) is mean capillary Po2, and \( P_{mt} \) is mean tissue Po2. Under maximal O2 uptake conditions (\( V_{O2, max} \)), tissue Po2 is low and can be considered negligible compared to \( P_{cap} \) (12). \( D_{O2} \) represents a whole organ mass transfer coefficient. Hogan et al. (12) concluded that elevated plasma O2 solubility increases \( V_{O2, max} \) in proportion to the increase in convective O2 delivery and suggested that increasing the diffusion coefficient for O2 in plasma does not increase the whole muscle diffusivity.

Keipert et al. (16) measured O2 delivery in dogs ventilated with air and 100% oxygen. About 8–10% of total O2 content was dissolved in the PFC emulsion, but 25–30% of Vo2 was delivered by the PFC. Correspondingly, hemoglobin-bound O2 accounted for 46 and 15% of Vo2 for control and PFC cases, respectively. Keipert et al. (16) suggested that by serving as a first dispenser of O2, PFC leaves more O2 bound to hemoglobin to act as an O2 reserve. Vaslef and Goldstick (26) used a capillary tube oxygenator in a steady-state closed loop to study the effect of PFC addition to bovine blood on O2 uptake. It was found that for a 2.1% volume of PFC the outlet Po2 increased by 10–20%. A mathematical model

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of O₂ transport in tubes with PFC additives was developed by Shah and Mehra (22). The uptake of O₂ by a pure PFC emulsion and by blood is calculated as the respective fluid flows through a tube with a constant PO₂ along the tube wall to compare the O₂ transport properties of each fluid. Emulsions with varying PFC concentrations and blood of different hematocrits were considered, and O₂ flux density (moles/area/time) and content as a function of the distance from the entrance were determined. A shorter entrance length was required for blood saturation, in comparison to the PFC emulsions. Unreasonably high concentrations of PFC are required to match the O₂-carrying capacity of blood when the wall PO₂ corresponds to values for ambient air; however, the O₂ content of a PFC emulsion can match that of blood at normal conditions when the wall PO₂ corresponds to a 100% O₂ environment.

In this paper, we use characteristics of working hamster retractor muscle to assess the potential reduction in intracapillary resistance by the addition of PFC in anticipation of the development of an experimental model. Characteristics of this muscle have been studied extensively in parallel with mathematical modeling (5–7, 18, 23, 28). The mathematical model developed here includes plasma O₂ solubility as a parameter so that the effect of PFC can be simulated. There is evidence from in vitro studies that the PFC may increase the intracapillary O₂ transport (characterized by a reduction in critical end-capillary PO₂ or an increased mass transfer coefficient) by the addition of PFC.

Our hypothesis is that the presence of PFC in the plasma will increase the intracapillary O₂ transport conductance (mass transfer coefficient). To test our hypothesis, the O₂ content of the erythrocyte is held constant and the mass transfer coefficient is calculated as a function of plasma O₂ solubility.

**MATHEMATICAL MODEL**

This section describes a model of O₂ transport that includes a radial plasma solubility distribution to assess the effect of intravascular fluorocarbon on PO₂ distributions and the intracapillary mass transfer coefficient. The model uses morphologically observed parameters and assumes that no heterogeneity among blood capillaries is present.

The model considers a single capillary surrounded by a cylindrical volume of tissue and includes both intra- and extracapillary regions. A schematic for this model is shown in Fig. 1. The equations are written in the frame of reference of a single erythrocyte. Thus the capillary wall, interstitial fluid, and tissue regions move relative to the erythrocyte and its surrounding plasma. Periodic boundary conditions are imposed at the axial ends of the domain, and the PO₂ in the core of the erythrocyte is held constant. This allows us to estimate the capillary mass transfer coefficient. The features of the model are described here, and the equations and their descriptions are given in the Appendix.

Intracapillary transport. The intracapillary geometry is identical to the model considered in a previous paper (20), in which the capillary lumen is assumed to contain plasma and equally spaced erythrocytes modeled as cylinders containing hemoglobin. The axisymmetric equations are solved in a domain containing a single erythrocyte with periodic boundary conditions, meaning that PO₂ differences between adjacent erythrocytes are not considered. Plasma convection is neglected because its effect on O₂ transport has been shown to be small (1). Thus the erythrocyte and its surrounding plasma are stationary (no convection) relative to the moving capillary wall, interstitial fluid, and tissue regions. A capillary mass transfer coefficient is calculated to account for O₂ diffusion within the erythrocyte and plasma and the nonequilibrium concentration boundary layer in the erythrocyte resulting from oxyhemoglobin dissociation kinetics. The intraerythrocyte transport resistance is calculated using the results of the kinetic boundary layer analysis of Clark et al. (3). Fluorocarbon accumulation near the wall of a capillary tube with a 3-mm diameter has been observed (15). In a smaller capillary tube of 200-µm diameter, platelets and microspheres of similar dimensions were seen to accumulate near the wall (25). Braun et al. (2) proposed that because the fluorocarbon droplets have a median diameter of 0.25 µm, a near-wall excess may occur in capillary vessels. Although it has not been observed in the vessels within the tissue, a radial plasma solubility distribution is considered here to simulate fluorocarbon accumulation near the wall to investigate its possible effects.

Extracapillary transport. The capillary wall and interstitium are modeled as annular regions of finite thickness with...
appropriate transport properties. O₂ consumption in these regions is not considered, because they occupy only a small volume compared to the tissue region. The muscle fibers are assumed to contain myoglobin and to consume O₂ at a constant rate corresponding to working hamster retractor muscle.

PARAMETERS

The parameters used in this study were chosen to represent working hamster retractor muscle. Most of the parameters specific to this muscle were taken from Ellsworth et al. (7) except where noted. Values for most other parameters are those used by Roy and Popel (20).

Intracapillary parameters. Erythrocyte volume (V_rbc) = 69.3 \times 10^{-12} \text{ cm}^3 (21) remains constant in all our simulations. Microscopic observations of single capillaries provided average erythrocyte length (L_{rbc}) = 8.16 \mu \text{m} (5). Because this value was found to depend on hamster age, we used an interpolated value for 34-day-old hamsters, the average age of hamsters considered by Ellsworth et al. (7).

Erythrocyte velocity (V_rbc) was obtained by averaging the mean velocities observed in arteriolar and venular capillaries at rest (7) and using a factor of 5 to estimate erythrocyte velocity in working hamster retractor. This factor for increase is based on velocity measurements in rat skeletal muscle at rest and during contractions (13). For working muscle, we used V_rbc = 4.67 \times 10^{-2} \text{ cm/s}.

The average of the mean linear densities observed in arteriolar and venular capillaries (632 cells/cm² Ref. 7) is used to determine the reference capillary hematocrit (H = 0.43). The mean radius observed for arteriolar and venular capillaries (r_p) = 1.8 \mu \text{m} (7) is used in our model. These values are consistent with subsequent measurements in this muscle (23).

For consistency, we used values of the Hill coefficient (n) = 2.2 and PO₂ corresponding to 50% hemoglobin saturation (P_{SO_2} = 29.3 torr (corrected for pH and pCO₂), for the Hill equation cited by Ellsworth et al. (7). With the use of these parameters in the Hill equation and the average of the observed saturation values in arteriolar and venular capillaries (S = 0.5035; Ref. 7), we obtained an erythrocyte core PO₂ (P_r) = 29.5 torr. The effect of erythrocyte saturation has been studied (8, 27), and it was found that the mass transfer coefficient was only weakly dependent on P_r; thus it is not varied in this study.

Extracapillary parameters. On the basis of in vivo microscopic intercapillary distances (7), capillary density was set to 1,435 capillaries/mm². This value for resting muscle is used in our simulation of working muscle on the basis of our assumption that capillary recruitment is small in skeletal muscles of animals of this size (13).

The working muscle consumption assumed by Ellsworth et al. (7) as 10 times the resting muscle consumption of 0.89 ml O₂·100 g⁻¹·min⁻¹ measured by Sullivan and Pittman (24) is uniformly distributed throughout the muscle tissue. Estimates for this muscle based on mitochondrial volume density predict that the maximum consumption (VO₂_max) would be greater than the resting consumption by a factor of 21 (6).

Facilitation of O₂ diffusion is modeled using a myoglobin concentration (N_{MB}) of 0.4 mM in hamster retractor measured by Meng et al. (18) and a myoglobin diffusion coefficient (D_{MB}) of 1.73 \times 10^{-7} \text{ cm}²/\text{s} reported by Jürgens et al. (14).

RESULTS

PO₂ distribution. To simulate the effect of fluorocarbon, we used the model described here to assess the impact of an increase in plasma solubility. The reference value α₀ = 2.82 \times 10^{-3} \text{ ml O}_2·\text{ml}⁻¹·\text{torr}⁻¹ was increased by a factor of 1.7 as in the experiments of Hogan et al. (12).

If, however, the amount of fluorocarbon required to produce such an increase in solubility were concentrated in the plasma adjacent to the endothelium, α_p would retain its normal value between the erythrocytes, but the fluorocarbon concentration near the endothelium would be increased by a factor ξ

\[ ξ = \frac{\pi r_p^2 L_{tot} - V_{rbc}}{\pi (r_p^2 - r_{rbc}) L_{tot}} \]

where L_{tot} is total length of the tissue cylinder. The value of ξ for the intracapillary dimensions specified in parameters was 3.4, resulting in a value of α_p = α₀ for r < r_{rbc} and α_p = 3.4α₀ for r_{rbc} ≤ r < r_p. An additional simulation is performed with α_p = 3.4α₀ in the entire domain.

The results demonstrate an increase in PO₂ in the entire plasma domain with increases in plasma solubility. Figure 2 shows the radial PO₂ profiles in the plasma through the erythrocyte center as the plasma solubility is increased to 1.7 and 3.4 times its normal value. The effect of concentrating the solubility increase in the plasma near the endothelium α = α(r) is also shown in Fig. 2; the overall PO₂ is higher compared with the case in which the solubility enhancement is equally distributed. The same trend is evident in the PO₂ profiles through the center of the plasma gap (Fig. 3).
and axial PO$_2$ distributions through various sections of the domain close to the erythrocyte. Further illustrated in Fig. 4, which shows the PO$_2$ profiles in the axial direction at the inner capillary wall. Note the “zone of influence” in the regions of the domain close to the erythrocyte.

Mass transfer coefficient. With the PO$_2$ distribution in the entire domain, we can calculate a number of derived quantities in addition to determining the radial and axial PO$_2$ distributions through various sections of the domain. The flux of oxygen leaving the erythrocyte (J$_{rbc}$; mol/s) is calculated from

$$J_{rbc} = J_b + J_{\epsilon} + J_{L}$$

(3)

where $J_b$ is the total flux leaving the left erythrocyte basal surface, $J_L$ is the total flux leaving the right basal surface, and $J_{\epsilon}$ is the total flux leaving the lateral surface. Values of $J_b$ and $J_L$ are calculated from

$$J_b = \int_0^{r_{rbc}} 2\pi r \frac{\partial (\alpha_r P)}{\partial z} \, dr$$

(4)

where $P$ is PO$_2$ at the erythrocyte membrane, $z$ is the axial position, and $J_{\epsilon}$ is given by

$$J_{\epsilon} = 2\pi r_{rbc} \int_{-L/2}^{+L/2} \frac{\partial (\alpha_r P)}{\partial r} \, dz$$

(5)

The intracapillary mass transfer coefficient $k_{cap}$ is defined in terms of $P_c$ and the PO$_2$ and flux at the capillary wall [$P_p(z)$ and $J_p(z)$]

$$\bar{J}_p = k_{cap} \cdot (P_c - P_p)$$

(6)

where the overbar indicates the mean value, with

$$\bar{J}_p = L_{tot}^{-1} \int_{-L_{tot}/2}^{+L_{tot}/2} J_p(z) \, dz$$

(7)

$$P_p = L_{tot}^{-1} \int_{-L_{tot}/2}^{+L_{tot}/2} P_p(z) \, dz$$

(8)

Here we have defined the average mass transfer coefficient per cell ($k_{cap}$) based on the average flux and PO$_2$ along the capillary wall. The mass transfer coefficient per unit length of the capillary wall ($k_{cap}$) is given by

$$k_{cap} = \frac{\bar{J}_p}{L_{tot}}$$

(9)

For the reference case, $J_{rbc}/J_{rbc} = 0.08$ (leading edge), $J_{rbc}/J_{rbc} = 0.08$ (trailing edge), and $J_{rbc}/J_{rbc} = 0.84$, i.e., 84% of the O$_2$ leaves the erythrocyte through its lateral surface. The reference value of $J_{rbc}$ was the same in all cases because tissue O$_2$ consumption was the same, but the value of $J_{\epsilon}$ was found to increase when fluorocarbon was introduced in the plasma sleeve region. The reference value of the intracapillary mass transfer coefficient $k_{cap}$ was calculated to be $6.3 \times 10^{-12}$ ml O$_2 \cdot s^{-1} \cdot$torr$^{-1}$.

The absolute values of $k_{cap}$ and $\hat{k}_{cap}$ are shown in Fig. 5, A and B; at the reference hematocrit (H = 0.43), increasing plasma solubility by a factor of 1.7 increased $k_{cap}$ by a factor of 1.18, and increasing $\alpha_r$ by 3.4 increased $k_{cap}$ by a factor of 1.40. The effect of concentrating the plasma solubility enhancement in the layer near the endothelium was to increase $k_{cap}$ by 6% over the evenly distributed case.
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Figure 5. Intracapillary mass transfer coefficient ($k_{cap}$) as a function of plasma solubility at reference hematocrit ($H = 43\%$) and $H = 25\%$. A: $k_{cap}$ (per cell), B: $k_{cap}$ (per unit length of capillary).

Also shown in Fig. 5 is the effect of increased plasma solubility at a lower hematocrit ($H = 0.25$). Although the trends are similar, the magnitude of the increases in the mass transfer coefficient are smaller. Increasing plasma solubility by a factor of 1.7 increased $k_{cap}$ by a factor of 1.14, and increasing $k_{a}$ by 3.4 increased $k_{cap}$ by a factor of 1.31. The effect of concentrating the plasma solubility enhancement in the layer near the endothelium to increase $k_{cap}$ by 4.5%. The corresponding increases are the same for $k_{cap}$.

It is also instructive to examine the intracapillary transport resistance as a fraction of the total resistance along the pathway from the erythrocyte to the mitochondria, as defined previously (20). The model predicts a decrease in intracapillary resistance fraction with increasing solubility. The intracapillary resistance as a fraction of the total resistance between the erythrocyte and the mitochondria at the reference hematocrit is 0.43 for normal plasma, 0.40 for a relative solubility increase of 1.7, 0.36 for a relative solubility increase of 3.4, and 0.39 for the case where the PFC solubility increase is concentrated in the sleeve between the erythrocyte and the endothelium. The associated changes in the total transport conductance from the erythrocyte to the mitochondria, relative to the total conductance with normal plasma are 1.08 for a relative solubility increase of 1.7, 1.17 for a relative solubility increase of 3.4, and 1.11 for the case where the PFC solubility increase is concentrated in the sleeve between the erythrocyte and the endothelium. At $H = 0.25$ the intracapillary resistance as a fraction of the total resistance between the erythrocyte and the mitochondria is 0.64 for normal plasma, 0.61 for a relative solubility increase of 1.7, 0.58 for a relative solubility increase of 3.4, and 0.60 for the case where the PFC solubility increase is concentrated in the sleeve between the erythrocyte and the endothelium.

Sensitivity analysis. The predictions of the model depend on the physiological mechanisms represented and the physiological properties that determine their magnitude. Although well characterized, some physiological properties of the hamster retractor muscle have yet to be measured. The sensitivity of the mathematical model to several input parameters was tested previously (20), using a different solution method, for the dog vastus medialis muscle at VO$_2$ max. Only the parameters that affect the intracapillary mass transfer coefficient are discussed here. It was found that if the oxyhemoglobin dissociation rate constant ($k_d$) was altered from the standard $k_d = 44$ s$^{-1}$ to $k_d = 22$ s$^{-1}$ and $k_d = 88$ s$^{-1}$, $k_{cap}$ decreased 17% and increased 22%, respectively. When the value of $P_{SO_2}$ was lowered from 37.2 to 30.8 torr, $k_{cap}$ increased by 10%.

The sensitivity of the present model to variations in velocity and capillary radius was tested for an increase in O$_2$ solubility in plasma of $a = 1.7a_{0}$ at $H = 0.43$. The velocity was minimized (stationary case) and increased to twice and five times the reference velocity. The capillary radius used was the average of the mean values measured at the arteriolar and venular ends, 1.8 µm. The average of the standard deviations in the radial measurements at both ends of the capillary was 0.175 µm. The capillary radius was varied by one and two standard deviations, and $k_{cap}$ was calculated for the new geometry. In each case the geometry was altered so that the hematocrit remained fixed at $H = 0.43$ and the plasma sleeve, the gap between the lateral wall of the erythrocyte and the capillary wall, remained at 0.18 µm. The mass transfer coefficient changed by 2 and 0%, respectively when the radius was decreased and increased by one
standard deviation and changed by 8 and 1% when the radius was decreased and increased by two standard deviations.

**DISCUSSION**

The solubility of O₂ in plasma was increased ~70% at H₂₅₅ = 0.25 in the measurements made on the dog gastrocnemius muscle (12). No appreciable difference in the whole muscle diffusivity was found. The same increase in solubility in the current model of the hamster retractor muscle predicts an increase in the intracapillary mass transfer coefficient of 14% and the whole muscle O₂ conductance of 9% at H = 0.25, assuming no heterogeneity in the capillaries. The increase in the whole muscle O₂ conductance at the higher reference hematocrit, H = 0.43, was roughly the same. Therefore, the predicted increase is fairly small. It should be kept in mind that these calculations pertain to the hamster retractor muscle, whereas the results of Hogan et al. (12) are for dog gastrocnemius muscle. We are not able to repeat our calculations for the gastrocnemius muscle because most morphological and biophysical parameters are not available.

It was also shown through measurements in the dog gastrocnemius muscle by Hogan et al. (11) that whole diffusivity depends on hematocrit. The relationship between hematocrit and increased plasma O₂ solubility can be examined from the results of this study. It was expected that the mass transfer coefficient would show a larger proportional increase with increased plasma O₂ solubility at lower hematocrit. This was not the case, although the mass transfer coefficient did indeed increase in every case. Federstui and Popel (8) showed that increased erythrocyte spacing decreases the mass transfer coefficient. By fixing Pₐ and therefore the O₂ content of the core of the erythrocyte, we have isolated the diffusional characteristics of increased plasma solubility. The mass transfer coefficient (Eq. 6) is defined in terms of the partial pressure of O₂ in the cell (Pₐ). The presence of a cell in the capillary is implied so that, with this definition and the geometry of our model, hematocrit is taken to zero by extending the axial length of the domain toward infinity. Estimates of the O₂ transfer at zero hematocrit as a function of PFC concentration were presented previously (22).

The model of O₂ transport developed has been used to study the effects of plasma O₂ solubility on the transport resistance of O₂ from the cell to the capillary wall. This is only one aspect of the transport of O₂ from the cell to the capillary wall. The simulations predict that Po₂ in the plasma and tissue surrounding the capillary increases with increasing fluorocarbon concentration. The simulations show that at fixed erythrocyte saturation, higher levels of Po₂ in the tissue are related to higher Po₂ levels in the plasma caused by increased solubility. Increasing the plasma solubility increases the intracapillary mass transfer coefficient (decreases transport resistance). The result is that for the same flux of O₂ supplied to the tissue the drop in Po₂ from the erythrocyte to the capillary wall is smaller. Concentrating the increase in plasma solubility in the plasma sleeve between the erythrocyte and the endothelium results in only a small increase compared with the case in which the solubility enhancement is evenly distributed. Therefore, for the muscle and physiological conditions considered in this work, leading-order effects of perfluorocarbon additives can be understood by considering a constant increase in plasma solubility.

**APPENDIX**

Model Equations

The appendix describes a model of O₂ transport that includes a radial plasma solubility distribution to assess the effect of intravascular fluorocarbon on Po₂ distributions and the intracapillary mass transfer coefficient. The model uses morphologically observed parameters and assumes that no heterogeneity among blood capillaries is present. The axisymmetric equations are solved in a domain containing a single erythrocyte with periodic boundary conditions, meaning that Po₂ differences between adjacent erythrocytes are not considered.

Intracapillary transport. Values of the erythrocyte linear density (LD), defined as the number of cells per unit length along the capillary, and erythrocyte length (Lₑ) are measured experimentally; these values yield the length of the plasma gap (Lₚ) from

\[
LD = (Lₑ + Lₚ)^{-1}
\]  

(A1)

and define the total length of the tissue cylinder, Lₜₜ = Lₑ + Lₚ. The specified erythrocyte volume Vₑ is used to calculate erythrocyte radius rₑ from

\[
Vₑ = \pi rₑ^2 Lₑ
\]  

(A2)

Given a specified value of the inner capillary radius rₓ, the capillary hematocrit (Hₑ) can then be calculated from

\[
Hₑ = \frac{rₑ^2 Lₑ}{rₓ^2 Lₜₜ}
\]  

(A3)

The local flux density out of the erythrocyte (j) is calculated using the results of the kinetic boundary layer analysis of Clark et al. (3)

\[
j(Pₑ, P) = (Pₑ - P) \cdot (Dₑαₑkₑ \cdot Pₑ Nₑ) \frac{1}{2}
\]  

(A4)

where Pₑ is the Po₂ in the core of the erythrocyte, P is the Po₂ at the erythrocyte membrane, Dₑ is the diffusion coefficient of free O₂ inside the erythrocyte, αₑ is the intraerythrocyte O₂ solubility coefficient, kₑ is the oxyhemoglobin dissociation rate constant, Pₑ Nₑ is the Po₂ corresponding to 50% hemoglobin (Hb) saturation, Nₑ is the hemate concentration inside the
erythrocyte, and \( q \) is a dimensionless flux density given by

\[
q(P_c, P) = \left[ 2(1 - S_c) \frac{(P/P_{50})^{n-1}}{n+1} - 2S_c \frac{P}{P_{50}} \right] + \frac{2n}{(n+1)(1 - S_c)^{1/n}} q_{\text{tot}} \tag{A5}
\]

The saturation \( S_c = S(P_c) \) is determined from Hill's equation for the equilibrium oxyhemoglobin dissociation curve

\[
S = \frac{(P/P_{50})^n}{1 + (P/P_{50})^n} \tag{A6}
\]

where \( n \) is the Hill coefficient.

\( P_O_2 \) varies continuously over the erythrocyte surface; at each point on the erythrocyte is determined by continuity with the plasma flux density at the erythrocyte surface, calculated from

\[
j = -D_p \frac{\partial (\alpha_i P)}{\partial N} \tag{A7}
\]

where \( N \) is the surface normal.

In the plasma

\[
\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial (\alpha_i P)}{\partial r} \right) + \frac{\partial^2 (\alpha_i P)}{\partial z^2} = 0 \tag{A8}
\]

Extracapillary transport. \( O_2 \) diffusion inside the capillary wall was modeled by

\[
-\alpha_w \nu_{\text{erc}} \frac{\partial P}{\partial z} = D_w \alpha_w \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P}{\partial r} \right) + \frac{\partial^2 P}{\partial z^2} \right] \tag{A9}
\]

In the interstitial fluid layer

\[
-\alpha_i \nu_{\text{erc}} \frac{\partial P}{\partial z} = D_i \alpha_i \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P}{\partial r} \right) + \frac{\partial^2 P}{\partial z^2} \right] \tag{A10}
\]

where \( \nu_{\text{erc}} \) is the erythrocyte velocity; the convective term appears in this equation because it is written in the erythrocyte frame of reference.

In the tissue region

\[
-\nu_{\text{erc}} \frac{\partial}{\partial z} [\alpha_i P + N_{MB}(S_{MB}(P))] = D_{MB} \alpha_i \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P}{\partial r} \right) + \frac{\partial^2 P}{\partial z^2} \right] + D_{MB} N_{MB} \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial S_{MB}}{\partial r} \right) + \frac{\partial^2 S_{MB}}{\partial z^2} \right] - M \tag{A11}
\]

where \( M \) represents a constant consumption rate. As in the previous model (20), free and myoglobin bound \( O_2 \) are assumed to be in equilibrium, \( S_{MB} = S_{MB}(P) \).

The boundary condition at the edge of the tissue cylinder is

\[
\frac{\partial P}{\partial r} \bigg|_{r=r_t} = 0 \tag{A12}
\]

At the erythrocyte-plasma interface, \( P_O_2 \) is determined by Eq. A7. Periodic boundary conditions for \( P_O_2 \) were used for all regions in the axial direction. The core erythrocyte \( P_O_2 (P) \) was assumed to remain constant.

Numerical method. The above equations were solved in dimensionless form using finite-difference approximations in a finite-volume formulation. Time-dependent terms were added, and time marching was used to find the steady-state solution with the Crank-Nicolson method. The resulting set of linear equations was solved iteratively at each time step using Gauss-Seidel line relaxation. The grid size was 315 \( \times \) 96 for the normal hematocrit case (H = 0.43) and 325 \( \times \) 166 for the low-hematocrit case (H = 0.25). Hematocrit was decreased by keeping the erythrocyte dimensions fixed and increasing the axial dimensions of the entire domain. A time step corresponding to the characteristic diffusion time in the plasma was used for all runs.

A linearized version of Eq. A5 for \( q(P_c, P) \) was used for values of \( P \) close to \( P_c \); because the finite-difference equations contain an expression with the term \( dq/dP \), which is singular at \( P = P_c \). Initial values for the \( P_O_2 \) profile in the domain were generated by using the one-dimensional equations for radial diffusion in each region. The equations were solved with specified \( P_O_2 \) boundary conditions for the plasma adjacent to the erythrocyte until the maximum relative difference in the profile from one time step to the next was \( < 10^{-4} \). This profile was used as the initial condition to solve the full set of equations given above using the boundary condition for the flux density at the erythrocyte surface expressed by Eq. A4. The final maximum relative difference between time steps for all runs was \( < 5 \times 10^{-5} \). The calculated flux of \( O_2 \) (mole/time) out of each erythrocyte and out of each layer (inner and outer capillary wall, interstitial fluid) agreed with the total consumption

\[
M_{\text{tot}} = \pi (r_t^2 - r_i^2) L dM \tag{A13}
\]

to within 4% in each case.

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