Diffusing capacity reexamined: relative roles of diffusion and chemical reaction in red cell uptake of $O_2$, CO, CO$_2$, and NO

Saikat Chakraborty, Vemuri Balakotaia, and Akhil Bidani

Diffusing capacity reexamined: relative roles of diffusion and chemical reaction in red cell uptake of $O_2$, CO, CO$_2$, and NO. J Appl Physiol 97: 2284–2302, 2004. First published August 20, 2004; doi:10.1152/japplphysiol.00469.2004.—This paper presents an analytical expression for the diffusing capacity ($\Theta$) of the red blood cell (RBC) for any reactive gas in terms of size and shape of the RBC, thickness of the unstirred plasma layer surrounding the RBC, diffusivities and solubilities of the gas in RBC and boundary layer, hematocrit, and the slope of the dissociation curve. The expression for $\Theta$ has been derived by spatial averaging of the fundamental convection-diffusion-reaction equation for $O_2$ in the RBC and has been generalized to all cell shapes and for other reactive gases such as CO, NO, and CO$_2$. The effects of size and shape of the RBC, thickness of the unstirred plasma layer, hemoglobin concentration, and hematocrit on $\Theta$ have been analyzed, and the analytically obtained expression for $\Theta$ has been validated by comparison with different sets of existing experimental data for CO and CO$_2$. Our results indicate that the discoidal shape of the human RBC with average dimensions of 1.6-μm thickness and 8-μm diameter is close to optimal design for $O_2$ uptake and that the true reaction velocity in the RBC is suppressed significantly by the mass transfer resistance in the surrounding unstirred layer. In vitro measurements using rapid-mixing technique, which measures $\Theta$, in the presence of artificially created large boundary layers, substantially underpredicts the in vivo diffusing capacity of the RBC in the diffusion-controlled regime. Depending on the conditions in the RBC, uptake of less reactive gases (such as CO) undergoes transition from reaction-limited to diffusion-limited regime. For a constant set of morphological parameters, the theoretical expression for $\Theta$ predicts that $\Theta_{NO} > \Theta_{CO} > \Theta_{O_2} > \Theta_{CO_2}$.

THE DIFFUSING CAPACITY OF the red blood cell (RBC), $\Theta$, is the effective (or mass transfer-disguised) reaction rate between a reactive gas and hemoglobin in the RBC and depends on three physical and chemical processes, namely, internal mass transfer in the RBC due to finite rates of diffusion of the gas and hemoglobin inside the RBC, external mass transfer (due to diffusional gradients of the gas) in the stagnant plasma layer surrounding the RBC, and the actual rate of reaction between the dissolved gas and hemoglobin within the RBC.

The term $\Theta$ first appeared in the footnote of a 1954 paper of Forster et al. (14). In 1957, Roughton and Forster in their classic paper (46) proposed that resistances offered by the capillary membrane ($1/D_M$) and reaction rate in the RBC ($1/\Theta V_c$) are in series and therefore could be summed up to give the total resistance to gas transfer ($1/D_t$) between the alveolar gas and the RBC, and this relationship is given by

$$\frac{1}{D_t} = \frac{1}{D_M} + \frac{1}{\Theta V_c}$$

(1)

where $D_t$ is the overall diffusing capacity of the lung, $D_M$ is the diffusing capacity of the membrane separating the alveolar air from the blood, $V_c$ is the total volume in milliliters of the blood in the lung capillaries exposed to alveolar air, and $\Theta$ is the diffusing capacity of the RBC. In an attempt to account for the diffusional resistance in the plasma, Crapo et al. (8) defined $D_M$ in Eq. 1 as

$$\frac{1}{D_M} = \frac{1}{D_t} + \frac{1}{D_p}$$

(2)

with

$$D_t = K_t \frac{S_a + S_c}{2 \tau_{th}}$$

(3)

$$D_p = K_p \frac{S_c}{\tau_{hp}}$$

(4)

where $D_t$ is the tissue component of diffusing capacity; $D_p$ is the plasma component of diffusing capacity; $K_t$ and $K_p$ are the permeation coefficients of the gas in the tissue and the plasma, respectively; $S_a$ and $S_c$ are the surface areas of air-tissue interface and tissue-blood interface, respectively; and $\tau_{th}$ and $\tau_{hp}$ are the (harmonic) mean thicknesses of the tissue and the plasma, respectively.

In a historical review of the overall diffusing capacity ($D_t$) and its components ($D_M$ and $\Theta V_c$), Hughes and Bates (31) summarized the experimental efforts for evaluating $\Theta$ (for $O_2$ and CO) in the last 50 years. As mentioned in this paper, Holland (28), Forster (13), Reeves and Park (44), and Borland and Cox (4) used direct and indirect ways of measuring diffusing capacity of the RBC.

Staub et al. (49) measured the rate of reaction between $O_2$ and hemoglobin in the RBC using a continuous-flow rapid-reaction apparatus and suggested an empirical formula for diffusing capacity of $O_2$ ($\Theta_o_2$) based on the reaction rate, which is given by

$$\Theta_o_2 = \frac{60 \times 0.2}{22.4} \times k'_c \frac{(1 - S)}{760}$$

(5)

where $k'_c$ is the rate constant for the reaction with units of Torr per second, S is the fractional $O_2$ saturation of the RBC, and

Address for reprint requests and other correspondence: V. Balakotaia, Dept. of Chemical Engineering, University of Houston, Houston, TX 77204 (E-mail: bala@uh.edu) or A. Bidani, Dept. of Internal Medicine, Univ. of Texas Medical School, Houston, TX 77030 (E-mail: akhil.bidani@uth.tmc.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
The expression for the diffusing capacity (\(D_{LO}\)) in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.

The fundamental mechanism of uptake of a reactive gas in the RBC involves coupled convection-diffusion-reaction (CDR) of the gas and hemoglobin in the RBC and diffusion of the gas in the stagnant plasma layer. In this paper, we derive an analytical expression of the diffusion capacity (\(\Theta\)) for reactive gases in RBCs by spatially averaging the equations over the volume of the RBC.
orientation as it convects along blood vessels of different diameters. Average dimensions of this discoid are 8 μm in diameter and 1.6 μm in thickness, and Fig. 2 shows the discoid (or finite cylinder) model of an RBC of diameter D and thickness (or height) H.

**Governing Equations**

The diffusion-reaction equations in Lagrangian coordinates for a single RBC of any arbitrary geometry and volume Ω, and external surface area ∂Ω are given by

\[
\frac{dP_{\text{rc}}}{dt} = D_{\text{rc}} \frac{\partial^{2}P_{\text{rc}}}{\partial x^{2}} - R(P_{\text{rc}}, S) \tag{7}
\]

where \(P_{\text{rc}}\) is the partial pressure of dissolved O2 in the RBC, \(S\) is the (fractional) hemoglobin O2 saturation, \(\nabla^{2}\) is the three-dimensional Laplacian in the local coordinate in the RBC, \(D_{\text{rc}}\) and \(D_{\text{Hb}}\) are the diffusion coefficients of O2 and hemoglobin inside the RBC, \(R(P_{\text{rc}}, S)\) is the net rate of conversion of physically dissolved O2 to hemoglobin bound O2 by chemical reaction [see APPENDIX A for details on kinetics of reaction between O2 and hemoglobin and an expression for \(R(P_{\text{rc}}, S)\)], \([\text{Hb}]_{T}\) is the total intraerythrocytic hemoglobin (free + bound), and \(\alpha_{E}\) is the solubility of O2 in the RBC. Equations 7 and 8 are subject to the initial condition given by

\[
\begin{align*}
P_{\text{rc}}(t = 0) &= P_{\text{V}O_{2}} \\
S(t = 0) &= S_{0}
\end{align*}
\]

and the boundary conditions given by

\[
\nabla \cdot P_{\text{rc}} = 0 \text{ at the center of the RBC} \tag{11}
\]

(for symmetrical geometries),

\[
\alpha_{E} D_{\text{rc}} \nabla \cdot P_{\text{rc}} = \eta(P_{\text{rc}} - P_{\text{bl}}) \text{ on } \partial \Omega \tag{12}
\]

and

\[
\nabla \cdot S = 0 \text{ at the center of the RBC} \tag{13}
\]

(for symmetrical geometries)

\[
\nabla \cdot S = 0 \text{ on } \partial \Omega, \tag{14}
\]

where \(P_{\text{V}O_{2}}\) is the mixed venous partial pressure of O2 and \(P_{\text{bl}}\) is the spatially averaged partial pressure of dissolved O2 in the plasma. It has been shown (34, 39) that a thin unstirred plasma layer is formed around the surface of the RBC and retards O2 transfer from the plasma, and \(\eta\) in Eq. 12 is the mass transfer coefficient in the unstirred layer that quantifies the transfer resistance between the RBC and the plasma. An expression for \(\eta\) in terms of measurable variables could be derived by solving the coupled CDR equation of the RBC with the unstirred (boundary) layer surrounding it (please see APPENDIX B for derivation) and is obtained as

\[
\eta = \frac{\alpha_{E} D_{\text{bl}}}{\delta} \tag{15}
\]

where \(\delta\) is the thickness of the boundary layer, \(\alpha_{E}\) is the solubility of dissolved O2 in the stagnant layer, and \(D_{\text{bl}}\) is the diffusion coefficient of O2 in the layer.

Although it is possible to solve Eqs. 7–13 numerically (36) using the reaction kinetics shown in APPENDIX A, we use the dissociation relation between O2 and hemoglobin (APPENDIX A shows the dissociation relation used in this paper), which is expressed as

\[
S = H(P_{\text{rc}}) \tag{16}
\]

and the slope of the dissociation curve is given by

\[
\beta = \frac{\partial S}{\partial P_{\text{rc}}} \tag{17}
\]

This approach has the dual advantage of eliminating one of the variables \((P_{\text{rc}}\) or \(S\)) from the model equations (Eqs. 7–13), while including the special case of infinitely fast reaction (which cannot be obtained by solving Eqs. 7–13 numerically).

Eliminating \(R(P_{\text{rc}}, S)\) from Eqs. 7 and 8, we obtain

\[
\begin{align*}
(1 + [\text{Hb}]_{T}) \frac{\partial P_{\text{rc}}}{\partial t} &= \left( D_{\text{rc}} + D_{\text{Hb}}[\text{Hb}]_{T} \right) \frac{\partial^{2}P_{\text{rc}}}{\partial x^{2}} \\
&+ D_{\text{Hb}} \frac{\partial S}{\partial P_{\text{rc}}} (\nabla P_{\text{rc}})^{2}
\end{align*}
\]

Calculating \((\partial^{2}S/\partial P_{\text{rc}}^{2})\) by using the O2 dissociation, we find that \(\partial^{2}S/\partial P_{\text{rc}}^{2}\) is very small in the normal range of \(P_{\text{rc}}\) values. For example, \(\partial^{2}S/\partial P_{\text{rc}}^{2} = 7.6 \times 10^{-4}\) at \(P_{\text{rc}} = 40\) Torr and decreases monotonically to \(-2.5 \times 10^{-2}\) at \(P_{\text{rc}} = 100\) Torr. Thus \(D_{\text{Hb}} \partial^{2}S/\partial P_{\text{rc}}^{2} \approx 10^{-11} \text{ cm}^{2} \text{ s}^{-1} \text{ Torr}^{-2}\) in human lung, as a result of which the second term in the right-hand side of Eq. 18 \(\ll\) than the first. Equation 18 could therefore be simplified to

\[
\frac{\partial P_{\text{rc}}}{\partial t} = D_{E} \nabla^{2}P_{\text{rc}} \tag{19}
\]

with initial and boundary conditions being given by Eqs. 9, 11, and 12, where \(D_{E}\) is given by

\[
D_{E} = \frac{D_{\text{rc}} + D_{\text{Hb}}[\text{Hb}]_{T} \frac{\beta}{\alpha_{E}}}{1 + [\text{Hb}]_{T} \frac{\beta}{\alpha_{E}}} \tag{20}
\]

We are interested in deriving an analytical expression of the O2 diffusing capacity of the RBC in terms of the average partial pressure of O2 in the RBC, \((P_{\text{rc}})\) (rather than the detailed...
profile of $P_{\text{rbc}}$, and would also like to obtain a generic solution that is applicable to RBCs of different shapes. To this end, instead of solving Eq. 19 numerically, we average it spatially over the volume of the RBC. We skip the details of the spatial averaging procedure in the body of the paper and have presented them in APPENDIX C.

The spatially averaged form of Eq. 19 in Eulerian coordinates is given by

$$\left(\alpha_E + \left[Hb\right]_T\beta\right) \left(\frac{\partial\langle P_{\text{rbc}}\rangle}{\partial t} + v_{\text{rbc}} \frac{\partial\langle P_{\text{rbc}}\rangle}{\partial x}\right)$$

$$= \alpha_{\text{bar}} \left(\frac{S}{V_{\text{rbc}}} \right) \left(1 + \frac{D_{\text{bl}}}{D_{\text{bc}}} \frac{\beta}{\alpha_E} \left(Hb\right)_T \left(\langle P_{\text{rbc}}\rangle - \langle P_{\text{rbc}}\rangle\right)\right)$$

with the initial condition

$$\langle P_{\text{rbc}}\rangle = P_{\text{V}}O_2, \text{ at } t = 0$$

where $v_{\text{rbc}}$ is the velocity of the RBC, $x$ is the axial coordinate along the length of the capillary, $(S/V)_{\text{rbc}}$ is the surface area-to-volume ratio of the RBC, and $S_{\text{bar}}$ is the internal Sherwood number (or dimensionless internal mass transfer coefficient) of the RBC, which has been tabulated for different RBC shapes and geometries in Table 1. An analytical expression for $S_{\text{bar}}$ for a discoid-shaped RBC as a function of its ratio of height ($H$) to diameter ($D$) has been given in Eq. 124 in APPENDIX C. Figure 3 shows the variation of $S_{\text{bar}}$ with aspect ratio $H/D$ for a finite cylinder or discoid (shown in Fig. 2). Normal RBCs with average dimensions of 8 $\mu$m in diameter and 1.6 $\mu$m in thickness or height have $H/D = 0.2$ and therefore (from Eq. 124) have $S_{\text{bar}} = 2$.

**Analytical Expression for $O_2$-Diffusing Capacity of RBC**

The total $O_2$ carried by the RBC (per unit time per unit volume) is the summation of the dissolved free $O_2$ in the RBC and the $O_2$ carried in bound form (i.e., HbO$_2$). Thus the convective derivative may be expressed as

$$\left(\alpha_E + \left[Hb\right]_T\beta\right) \frac{D\langle P_{\text{rbc}}\rangle}{Dt} \left[^{\text{free dissolved } O_2}\right] + \left[Hb\right]_T \frac{D\langle P_{\text{rbc}}\rangle}{Dt} \left[^{\text{bound oxygen (HbO}_2)}\right]$$

$$= (\alpha_E + \left[Hb\right]_T\beta) \frac{D(P_{\text{rbc}})}{Dt}$$

where $\beta = dS/d(P_{\text{rbc}})$. Equating Eqs. 21 and 22, the equation for total $O_2$ transport from plasma to a single RBC is obtained as

$$\left(\alpha_E + \left[Hb\right]_T\beta\right) \left(\frac{\partial\langle P_{\text{rbc}}\rangle}{\partial t} + v_{\text{rbc}} \frac{\partial\langle P_{\text{rbc}}\rangle}{\partial x}\right) = \Theta(\langle P_{\text{pl}}\rangle - \langle P_{\text{rbc}}\rangle)$$

where $\Theta$ is the diffusing capacity of a single RBC, which is given by

$$\Theta = \alpha_{\text{bar}} \left(\frac{S}{V}\right) \left(1 + \frac{D_{\text{bl}}}{D_{\text{bc}}} \frac{\beta}{\alpha_E} \left[Hb\right]_T \langle P_{\text{rbc}}\rangle\right)$$

As mentioned earlier, the diffusing capacity $\Theta$ includes the effect of diffusional gradients within the RBC [through the term $(1/S_{\text{bar}})(V/S)_{\text{rbc}}$ in the denominator of Eq. 24], diffusional resistance in the stagnant plasma layer (through the term $\delta/d(D_{\text{bl}}$ in the denominator of Eq. 24), and the effect of facilitated transport of $O_2$ due to reactive coupling with hemoglobin [through the term $(D_{\text{bl}}/D_{\text{bc}})([Hb]_T(\beta/\alpha_E))$.]

The flux of $O_2$ from the plasma to a RBC per unit volume of blood, $N_{\text{rbc}}$, is given by

$$N_{\text{rbc}} = \Theta(\langle P_{\text{pl}}\rangle - \langle P_{\text{rbc}}\rangle)$$

where

$$\Theta = h\Theta$$

and $h$ is the hematocrit. Thus we obtain the diffusing capacity of the RBC per unit volume of blood ($\Theta_h$) as

$$\Theta_h = h\Theta$$

**Table 1. Shape factors for different red blood cell geometries**

<table>
<thead>
<tr>
<th>Red Cell Geometry</th>
<th>Dimensionless Internal Mass Transfer Coefficient ($S_{\text{bar}}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat plate</td>
<td>3</td>
</tr>
<tr>
<td>Sphere</td>
<td>5/3</td>
</tr>
<tr>
<td>Infinite cylinder</td>
<td>2</td>
</tr>
<tr>
<td>Finite cylinder/discoid (of height $H$, Diameter $D$)</td>
<td>$H/D$</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

**Equation 27** represents an analytical expression for the diffusing capacity of the RBC of any shape (quantified by the dimensionless internal mass transfer coefficient of the RBC, $S_{\text{bar}}$), volume $V$, surface area $S$, surrounded by an unstirred plasma layer of thickness $\delta$, where $\alpha_E$ and $D_{\text{bc}}$ are the solubility and diffusivity of $O_2$ in the RBC, respectively; $\alpha_{\text{bar}}$ and $D_{\text{bl}}$ are the $O_2$ solubility and diffusivity in the unstirred layer, respectively; $D_{\text{bl}}$ is the diffusion coefficient of hemoglobin in RBC; $[Hb]_T$ is the total hemoglobin concentration in the RBC; and $\beta$ is the slope of the $O_2$ dissociation curve.

In Eq. 27, $\delta/D_{\text{bl}}$ quantifies the external mass transfer resistance of the RBC, whereas $(V/S)_{\text{rbc}}/(S_{\text{bar}}D_{\text{bc}})$ is a measure of the internal mass transfer resistance in the RBC.

Although derived using the specific example of $O_2$, the expression for diffusing capacity of the RBC (Eq. 27) is generic and could be used for all reactive gases in the transport-limited regime (i.e., when reaction equilibrium is rapidly achieved). The effects of simultaneous binding of two (or more) reactive gases to the same ligand or the coupling between the transport of two gases could be captured by appropriately modifying the slope of the dissociation curve of the reactive gas, $\beta$. For example, the effect of $PCO_2$ or pH on the diffusing capacity of $O_2$ ($\Theta_{O_2}$) could be easily incorporated by evaluating $\beta$ in Eq. 17 by using a dissociation relation in which $S = S(P_{\text{bar}}, pH)$, such as the one proposed by Gomez...
[Please see APPENDIX A for the dissociation relation proposed by Gomez. However, in the calculations that follow, we ignore this effect and use the dissociation relation proposed by Severinghaus (47), which is also given in APPENDIX A]. Similarly, the effect of simultaneous binding of two gases (such as CO and O2 or NO and O2) to hemoglobin on $\Theta_t$ could be captured by using the appropriate expression of $\beta$ in Eq. 27. This has been illustrated in a later section (Other Reactive Gases).

RESULTS AND DISCUSSION

Effects of Morphological Parameters on Oxygen Diffusing Capacity

In this section, we explore the effect of different parameters such as size and shape of RBCs, thickness of the stagnant plasma layer, and hematocrit on the O2 uptake of the RBC, using the expression for $\Theta_t$ given in Eq. 27.

Figure 4 illustrates the effect of facilitated transport on $\Theta_t$. Calculations for Fig. 4 were performed using a discoid model, for a typical RBC of volume $= 94.1 \mu m^3$ and surface area $= 134.1 \mu m^2$, with $(V/S)_{rbc} = 0.7017 \mu m$ and $Sh_t = 2$. As could be seen from the figure, in the presence of facilitated diffusion, the enhancement of O2 uptake by the RBC could be as large as 6.3 times (attained at a $P_{rbc} = 20$ Torr). Groebe and Thews (22) report a maximum enhancement factor of 7 obtained at $P_{rbc} = 20$ Torr. As shown in Fig. 4, in the absence of facilitated diffusion ($[Hb]_{r} = 0$), $\Theta_t$ is independent of the O2 partial pressure in the RBC and is given by

$$\Theta_t = \frac{h \alpha_{bl} \left( \frac{S}{V} \right)_{rbc}}{\delta + \frac{1}{D_{bl} Sh_{rbc} S_{rbc}}} \quad (28)$$

Figure 5 illustrates the effect of the shape of RBCs on its O2 diffusing capacity by comparing the values of $\Theta_t$ for discoidal and spherical shapes of RBCs of the same volume and the flat plate model with thickness equivalent to the average thickness of a standard RBC. For the discoid model, calculations were performed for a typical RBC of volume $= 94.1 \mu m^3$ and surface area $= 134.1 \mu m^2$, with $(V/S)_{rbc} = 0.7017 \mu m$ and $Sh_t = 2$. For the spherical model, the volume of the RBC was taken as $94.1 \mu m^3$ and $Sh_t = 5/3$. For the flat plate model, the thickness of the RBC, $2b$, was taken as 1.6 $\mu m$ and $Sh_t = 3$. For all cases, the thickness of the stagnant layer, $\delta$, was taken (39) as 0.75 $\mu m$. Comparison of results shows that the discoidal shape of the RBC is close to optimal design as far as O2
uptake is concerned, whereas the spherical shape is the least efficient one. The reason for this observation could be attributed to the fact that, for a given volume of an RBC, the discoid shape provides the maximum surface area per unit volume, whereas the spherical shape provides the minimum. Therefore, nonmammalian RBCs that are ellipsoidal in shape have lower O2 diffusing capacity than mammalian ones (which are biconcave discs). It could also be noted from Fig. 5 that the difference between the discoidal and flat plate models is negligible, thus validating previous attempts (6, 38, 39) of modeling the normal RBC as a thin flat plate or sheet.

Figure 6 shows the effect of the thickness of the stagnant layer (δ) on Θr for a discoidal model of a RBC of (V/S)rbc = 0.7017 μm. As could be guessed intuitively, a thicker stagnant layer would result in enhanced external mass transfer resistance, thus decreasing the value of Θr. As could be observed from Fig. 6, the thickness of the stagnant layer affects Θr more at lower O2 partial pressures than at higher ones, because the effect of facilitated transport decreases steadily as O2 tension in the RBC increases. In the limit of δ → 0 (i.e., when there is no stagnant plasma layer surrounding the RBC), the external mass transfer resistance to O2 uptake vanishes and Θr (from Eq. 27) is given by

\[ \Theta_r = h\Theta = h\epsilon_{st}Sh\left(\frac{S}{V}\right)_{rbc} \left( D_{rbc} + D_{Hb}[Hb]_r \frac{\beta}{\alpha L} \right) \]

For a discoidal RBC with a (V/S)rbc = 0.7017 μm and δ = 0.75 μm, the ratio of internal to external resistance is approximately equal to 2.3. Therefore, as shown in Fig. 6, decreasing the stagnant layer thickness from 0.75 μm to 0 increases Θr by a factor of 2.5.

Figure 7 explores the effect of the thickness on the RBC on Θr by using the flat plate model for δ = 0.75 μm. Although a 25% increase in red cell thickness (over its normal value of 1.6 μm) reduces its O2 diffusing capacity by (a maximum of) 25%, a 25% reduction in thickness increases Θr by 44%. Therefore, for a given red cell volume and hematocrit, thinner cells have significantly higher O2 diffusing capacity than normal ones.

Figure 8 illustrates the effect of anemia on the O2 uptake capacity of the RBC. Because Θr (in Eq. 27) is proportional to the hematocrit h, its value decreases linearly with decreasing hematocrit, as shown in Fig. 8. The nature of the curves in Fig. 8 suggests that O2 uptake by the RBC is further reduced if anemia (or low hematocrit) is accompanied by low (Prc), caused by ventilation-perfusion heterogeneities or under pathophysiological conditions.
Experimental Verification of Model Predictions

In this section, we compare our model predictions of \( \Theta_t \) with two sets of experimental results existing in the literature.

One of the earliest experimental measurements of \( \Theta_t \) was done by Staub et al. (49). Staub and coworkers measured the \( O_2 \) uptake using the classical Hartridge-Roughton continuous-flow rapid-reactions apparatus. The internal diameter of the observation tube used by them is 10 mm, whereas the inner diameter of a typical pulmonary capillary is around 10 \( \mu \)m. As a result, thick boundary layers are formed around the RBC in the observation tube, leading to large external mass transfer resistances that reduce the \( O_2 \) diffusing capacity of the RBC considerably. Figure 9 compares the values of \( \Theta_t \) obtained using Eq. 27 for the discoidal model with the experimental data of Staub et al. (In Fig. 9, open circles represent Staub et al.’s data and the dotted line represents model predictions for \( \delta = 2 \) \( \mu \)m). As could be noted from the figure, the theoretical curve for \( \Theta_t \) for a boundary layer thickness of \( \delta = 2 \) \( \mu \)m corresponds closely to the experimental data of Staub et al., suggesting the presence of large plasma boundary layers around the RBC in their experimental measurements.

In the 70 years that have followed the development of the Hartridge-Roughton technique, the rapid-mixing technique has undergone technical improvements. Despite these advances, uncertainty exists about the measurements made with this technique primarily because of the thickness of the unstirred plasma boundary layer surrounding the RBC. Several authors (6, 29, 32, 52, 57) have reported values of unstirred layer thickness that vary between 1 and 15 \( \mu \)m, and Weibel (55) pointed out that the mean (harmonic) thickness of the unstirred layer in pulmonary capillaries is 0.5 \( \mu \)m. Thus the values of \( \Theta_t \) measured by rapid-mixing technique are disguised by mass-transfer limitations in the boundary layer and are therefore significantly lower than those that might be present in the pulmonary capillaries. Realizing this, Heidelberger and Reeves (25) used a planar monolayer of whole blood sandwiched between two Gore-Tex membranes to study \( O_2 \) uptake while varying the partial pressure of \( O_2 \) from 0 to 104 Torr. Figure 9 compares values of \( \Theta_t \) based on the experimental measurements of Heidelberger and Reeves (26) with the model predictions for an unstirred layer thickness of 0.5 \( \mu \)m, as suggested by Weibel. In Fig. 9, squares represent Heidelberger and Reeves’ data and the solid line represents the model predictions for \( \delta = 0.5 \) \( \mu \)m. As could be noted from the figure, both qualitative and quantitative agreement is obtained between theoretical and experimental values of \( \Theta_t \).

Other Reactive Gases

Although derived using the specific example of \( O_2 \), the expression for diffusing capacity of the RBC (Eq. 27) is generic and applicable to other reactive gases with appropriate modification. In this section, we obtain \( \Theta_t \) for other reactive gases of practical interest, such as CO, \( CO_2 \), and NO.

Carbon monoxide. The overall kinetics for reaction between a reactive gas \( X \) (e.g., \( O_2 \), NO, CO) and hemoglobin in the RBC is given by

\[
\frac{k_X}{k_s} \quad Hb + X \rightleftharpoons HbX \quad (30)
\]

and

\[
R_X = \frac{d}{dt}[HbX] = \frac{k_s}{k_X} [Hb] [X] - k_X [HbX] \quad (31)
\]

where \( k_s \) and \( k_X \) are the forward (or association) and reverse (or dissociation) rates, respectively, and the equilibrium constant \( K_X = k_X/k_s \). Table 2 reproduces the values of \( k_s \), \( k_X \), and \( K_X \) for \( O_2 \), CO, and NO binding to high-affinity form (R state) of human deoxyHBA, from Olson et al. (42). It could be noted from Table 2 whereas the association rate constants for \( O_2 \) and NO are of the same order of magnitude, that of CO is only 10\% that of \( O_2 \) (\( k_{CO}/k_{O2} = 0.09 \)). On the other hand, the dissociation rate constants of both CO and NO are very small compared with \( O_2 \) (\( k_{CO} = 4 \times 10^{-4} \mu M^{-1} s^{-1}, k_{NO} = 1.5 \times 10^{-9} \mu M^{-1} s^{-1} \)), as a result of which both CO and NO have much higher affinity for hemoglobin than \( O_2 \) (\( M_{CO} = 234, M_{NO} = 6.25 \times 10^{6} \)). This implies that although the overall reaction for CO and NO with hemoglobin can practically be considered as irreversible, the rate of binding of CO to hemoglobin is slow because \( k_{CO} \) is small. As pointed out by Olson et al. (42), the rate-limiting step for CO binding is internal bond formation with heme iron. Also, as observed by Johnson et al. (33), “because of the marked differences in reaction velocities between CO and NO with hemoglobin, measurements of DL_{CO} and DL_{NO} provide

<table>
<thead>
<tr>
<th>Gas (X)</th>
<th>( k_s ), ( \mu M^{-1} s^{-1} )</th>
<th>( k_X ), ( \mu M^{-1} s^{-1} )</th>
<th>( K_X ), ( \mu M^{-1} )</th>
<th>( M_X = K_X/k_s )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( O_2 )</td>
<td>66</td>
<td>20</td>
<td>3.2</td>
<td>1</td>
</tr>
<tr>
<td>CO</td>
<td>6</td>
<td>0.008</td>
<td>750</td>
<td>234</td>
</tr>
<tr>
<td>NO</td>
<td>60</td>
<td>0.00003</td>
<td>2 \times 10^6</td>
<td>6.25 \times 10^5</td>
</tr>
</tbody>
</table>

\( k_s \), association rate; \( k_X \), dissociation rate; \( K_X \), equilibrium constant.

Table 2. Typical rate constants (R-state parameters) for \( O_2 \), CO, and NO binding to human Hb at \( pH = 7, 20–25^\circ C \).
uniquely different and complementary information about the pulmonary capillary bed.”

It was first recognized by Gibson and Roughton (17) and Roughton and Forster (46) that, at low CO tension, the uptake of CO by the RBC is purely limited by the rate of binding of CO to oxyhemoglobin. This was later also verified by the experiments of Reeves and Park (44) in which they measured spectrophotometrically the simultaneous rates of uptake of CO and O2 in intact RBCs contained in whole blood thin films (created by spreading <1 μl of whole blood between two Gore-Tex membranes) that minimize extracellular diffusion barriers due to unstirred layers, which were estimated to be between 0.1 and 0.5 μm. They applied a simultaneous step change of PO2 from 40 to 100 and PCO from 0 to 2.1 Torr and observed that the combination of deoxyhemoglobin with O2 is largely completed within the first 40 ms before significant CO uptake occurs. On the basis of their measurements of unsteady-state uptake of CO in the RBC, Reeves and Park observed that “in vivo, in normoxia and hyperoxia, red cell CO uptake rate is wholly reaction rate limited and that pulmonary capillary red cell CO diffusion equilibrium is rapidly achieved.”

However, it was observed by Reeves and Park (44) that as “PO2 falls from 100 toward zero there is a marked increase in CO uptake process from a reaction- (or kinetic-) limited regime to a diffusion-limited regime.” Thus, under hypoxic conditions, both CO and O2 bind to reduced hemoglobin through competitive-parallel reactions. In addition, when PCO (i.e., CO concentration) is high, the rate of CO binding to deoxyhemoglobin, which is given proportional to PCO, also increases, shifting the CO uptake process from a reaction- (or kinetic-) limited regime to a diffusion-limited regime.

Thus the uptake process of CO by hemoglobin occurs in two separate regimes, namely reaction (or kinetically) limited and diffusion limited, depending on the values of PCO and PO2. Because the physics of the uptake process in these two regimes are completely different, we derive expressions for ΘCO in the two regimes separately.

**REACTION-LIMITED REGIME.** In the reaction-controlled regime, the binding of CO to hemoglobin is essentially a slow irreversible replacement reaction between oxyhemoglobin and CO, the kinetics of which has been modeled by Gibson and Roughton (17) as

\[ \frac{k'_4}{k_4} \]

\[ \text{Hb}_4 \text{O}_6 \overset{k'_4}{\rightleftharpoons} \text{Hb}_4 \text{O}_6 + \text{O}_2 \]

\[ \frac{l'_3}{l_3} \]

\[ \text{Hb}_4 \text{O}_6 + \text{CO} \overset{l'_3}{\rightleftharpoons} \text{Hb}_4 \text{O}_6(\text{CO}) \]

\[ \frac{k'_1}{k_1} \]

\[ \text{Hb}_4 \text{O}_6(\text{CO}) \overset{k'_1}{\rightleftharpoons} \text{Hb}_4 \text{O}_6(\text{CO}) + \text{O}_2 \]

\[ \frac{l'_2}{l_2} \]

\[ \text{Hb}_4 \text{O}_6(\text{CO}) + \text{CO} \overset{l'_2}{\rightleftharpoons} \text{Hb}_4 \text{O}_6(\text{CO})_2 + \text{O}_2 \]

where

\[ k_4 : k_{31} : k_{22} : k_{33} :: 4 : 3 : 2 : 1 \]

\[ l_4 : l_{31} : l_{22} : l_{33} :: 4 : 3 : 2 : 1 \]

\[ k'_1 = k'_{31} = k_{22} = k'_{33} \]

\[ l'_1 = l'_{31} = l'_{22} = l'_{33} \]

and the overall reaction rate of CO binding to oxyhemoglobin (R\text{COHb}) was obtained by Gibson and Roughton (17) as

\[ R_{\text{COHb}} = \frac{k_4[\text{CO}][\text{O}_2][\text{Hb}]}{4(k'_1 l'_4)}, \]

where \( k_4 \) was measured by Gibson (15) in human blood at a pH of 7.1 and a temperature of 19°C as 26 s–1 with activation energy of 18.4 kcal, and \( k'_1 l'_4 \) as 3, the ratio being independent of temperature. As calculated by Reeves and Park (44) using the data of Gibson, \( k_4 \) for human hemoglobin at 37°C is 157 s–1.

As in the case of O2 binding to hemoglobin, the diffusion-reaction equations in Lagrangian coordinates for binding of CO to oxyhemoglobin in a single RBC is given by

\[ \alpha_{\text{E,CO}} \frac{\partial P_{\text{bc,CO}}}{\partial t} = D_{\text{bc,CO}} \alpha_{\text{E,CO}} \nabla^2 P_{\text{bc,CO}} - R_{\text{COHb}} \]

\[ \frac{\partial [\text{COHb}]}{\partial t} = D_{\text{COHb}} \nabla^2 [\text{COHb}] + R_{\text{COHb}} \]

where \( P_{\text{bc,CO}} \) is the partial pressure of free O2 in the RBC, \([\text{COHb}]\) is the concentration of carboxyhemoglobin (COHb) in the RBC, \( D_{\text{bc,CO}} \) and \( D_{\text{COHb}} \) are the diffusion coefficients of CO and COHb inside the RBC, \( R_{\text{COHb}} \) is the net rate of binding of free CO to oxyhemoglobin, and \( \alpha_{\text{E,CO}} \) is the solubility of CO in the RBC. Equations 33–34 are subject to the initial conditions (for the case of a single-breath measurement of CO diffusing capacity) given by

\[ P_{\text{bc,CO}}(t = 0) = P_{\text{colar}}[\text{COHb}] = 0 \text{ at } t = 0 \]

and the boundary conditions given by

\[ \nabla \cdot P_{\text{bc,CO}} = 0, \text{ and } \nabla \cdot [\text{COHb}] = 0, \]

at the center of the red cell,

\[ \alpha_{\text{E,CO}} D_{\text{bc,CO}} \nabla \cdot P_{\text{bc,CO}} = \eta(P_{\text{pl,CO}} - P_{\text{bc,CO}}), \]
and \( \nabla \cdot [\text{COHb}] = 0 \), on surface of the RBC.

(37)

where \( \eta = (\alpha_{bl,CO}D_{bl,CO})/\delta \) (please see Appendix B for derivation).

Applying the spatial averaging procedure outlined in Appendix C, we average Eqs. 33–37 over the volume of a single RBC to obtain the spatially averaged equations in Eulerian coordinates as

\[
\alpha_{ECO} \frac{\partial P_{rbc,CO}}{\partial t} = \frac{\delta}{D_{bl,CO}} \left[ \frac{\nabla}{V} \right]_{rbc} \left( \frac{\partial P_{rbc,CO}}{\partial t} \right) - P_{rbc,CO} - R_{COHb}
\]

\[
\frac{D[\text{COHb}]}{Dr} = R_{COHb}
\]

(38)

where the symbols \( P_{rbc,CO} \), \( \text{[COHb]} \), and \( R_{COHb} \) now represent volume-averaged quantities.

Experimental observations of Reeves and Park (44) have shown that the uptake of CO in the RBC in low-\( P_{CO} \) conditions is purely reaction limited, with diffusion equilibrium being rapidly achieved. Here, we verify this observation using a time-scale analysis. For the case of a single-breath test of CO diffusing capacity, \( P_{CO} = 2.1 \) Torr, and the characteristic reaction time,

\[
t_{r,CO} = \frac{1}{k_{CO}[\text{CO}]} = \frac{1}{k_{CO}D_{rbc,CO}P_{CO}}
\]

\[= 0.068 \text{ s} \quad \text{(using values from Table 2 and Appendix A),}
\]

the characteristic internal diffusion time \( (t_{D,CO}) \),

\[
t_{D,CO} = \left( \frac{V}{S} \right)_{rbc} \frac{1}{D_{rbc,CO}}
\]

\[= 4.84 \times 10^{-4} \text{ s,}
\]

and the characteristic external diffusion time \( (t_{Dx,CO}) \) (for a unstirred layer thickness of 0.5 \( \mu \)m),

\[
t_{Dx,CO} = \frac{\delta^2}{D_{bl,CO}}
\]

\[= 1.8 \times 10^{-4} \text{ s}
\]

Therefore, the ratio of total diffusion time to reaction time, \( \mathcal{R} \), is given by

\[
\mathcal{R} = \frac{t_{Dx,CO} + t_{D,CO}}{t_{r,CO}} = \left( \frac{\left( \frac{V}{S} \right)_{rbc}}{D_{rbc,CO} + \frac{\delta^2}{D_{bl,CO}}} \right) k_{CO} \alpha_{rbc,CO} P_{CO}
\]

\[= 9.76 \times 10^{-3}.
\]

Because \( \mathcal{R} \ll 1 \) (or, in other words, total diffusion time \( \ll \) reaction time) for the conditions under which a single-breath diffusing capacity test of CO is performed, it is evident that diffusion equilibrium is attained very rapidly. Thus, under such low CO concentrations (in normoxia and hyperoxia), the uptake of CO is not limited by intracellular diffusion in the RBC but by the rate of reactive binding between CO and oxyhemoglobin. Therefore, under conditions of diffusion equilibrium and such low values of \( P_{CO} \), internal as well as external diffusional gradients of CO in the RBC are negligible, and it is reasonable to assume

\[
P_{rbc,CO} \approx (P_{pl,CO}) = P_{CO}
\]

(40)

where \( P_{CO} \) is the partial pressure of inspired CO in the single-breath CO diffusing capacity test. Using the above simplifying assumption (Eq. 40), we ignore Eq. 38 and evaluate the diffusing capacity of CO using Eq. 39 alone at constant values of \( P_{CO} \) and \( P_{O2} \). Because

\[
\text{[}O_2\text{Hb} \text{]} + \text{[}\text{COHb} \text{]} \approx \left[ \text{Hb} \right]_T
\]

(41)

Eq. 39 could be written as

\[
\frac{D[\text{O}_2\text{Hb}]}{Dr} = R_{COHb}
\]

\[= \frac{k_{[CO]}[O_2\text{Hb}]}{4 \left( \frac{k_4}{l^4} [O_2] + [CO] \right)}
\]

(42)

\[= \frac{k_{PCO}[O_2\text{Hb}]}{4 \left( \frac{k_4}{l^4} \alpha_{O2} P_{O2} + P_{CO} \right)}
\]

with the initial condition being given by

\[
[O_2\text{Hb}] \approx [\text{Hb}]_T \text{ at } t = 0
\]

(43)

Integrating Eqs. 42–43 at constant values of \( P_{CO} \) and \( P_{O2} \), we obtain

\[
[O_2\text{Hb}] = [\text{Hb}]_T \exp(-\Lambda t)
\]

(44)

where

\[
\Lambda = \frac{k_{PCO}}{4 \left( \frac{k_4}{l^4} \alpha_{O2} P_{O2} + P_{CO} \right)}
\]

(45)

Using Eqs. 42, 44, and 45, the time-dependent uptake rate of CO is given by

\[
\frac{D[\text{COHb}]}{Dr} = \frac{k_{PCO} [\text{Hb}]_T}{4 \left( \frac{k_4}{l^4} \alpha_{O2} P_{O2} + P_{CO} \right)} \exp(-\Lambda t)
\]

(46)

By definition, \( \Theta_{CO} \) for a single RBC is given by

\[
\Theta_{CO} P_{CO} = \frac{D[\text{COHb}]}{Dr}
\]

(47)

i.e.,

\[
\Theta_{CO} = \frac{k_{[\text{Hb}]_T}}{4 \left( \frac{k_4}{l^4} \alpha_{O2} P_{O2} + P_{CO} \right)} \exp(-\Lambda t)
\]

(48)

and the diffusing capacity of CO per unit volume of blood, \( \Theta_{I,CO} \), is obtained by simply multiplying \( \Theta_{CO} \) by the hematocrit \( h \) and is given by
\[ \Theta_{t, CO} = h\Theta_{CO} \]
\[ = \frac{h [Hb]_t k_4}{4\left(\frac{k'_4}{l'_4} \alpha_{CO} \frac{P_{O_2} + PCO}{P_{CO}}\right)} \exp(-\Delta t) \]  
\[ \Theta_{t, CO|t=0} = \frac{h [Hb]_t k_4}{P_{CO} l'_4} \int_{t=0}^{t_{test}} \Theta_{t, CO} \, dt \]
\[ = \frac{h [Hb]_t k_4}{P_{CO} l'_4} \left[ 1 - \exp\left(-\frac{k_4' \alpha_{CO} t_{test}}{4\left(\frac{k'_4}{l'_4} \alpha_{CO} P_{O_2} + P_{CO}\right)}\right) \right] \]

The time-averaged value of \( \Theta_{t, CO} \) obtained over a (10-s) single-breath measurement of CO diffusing capacity is given by

Figure 10 shows the variation of \( \Theta_{t, CO} \) with time by plotting Eq. 49 for a 10-s-long single-breath test of CO diffusing capacity, where \( P_{CO} = 2.1 \) Torr. Plots of \( \Theta_{t, CO} \) for different values of \( P_{O_2} \) are shown in Fig. 10. As could be seen from the figure, \( \Theta_{t, CO} \) is maximum at \( t = 0 \) and decreases exponentially with increasing time. Figure 10 also shows that \( \Theta_{t, CO|t=0} \) decreases significantly as \( P_{O_2} \) increases, where \( \Theta_{t, CO|t=0} \) is obtained from Eq. 49 as

\[ \Theta_{t, CO|t=0} = \frac{h [Hb]_t k_4}{4\left(\frac{k'_4}{l'_4} \alpha_{CO} \frac{P_{O_2} + PCO}{P_{CO}}\right)} \exp(-\Delta t) \]

The following values have been used corresponding to a single-breath test of CO diffusing capacity: \( P_{CO} = 2.1 \) Torr, \( t_{test} = 10 \) s, \( k_4/l'_4 = 3 \), as obtained by Gibson and Roughton (17), and \( k_4 = 157 \) s\(^{-1}\) at 37°C, as calculated by Reeves and Park (44) using Gibson and Roughton’s data. As could be seen from Fig. 11, the analytical expressions of \( \Theta_{t, CO} \) and \( \Theta_{t, CO|t=0} \) given by Eqs. 51 and 50, respectively, agree very well, both qualitatively and quantitatively, with the experimental measurements available in the literature. Needless to mention that in the kinetically controlled regime, \( \Theta_{t, CO} \) decreases as \( P_{O_2} \) increases, a feature that, although not obvious from Eq. 51, is evident from Fig. 11.

\[ \Theta_{t, CO|t=0} = \frac{1}{t_{test}} \int_{t=0}^{t_{test}} \Theta_{t, CO} \, dt \]

where \( t_{test} \) is the duration of the CO diffusing capacity measurement.

Based on experimental measurements, several empirical expressions for evaluation of \( \Theta_{t, CO} \) are available in the literature (13, 28, 44, 46), which have been tabulated in Table 3.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\( t_{CO} \) & References \\
\hline
0.73 + 0.0058 \( P_{O_2} \) & Roughton and Forster (46) \\
1.08 + 0.00647 \( P_{O_2} \) & Holland (28) \\
(1.3 + 0.0041 \( P_{O_2} \)) \left( 1 + 0.36 \frac{\alpha_{CO} PCO}{\alpha_{CO} P_{O_2}} \right) & Forster (13) \\
0.00211 P_{CO} + 0.00787 \( P_{O_2} \) & Reeves and Park (44) \\
\hline
\end{tabular}
\end{table}

\( \Theta_{t, CO|t=0} \) is the initial value of diffusing capacity of CO; \( \Theta_{t, CO} \) is the variation of diffusing capacity of CO with time by plotting Eq. 51.

Figure 11 compares the analytical expression of \( \Theta_{t, CO|t=0} \) obtained above (Eq. 51) as well the initial value of diffusing capacity of CO (\( \Theta_{t, CO|t=0} \)), given by Eq. 50, with the four expressions given in Table 3. In evaluation of \( \Theta_{t, CO|t=0} \) using Eq. 50 and \( \Theta_{t, CO|t=0} \) using Eq. 51, the following values have been used

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig10.png}
\caption{Variation of diffusing capacity of CO (\( \Theta_{t, CO} \)) (given by Eq. 49) with time during a 10-s-long single-breath test of CO diffusing capacity, for different values of \( P_{O_2} \).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig11.png}
\caption{Variation of \( \Theta_{t, CO} \) with \( P_{O_2} \) at partial pressure of CO (\( PCO \)) = 2.1 Torr. (Curves A–D refer to empirical expressions of \( \Theta_{t, CO} \) available in the literature obtained by using experimental data, which have been listed in Table 3. Curves F and E represent values from the present study based on initial rate and average rate over 10 s, respectively.)}
\end{figure}
where \( \Theta_{t,CO} \) and \( \Theta_{t,CO} \) given by Eqs. 50 and 51, respectively. Although curves B–D in Fig. 11 are based on measurements of initial rates of reaction between CO and oxyhemoglobin, the measured values of \( \Theta_{t,CO} \) are lower than the analytically obtained one, \( \Theta_{t,CO} \) (curve F). This could be attributed to the presence of unstirred layers of finite thickness in the experimental measurements, whereas the analytical expression (Eq. 50) has been obtained for the ideal case in which no unstirred layer is present. It may also be noted from Fig. 10 that \( \Theta_{t,CO} \) decreases exponentially with increasing time, and, therefore, the initial value of \( \Theta_{t,CO} \) is invariably higher than the time-averaged value of \( \Theta_{t,CO} \). For \( \text{PO}_2 \) > 300 Torr, this decrease is slow, as a result of which \( \Theta_{t,CO} \) is given (as in the case of \( \text{O}_2 \)). The treatment of this case is similar to that of \( \text{O}_2 \). The \( \text{CO} \) is assumed to be irreversible. Thus, for the case of \( \text{O}_2 \) and \( \text{CO} \), respectively; \( \text{M}_{CO} \) is the relative affinity of hemoglobin for \( \text{CO} \) compared with \( \text{O}_2 \), given in Table 2; and the function \( H \) is the same function as the usual dissociation curve for \( \text{O}_2 \) expressed as \( S_{CO} = H(\text{P}_{\text{rc}}) \) as in Eq. 88. Using Eqs. 52–53, we obtain

\[
S_{CO} = \frac{M_{CO} \text{PCO}}{\text{P}_{\text{O}_2} + M_{CO} \text{PCO}} \tag{52}
\]

\[
S_{CO} + S_{\text{O}_2} = H(\text{P}_{\text{rc}} + M \text{PCO}) \tag{53}
\]

where \( S_{CO} \) and \( S_{\text{O}_2} \) are the fractional saturation of \( \text{O}_2 \) and \( \text{CO} \), respectively; \( \text{P}_{\text{O}_2} \) and \( \text{PCO} \) are the average partial pressures of \( \text{O}_2 \) and \( \text{CO} \), respectively; \( M_{CO} \) is the relative affinity of hemoglobin for \( \text{CO} \) compared with \( \text{O}_2 \); and the function \( H \) is the same function as in Eq. 2 (and the function \( \text{H} \) is the same as the usual dissociation curve for \( \text{O}_2 \) expressed as \( S_{CO} = H(\text{P}_{\text{rc}}) \) as in Eq. 88. Using Eqs. 52–53, we obtain

\[
S_{CO} = \frac{M_{CO} \text{PCO}}{\text{P}_{\text{O}_2} + M_{CO} \text{PCO}} H(\text{P}_{\text{rc}} + M \text{PCO}) \tag{54}
\]

\[
\frac{\partial S_{CO}}{\partial \text{PCO}} = \frac{M_{CO} \text{PO}_2}{(\text{P}_{\text{O}_2} + M_{CO} \text{PCO})^2} + \frac{M_{CO} \text{PCO}}{\text{P}_{\text{O}_2} + M_{CO} \text{PCO}} \frac{\partial H}{\partial \text{PCO}} \tag{55}
\]

In the diffusion-limited regime, the reactions of \( \text{CO} \) and \( \text{O}_2 \) with deoxyhemoglobin attain equilibrium, and, therefore, the treatment of this case is similar to that of \( \text{O}_2 \). The \( \Theta_{t,CO} \) in this regime is given (as in the case of \( \Theta_{t,CO} \)) by

\[
\Theta_{t,CO} = h \alpha_{\text{SO}_2}(\text{S}) \frac{1 + \frac{D_{\text{Hb}}}{D_{\text{rc,CO}}} [\text{Hb}]_r}{\delta} + \frac{1}{D_{\text{S}, \text{CO}}} \frac{\delta}{\text{Sh} D_{\text{rc,CO}}} \frac{\text{S}}{\text{rc}} \tag{56}
\]

where \( \beta_{\text{CO}} \), the slope of the dissociation curve, given by Eq. 55, captures the effect that the binding of \( \text{O}_2 \) with deoxyhemoglobin exerts on \( \text{CO} \) binding. Table 4 compares the values of \( \Theta_{t,CO} \) (in ml·ml⁻¹·min⁻¹·Torr⁻¹) obtained by using Eq. 56 for an unstirred layer thickness of 0.5 μm with the experimental measurements of \( \Theta_{t,CO} \) by Reeves and Park (44) in the diffusion-limited regime (i.e., hypoxic with high \( \text{PCO} \)). Agreement is found to be good, and deviations between experimental results and model predictions are within the bounds of experimental errors. It must be stated that, in this mass-transfer-limited regime, \( \Theta_{t,\text{CO}} \) (like \( \Theta_{t,\text{O}_2} \)) is sensitive to the unstirred layer thickness.

### Table 4. Comparison of diffusing capacity of \( \text{CO} \) with experimental measurements of Reeves and Park in the diffusion limited regime

<table>
<thead>
<tr>
<th>( \text{PCO} ), Torr</th>
<th>( \text{PO}_2 ), Torr</th>
<th>( \Theta_{t, \text{CO}} ) Experimental (Reeves and Park (44))</th>
<th>( \Theta_{t, \text{CO}} ) Theoretical (Eq. 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>70</td>
<td>1.5</td>
<td>1.7</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
<td>1.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

\( \Theta_{t, \text{CO}} \) CO diffusing capacity of RBC, ml·ml⁻¹·min⁻¹·Torr⁻¹.

It must be mentioned that a quantitative analysis of simultaneous binding of \( \text{O}_2 \) and \( \text{CO} \) to deoxyhemoglobin was performed by Nicolson and Roughton (41) in 1950. The major difference between the cited work and the present one is that whereas the former is numerical calculation of increase in carboxyhemoglobin saturation in the RBC under reaction nonequilibrium conditions (i.e., in the reaction-limited regime), Eq. 56 presented above provides an analytical expression for diffusing capacity of the RBC under reaction equilibrium conditions (i.e., in the diffusion-limited regime), when the Haldane relations hold good (Eqs. 52–53). It may be argued that \( \text{CO} \) and \( \text{O}_2 \) bind to deoxyhemoglobin simultaneously only when \( \text{CO} \) and \( \text{O}_2 \) tensions are comparable, in which case the uptake occurs in the diffusion-limited regime (as discussed above). Moreover, although Nicolson and Roughton’s work was restricted to a slab geometry of the RBC, the present approach accommodates different red cell shapes and is applicable to other reacting gases such as \( \text{NO} \) and \( \text{CO}_2 \), as we shall illustrate in the following sections.

**Nitric oxide.** Table 2 presents the values of \( k_{\text{NO}} \), \( k_{\text{NO}} \), and \( M_{\text{NO}} \) for NO binding to high-affinity form (R state) of human deoxyHbA, from Olson et al. (42). \( M_{\text{NO}} \), the relative affinity of hemoglobin for NO compared with \( \text{O}_2 \) is approximately equal to 6.25 × 10⁻⁴, whereas the rate of forward reaction \( k_{\text{NO}} \) is of the same order of magnitude as that \( \text{O}_2 \). Thus it could be concluded that (like \( \text{O}_2 \)) the binding of \( \text{NO} \) to deoxyhemoglobin is fast and not reaction limited but diffusion limited, whereas, because of its high affinity toward hemoglobin (i.e., because \( M_{\text{NO}} \ll 1 \)), the binding of \( \text{NO} \) to hemoglobin (unlike \( \text{O}_2 \)) is assumed to be irreversible. Thus, for the case of simultaneous binding of \( \text{O}_2 \) and \( \text{NO} \) to deoxyhemoglobin, both the reactions are parallel and diffusion limited. We use the Haldane relations (23) to express the relation between HbNO and NO partial pressure (\( \text{P}_{\text{NO}} \)) and the dependence on \( \text{O}_2 \), under equilibrium conditions, which are given by

\[
S_{\text{NO}} = \frac{M_{\text{NO}} \text{P}_{\text{NO}}}{\text{PO}_2 + M_{\text{NO}} \text{P}_{\text{NO}}} \tag{57}
\]

\[
\text{S}_{\text{NO}} + \text{S}_{\text{O}_2} = 1 \tag{58}
\]

where Eq. 58 is a modified form of Eq. 53 that accounts for the high reactivity and affinity of NO with hemoglobin. Simplifying Eqs. 57–58, we obtain the fraction saturation of \( \text{NO} \) as

\[
\text{S}_{\text{NO}} = \frac{M_{\text{NO}} \text{P}_{\text{NO}}}{\text{PO}_2 + M_{\text{NO}} \text{P}_{\text{NO}}} \tag{59}
\]

and \( \beta_{\text{NO}} \), the slope of the NO dissociation curve as

\[
\frac{\delta S_{\text{NO}}}{\delta \text{P}_{\text{NO}}} = \frac{M_{\text{NO}} \text{P}_{\text{NO}}}{(\text{PO}_2 + M_{\text{NO}} \text{P}_{\text{NO}})^2} \tag{60}
\]
Perillo et al. (43) used chemiluminescent techniques to measure pulmonary diffusing capacity of NO. They used an initial inspiration of 5–10 ppm of NO and the average value of PNO (steady-state partial pressure of NO in the alveoli) measured in seven normal human subjects was 1.8 × 10⁻⁶ Torr. At such typically used low values of PNO, βNO could be simplified to

\[ \beta_{NO} = \frac{M_{NO}P_{O_2}}{(P_{O_2} + M_{NO}P_{NO})} \approx \frac{M_{NO}}{P_{O_2}} \]  

\[ = 6.25 \times 10^{-7}/\text{Torr at } P_{O_2} = 100 \text{ Torr} \]  

and because the uptake of NO due to reactive binding far exceeds that in the dissolved form, Θr,NO could also be simplified to

\[ \Theta_{r,NO} = \frac{M_{NO}h[S]}{P_{O_2}V_{rbc}D_{NO}} \left( \frac{D_{NO}}{D_{NO,NO}} \right) \]  

\[ \times \left[ \frac{[Hb]}{D_{NO,NO}} + \frac{1}{S_{rbc}D_{NO,NO}} \left( \frac{V}{S_{rbc}} \right)^{-1} \right] \]  

\[ = 1.64 \times 10^{6} \text{ ml NO} \cdot \text{ml blood}^{-1} \cdot \text{min}^{-1} \cdot \text{Torr}^{-1} \]  

for a discoidal RBC (i.e., Sh = 2) with δ ≈ 0.75 μm and (V/S)hbc = 0.7017 μm, or, in other words,

\[ \frac{1}{\Theta_{r,NO}} = 0.61 \times 10^{-6} \text{ min} \cdot \text{Torr at } P_{O_2} = 100 \text{ Torr, } \approx 0 \]  

indicating that, for highly reactive gases like NO, the diffusional resistance offered by the RBC, i.e., (Θr,NO)⁻¹, is negligible, and the total resistance offered by the capillary, DNO,⁻¹, is purely due to the resistance provided by the alveolar capillary membrane.

In the limit of vanishingly small stagnant layer thickness (i.e., δ → 0), Eq. 63 is given by

\[ \Theta_{r,NO} = \frac{M_{NO}}{P_{O_2}h[S]} \left[ \frac{D_{NO}}{D_{NO,NO}} \right] \]  

\[ \times \left[ \frac{[Hb]}{D_{NO,NO}} + \frac{1}{S_{rbc}D_{NO,NO}} \left( \frac{V}{S_{rbc}} \right)^{-1} \right] \]  

\[ = 4.2 \times 10^{6} \text{ ml NO} \cdot \text{ml blood}^{-1} \cdot \text{min}^{-1} \cdot \text{Torr}^{-1} \]  

It is also interesting to analyze the effect of O₂ partial pressure on Θr,NO, which as given by Eq. 63 is expected to decrease linearly as P₀₂ increases. As shown in Eq. 65, at P₀₂ of 100 Torr (i.e., normal human breathing in room air, inspired O₂ fraction = 21%), Θr,NO = 0.61 × 10⁻⁶ min/Torr. When pure O₂ is used, i.e., inspired O₂ fraction is increased to 100%, Θr,NO increases to 4.4 × 10⁻⁶ min/Torr, which is practically zero. Therefore, it might be concluded that, for most cases of practical interest, Θr,NO → 0 and remains almost unaffected by the O₂ partial pressure.

Carbon dioxide. It must be mentioned that though the expression for Θr, i.e., Eq. 27 has been derived for gases that bind with hemoglobin, it could easily be used with slight modifications to obtain the diffusing capacity of gases that react with other red cell constituents (instead of hemoglobin). In this section, we illustrate how to evaluate Θr by using a modified form of Eq. 27 for such gases by using the example of CO₂.

CO₂ is present in the blood in three different forms, namely, physically dissolved in plasma and RBC, bicarbonate ions (HCO₃⁻) in plasma and RBC, and carbamino compounds (R-NHCOO⁻) in RBC only. Apart from its transport in dissolved form, CO₂ in the RBC is transported primarily as bicarbonate ions (i.e., [R-NHCOO⁻] « [HCO₃⁻]), which are formed as a result of hydration of CO₂ catalyzed by the enzyme carbonic anhydrase (CA). The hydration reaction

\[ CA \]  

\[ CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^- \]  

is almost instantaneous owing to the presence of CA activity, which is very high within the RBC (acceleration factor A,CA ~ 6,000–10,000).

Because the rate of the above reaction primarily determines the rate of CO₂ transport in blood, we evaluate βCO₂ (and therefore Θr,CO₂) on the basis of this reaction.

When a slightly modified form of Eq. 27 is used, the diffusing capacity of the RBC for CO₂ (Θr,CO₂) is given by

\[ \Theta_{r,CO_2} = \frac{h[S]}{D_{NO,CO_2}D_{NO,NO}Shbc(S/V)} \]  

\[ \times \left[ \frac{[Hb]}{D_{NO,NO}} + \frac{1}{S_{rbc}D_{NO,NO}} \left( \frac{V}{S_{rbc}} \right)^{-1} \right] \]  

\[ \times \frac{\alpha_{E,CO_2} + \beta_{CO_2}}{D_{NO,CO_2}} \]  

where αₑ,CO₂ is the physical solubility of CO₂ in the blood, and

\[ \beta_{CO_2} = \frac{d[HCO_3^-]}{dP_{CO_2}} \]  

where [HCO₃⁻]rbc is the content of CO₂ in bicarbonate form in the RBC. Assuming [R-NHCOO⁻] « [HCO₃⁻], the total CO₂ present in the blood as HCO₃⁻ is given by

\[ [HCO_3^-]_{total} = [CO_2]_{total} - [CO_2]_{dissolved} \]  

\[ = [CO_2]_{total} - \alpha_{E,CO_2}P_{CO_2} \]  

The total amount of bicarbonate ions in the blood ([HCO₃⁻]rbc given by Eq. 71) is partitioned between the two phases, namely the RBC and the plasma, and the partition coefficient, which is obtained by using the principle of equality of electrochemical potentials in each phase (Gibbs-Donnan equilibrium), is given by

\[ \frac{[HCO_3^-]_{rbc}}{[HCO_3^-]_{plasma}} = 4.6 - 0.529 \text{ pHe} + (0.058 \text{ pHe} - 0.437) \text{ S} \]  

where [HCO₃⁻]rbc and [HCO₃⁻]plasma are the contents of bicarbonate ions in the RBC and the plasma, respectively; pHe is the pH in the plasma; and S is the fractional O₂ saturation in the RBC. Using Eqs. 71 and 72, we obtain

\[ [HCO_3^-]_{rbc} = ([CO_2]_{total} - \alpha_{E,CO_2}P_{CO_2} \]  

\[ \times \{1 - [5.6 - 0.529 \text{ pHe} + (0.058 \text{ pHe} - 0.437) \text{ S}]^{-1} \} \]  

Using Eqs. 70 and 73, we obtain βCO₂ (at any fixed O₂ saturation) as

\[ \beta_{CO_2} = \left( \frac{d[CO_2]_{total}}{dP_{CO_2}} - \alpha_{E,CO_2} \right) \]  

\[ \times \{1 - [5.6 - 0.529 \text{ pHe} + (0.058 \text{ pHe} - 0.437) \text{ S}]^{-1} \} \]  

and using Eqs. 69 and 74, we obtain Θr,CO₂ as
We use the data on $[CO_2]_{\text{total}}$ vs. $PCO_2$ given by Comroe et al. (7) at $pH_p = 7.4$, and $S = 0.7$ and $S = 0.975$, respectively, to calculate $\partial [CO_2]_{\text{total}} / \partial PCO_2$. Using these data, $\Theta_{CO_2}$ for a discoid-shaped RBC with $(V/S)_{rbc} = 0.7017$ μm and boundary layer thickness $\delta = 0.75$ μm, is obtained as

$$\Theta_{CO_2}(S = 0.7) = 23.3$$

$$\Theta_{CO_2}(S = 0.975) = 23.3$$

where $\Theta_{CO_2}$ is in ml·ml⁻¹·min⁻¹·Torr⁻¹ and $PCO_2$ is in Torr.

Figure 12 presents the plots of $\Theta_{CO_2}$ vs. $PCO_2$ for 70% and 97.5% $O_2$ saturation, using Eqs. 76 and 77, respectively. It could be noticed that, unlike in the case of $O_2$, $\Theta_{CO_2}$ decreases monotonically with increasing $CO_2$ tension, and the effect of $O_2$ saturation per se on $CO_2$ diffusing capacity is negligible. In vivo, however, the binding of $O_2$ to reduced hemoglobin in pulmonary capillaries releases Bohr protons (H⁺), and this tends to shift Eq. 68 to the left and alter the estimate of $\Theta_{CO_2}$. As could be noted from the figure, the magnitude of $\Theta_{CO_2}$ is up to 20 times larger than that of $O_2$ or $CO_2$, a range of values that is accepted in the existing literature. Experimental measurements of CO2 diffusing capacity in isolated dog lungs by Enns and Hill (9) show that the $CO_2$ diffusing capacity is 5–15 times greater than that of $CO$ or $O_2$.

**Limiting Cases**

On the basis of the above analysis, we summarize the limiting cases in the uptake of any reactive gas by the RBC by isolating the dominant physical phenomena.

**Facilitated transport.** As shown above, for highly reactive gases like NO, the uptake process is primarily transport limited, with the rate of facilitated transport being at least one order of magnitude higher than that of physical diffusion. In this limit, $\Theta_t$ is given by

$$\Theta_t = h \left( \frac{D_{bl}}{D_{rbc}} [Hb]_t \beta \left( \frac{\delta}{D_{bl}} + \frac{1}{Sh D_{rbc} (V/S)_{rbc}} \right) \right)^{-1}$$

*Equation 78* gives the effective reaction velocity in the RBC in the absence of any external mass-transfer limitation (or disguise).

For $O_2$, the above limit could be attained during exercise, i.e., at lower values of $(P_{rbc})$ (as is evident from Fig. 4), when facilitated transport dominates the uptake process. As is shown in Fig. 4, as $(P_{rbc})$ increases facilitated transport decreases considerably, and for $(P_{rbc}) > 80$ Torr, $\beta$ (and therefore facilitated diffusion) decreases linearly with increasing $(P_{rbc})$.

**Pure diffusion.** In the limit of high $O_2$ tension, i.e., $(P_{rbc}) > 200$ Torr, facilitated transport is negligible and the uptake process is purely through diffusion of physically dissolved $O_2$.

In this limit, $\Theta_t$ is given by

$$\Theta_t = \alpha_E \frac{S}{V_{rbc}}$$

*External mass transfer.** If there is no stagnant plasma layer surrounding the RBC, external mass transfer resistance is absent. In this limit of $\delta \to 0$, $\Theta_t$ is given by

$$\Theta_t = \alpha_E Sh \left( \frac{S}{V} \right)^2 \left( \frac{D_{rbc} + D_{bl}[Hb]_t \beta}{\alpha_E} \right)$$

As shown in the case of $O_2$ and NO, for a discoidal RBC of $\delta = 0.75$ μm and $(V/S)_{rbc} = 0.7017$ μm, the ratio of internal to external mass transfer resistance is ~2.3. Therefore, decreasing the stagnant layer thickness from 0.75 μm to 0 increases $\Theta_t$ by a factor of 2.5.

On the other hand, if the surrounding plasma is completely unstirred resulting in a large boundary layer around the RBC (as in the case of measurements done with a stopped-flow apparatus), then external mass transfer resistance $\ll$ internal mass transfer resistance and the uptake process is limited by the external mass transfer resistance due to the boundary layer. In this case, $\Theta_t$ is inversely proportional to the boundary layer thickness $\delta$ and independent of the internal mass transfer coefficient, $Sh$, and is given by

$$\Theta_t = h \alpha_E \frac{D_{bl}}{\delta} \left( 1 + \frac{D_{bl} [Hb]_t \beta}{\alpha_E} \right)$$

*Figure 12. Variation of CO2 diffusing capacity of the RBC ($\Theta_{CO_2}$) with partial pressure of CO2.*
Internal mass transfer. If internal mass transfer resistance $\gg$ external mass transfer resistance, or in other words

$$\frac{1}{Sh_D_{\text{rbc}}} \left( \frac{V}{S_{\text{rbc}}} \right) \gg \frac{\delta}{D_{\text{bl}}},$$

Eq. 82

$\Theta_i$ attains the same limit as given by Eq. 80. On the other hand, if internal mass transfer resistance $\ll$ external mass transfer resistance (i.e., the inequality sign in Eq. 82 is reversed), $\Theta_i$ attains the limit given by Eq. 81.

Mass Transfer Disguise of Reaction Velocity in the RBC

As defined earlier, the diffusing capacity of the RBC ($\Theta_i$) is the mass transfer-disguised effective rate of reaction between a reactive gas and hemoglobin in the RBC. The rate of uptake of most reactive gases is determined not by the intrinsic reaction rate of the gas with one (or more) of the RBC constituents but by the mass transfer-disguised effective reaction rate, $\Theta_i$. In other words, most gases of practical interest such as $O_2$, $CO_2$, NO, etc., react with RBC constituents fast enough so that the overall uptake process is mass transfer (diffusion and perfusion) limited. In terms of time scales, this implies that the time scales for internal and external mass transfer in the RBC are greater than that of reaction.

As illustrated in this paper, $\Theta_i$ is influenced significantly by both internal and external mass transfer resistances as well as by its affinity with hemoglobin and its reactivity (which determines the slope of the dissociation curve, $\beta$). The in vivo thickness of the unstirred plasma layer surrounding the RBC ($\delta$), which determines the external mass transfer resistance of the RBC, has been estimated to vary between 0.5 and 1 $\mu$m. The classical Hartridge-Roughton continuous-flow apparatus measures $\Theta_i$ in vitro in the presence of artificially created large (1–15 $\mu$m) boundary layers. As is evident from the present analysis, for gases that are in the transport-limited regime (such as $O_2$, $CO_2$, NO), the artificially created boundary layers could underpredict $\Theta_i$ by severalfold, whereas for less reactive gases that are in the reaction-controlled regime (such as CO), unstirred layers have negligible effect on $\Theta_i$. In other words, the more reactive the gas, more sensitive it is to external mass transfer limitations (i.e., to unstirred layer thickness) and, therefore, the larger is the experimental error. Heidellenger and Reeves (25) and Reeves and Park (44) circumvented this problem by measuring $\Theta_{i,CO}$ and $\Theta_{i,CO}$, respectively, of a planar monolayer of whole blood sandwiched between Gore-Tex membranes. As has been shown in Fig. 9, the theoretical expression for $\Theta_i$ (Eq. 27) could be used to determine the unstirred layer thickness in the in vitro experiments, which is otherwise difficult to measure.

Limitations of the Model

The present model has the following limitations.

We have ignored the effects of pulsatility of capillary blood flow on the boundary layer thickness ($\delta$) surrounding the RBC, which, in turn, affects the diffusing capacity. The effects of pulsatile nature of capillary blood flow and volume on gas exchange have been discussed in detail by Bidani et al. (3).

We have assumed the PCO to be constant while deriving the analytical expression for diffusing capacity of CO in the reaction-controlled regime.

Synergetic effects of $O_2$ and $CO_2$ binding concurrently to hemoglobin have been neglected.

The binding reaction between the gas and hemoglobin ($H_2O$ in case of $CO_2$) has been assumed to be fast enough so that the time scale required to attain chemical equilibrium is much smaller than the diffusion time scale in the RBC, or, in other words, the uptake occurs in the diffusion/transport-limited regime. This assumption is valid for most reactive gases of practical interest (except CO and $CO_2$ under certain conditions, as shown in Table 4). The hydration of $CO_2$ in the RBC is catalyzed by CA activity and is therefore assumed to be instantaneous. Despite the general validity of this assumption, it has been shown by Bidani (2) that the CA activity is vulnerable to inhibition. In such cases, the slope of $CO_2$ dissociation curve would depend on the acceleration factor ($ACA$) of the catalyst, and $\beta_{CO_2}$ (in Eq. 74) would be a function of $ACA$, along with $\text{pH}_b$ and $S$.

$CO_2$ transport, in vivo, is somewhat more complex because of mass transport ($HCO_3^-$ and $Cl^-$ exchange across the red cell membrane), different buffer capacities for plasma and RBC, and availability of the CA activity to plasma (2).

Our analysis on NO does not include recent controversies (20, 35, 40) of alternate sites or forms of NO binding to hemoglobin.

CONCLUSIONS

In this paper, we have derived an analytical expression for the diffusing capacity of the RBC for reactive gases. We start with the fundamental CDR equations that describe the transport and reaction rate processes of the reactive gas and hemoglobin in the RBC. We apply a spatial averaging procedure to the CDR equations to average them over the volume of the RBC and obtain simplified low-dimensional models that describe the net uptake of the gas in the RBC in terms of diffusing capacity ($\Theta_i$). As an outcome of the averaging process, an analytical expression of $\Theta_i$ (Eq. 27) is obtained in terms of size and shape of RBC, thickness of the stagnant plasma layer surrounding it, diffusivities and solubilities of the gas in the RBC and unstirred plasma layer, diffusivity and concentration of hemoglobin in the RBC, and hematocrit as well the $O_2$ dissociation curve.

Using Eq. 27, we explore the effects of the above-mentioned parameters on $\Theta_i$ for $O_2$ and therefore on the rate of $O_2$ uptake in the RBC. Calculations of $\Theta_{i,CO}$ for different shapes of RBCs show that the discoidal shape of the RBC is close to optimal design as far as $O_2$ uptake is concerned, whereas the spherical shape is the least efficient one. Equation 27 is useful to study the effects of deformation of the RBC on its $O_2$ uptake capacity, especially under pathophysiological conditions, like sickle cell anemia or diminished caliber of the microcirculation. We quantify the decrease in $\Theta_{i,CO}$ caused by increase in the thickness of the surrounding stagnant plasma layer and find that the thickness of the stagnant layer affects $\Theta_{i,CO}$ more at lower $O_2$ partial pressures than at higher ones. As far as the thickness of the RBC is concerned, we find that, for a given RBC volume and hematocrit, thinner cells have significantly higher $O_2$ diffusing capacity than normal RBCs. Using Eq. 27, we also analyze the effects of anemia on $\Theta_{i,CO}$. The diffusing capacity of the RBC is found to decrease linearly with decreasing hematocrit and is reduced further if anemia or low
hematocrit is accompanied by low \(P_{\text{Rbc}}\), caused by ventilation-perfusion heterogeneities or under pathophysiological conditions.

Comparisons of model predictions (for different values of unstirred layer thickness, \(\delta\)) have been made with the experimental data of Staub et al. (49) and Heidelberg and Reeves (25, 26). Although Staub et al.’s data agree qualitatively with our theoretical predictions for an unstirred layer thickness \(\delta\) of 2 \(\mu\)m, Heidelberg and Reeves’ data give qualitative as well as quantitative agreement with model predictions for \(\delta = 0.5\ \mu\)m. It has been shown that low values of \(\theta\), measured in vitro by using continuous-flow apparatus for rapid reactions are likely due to artificially created large unstirred layers surrounding the RBC. The uptake of most reactive gases such as \(\text{O}_2\), \(\text{CO}_2\), and \(\text{NO}\) (and also \(\text{CO}\) under certain conditions) occurs in the mass transfer limited regime, in which \(\theta\) is particularly sensitive to the unstirred layer thickness.

The analytical expression of \(\theta\) (given by Eq. 27) is valid for all reactive gases for which the uptake occurs in the mass-transfer-limited regime and has been applied to obtain values of \(\theta\), for \(\text{CO}\) (under hypoxic conditions), \(\text{CO}_2\), and \(\text{NO}\). The \(\theta\) values for \(\text{CO}\) agree very well with experimental data available in the literature, and \(\theta\) values for \(\text{CO}_2\) are found to be larger than that of \(\text{O}_2\) by one order of magnitude, whereas \(\theta\) for \(\text{NO}\) are \(\sim 10^6\), validating traditional views that the resistance provided by the RBC in case of \(\text{NO}\) binding is negligible and \((\theta_{\text{NO}})^{-1} \approx 0\).

Analysis of diffusing capacity of \(\text{CO}\) led us to the conclusion that at low values of \(P_{\text{CO}}\) (as in measurements of a single-breath test of \(\text{CO}\) diffusing capacity) under normoxic or hyperoxic condition, the uptake process is reaction controlled, whereas in the other limit of high \(P_{\text{CO}}\) and hypoxic condition it is diffusion controlled. In fact, it can be shown that such transition from a reaction-limited regime to a diffusion- (or transport-) limited regime also occurs for other reactive gases like \(\text{O}_2\) and \(\text{CO}_2\), depending on the conditions present in the RBC. On the basis of the above analysis, we identify the controlling regimes of the different reactive gases (\(\text{O}_2\), \(\text{CO}\), \(\text{CO}_2\), \(\text{NO}\)) in the RBC and tabulate them in Table 5. It is hoped that better understanding the transition of the uptake process of reactive gases at the level of RBCs from one controlling regime to another would improve our ability to quantify the overall pulmonary gas uptake.

### Table 5. Controlling regimes for uptake of reactive gases in the red blood cell

<table>
<thead>
<tr>
<th>Gas Reaction Condition</th>
<th>Binds to</th>
<th>Controlling Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{O}_2)</td>
<td>deoxyHb</td>
<td>Reaction limited</td>
</tr>
<tr>
<td>Low (P_{\text{O}_2})</td>
<td></td>
<td>Transport limited (diffusion or perfusion limited)</td>
</tr>
<tr>
<td>Normal physiological range ((\leq 100) Torr)</td>
<td>deoxyHb</td>
<td>Reaction limited</td>
</tr>
<tr>
<td>CO</td>
<td>o2Hb</td>
<td>Reaction limited</td>
</tr>
<tr>
<td>(P_{\text{CO}} &lt; 10) Torr, (P_{\text{O}_2} \geq 100) Torr</td>
<td>o2Hb</td>
<td>Reaction limited</td>
</tr>
<tr>
<td>(P_{\text{CO}} &lt; 10) Torr, (P_{\text{O}_2} &lt; 100) Torr</td>
<td>deoxyHb</td>
<td>Reaction limited</td>
</tr>
<tr>
<td>(P_{\text{CO}} &lt; 10) Torr, (P_{\text{O}_2} &lt; 70) Torr</td>
<td>deoxyHb</td>
<td>Diffusion limited</td>
</tr>
<tr>
<td>NO, ppm level or higher CO(_2)</td>
<td>deoxyHb</td>
<td>Diffusion limited</td>
</tr>
<tr>
<td>In presence of carbonic anhydrase</td>
<td>(\text{H}_2\text{O})</td>
<td>Transport limited (diffusion or perfusion limited)</td>
</tr>
<tr>
<td>In absence of carbonic anhydrase</td>
<td>(\text{H}_2\text{O})</td>
<td>Reaction limited</td>
</tr>
</tbody>
</table>

### APPENDIX A

The overall rate kinetics for reaction between \(\text{O}_2\) and hemoglobin in the RBC is given by

\[
\text{Hb} + \text{O}_2 \stackrel{k'}{\rightarrow} \text{HbO}_2
\]

and \(R(\text{P}_{\text{Rbc}},S)\) in Eq. 7 could be written as

\[
R(\text{P}_{\text{Rbc}},S) = \frac{d}{dt}[\text{HbO}_2] = k'[\text{Hb}][\text{O}_2] - k[\text{HbO}_2]
\]

where \(S = [\text{HbO}_2]/([\text{Hb}]+[\text{HbO}_2]) = [\text{HbO}_2]/[\text{Hb}]\). Experimentally, \(k'\) has been measured (16) as

\[
k' = 3.5 \times 10^9 \text{mol}^{-1} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}
\]

\[
= \frac{2.08}{N} \text{ s}^{-1} \cdot \text{Torr}^{-1}
\]

where \(N\) is the \(\text{O}_2\) capacity of 1 ml RBCs, and

\[
k = 42.5 \text{ s}^{-1}
\]

We use the dissociation relation proposed by Severinghaus (47), given by

\[
S = H(P_{\text{Rbc}}) = \frac{1}{1 + 23,400(P_{\text{Rbc}} + 150P_{\text{Rbc}}^{-1})^{-1}}
\]

where \(S\) is the fractional saturation of \(\text{O}_2\) in the RBC, which is related to the concentration of \(\text{O}_2\) in RBC \((C_{\text{Rbc}})\) by

\[
C_{\text{Rbc}} = 0.0134 \times [\text{Hb}]_T \times S + 0.00031 \times P_{\text{Rbc}} \text{ at 37°C}
\]

and \(P_{\text{Rbc}}\) (in Torr in Eqs. 88–89) is the partial pressure of dissolved \(\text{O}_2\) in the RBC.

To include the effect of plasma pH on \(\theta_{\text{O}_2}\), the \(\text{O}_2\) saturation relation proposed by Gomez (19) could be used instead of Eq. 88, which is given by

\[
S = G(P_{\text{Rbc}}, \text{pH}_p) = \frac{v}{1 + v}
\]

where

\[
v = 0.925 \times (\times 10^{-2} u P_{\text{Rbc}} + 2.8) \\
(\times 10^{-2} u P_{\text{Rbc}})^2 + 30 (\times 10^{-2} u P_{\text{Rbc}})^3
\]

\[
u = \{5.727 \exp[1.812(\text{pH}_p - 7.4)] + 4.273\}

\[
\times \{1.204 \exp[0.03536(37 - T)] - 0.204\}
\]

\(\alpha_{\text{O}_2}/\alpha_{\text{CO}} = 1.33\)
APPENDIX B

Derivation of Mass Transfer Coefficient in the Unstirred Plasma Layer

Here, we illustrate the derivation of the external mass transfer coefficient in the plasma boundary layer surrounding the RBC. Figure 13 shows the schematic of a RBC surrounded by a stagnant plasma layer. The steady-state mass balance equation for the above system is given by

$$\alpha D_{\text{rec}} \frac{d^2 P_{\text{re}}}{dy^2} = k P_{\text{re}}, \quad 0 < y < b$$

$$D_{\text{bi}} \frac{d^2 P_{\text{bi}}}{dy^2} = 0, \quad b < y < b + \delta$$

$$\frac{d P_{\text{re}}}{dy} = 0 @ y = 0$$

$$P_{\text{bl}} = \langle P_{\text{bi}} \rangle @ y = b + \delta$$

$$D_{\text{re}} \frac{d P_{\text{re}}}{dx} = D_{\text{bi}} \frac{d P_{\text{bi}}}{dx} @ x = b$$

$$P_{\text{re}}(x = b) = P_{\text{pl}}(x = b)$$

where $P_{\text{re}}$ is the partial pressure of O2 in RBC phase, $P_{\text{bi}}$ is the partial pressure of O2 in the boundary layer, $k$ is the pseudo-first-order rate constant, and $D_{\text{rec}}$ and $D_{\text{bi}}$ are the diffusion coefficients of O2 in the RBC and boundary layers, respectively. Here $b$ is the half thickness of the RBC, $\delta$ is the thickness of the unstirred layer, and $\alpha$ is the solubility of O2 in the RBC boundary layer. The solution of Eq. 93 is given by

$$P_{\text{re}} = \frac{\lambda_1 \cosh(\Delta x/b)}{\sinh(\Delta x/b)}[\lambda_1 - 1 + \lambda_1 \cosh(\Delta x/b)] 0 < x < b$$

$$P_{\text{bl}} = \frac{x/b + \lambda_1 \cosh(\Delta x/b)}{\lambda_1 - 1 + \lambda_1 \cosh(\Delta x/b)}, \quad b < x < b + \delta$$

where

$$\lambda_1 = \frac{D_{\text{bl}}}{D_{\text{re}}}$$

$$\lambda_2 = 1 + \frac{\delta}{b}$$

and the flux is given by

$$\frac{\partial P_{\text{re}}}{\partial \xi} = B_i \frac{\partial P_{\text{re}}}{\partial t'}$$

with

$$\frac{\partial P_{\text{re}}}{\partial \xi} = 0 \text{ at } \xi = 0$$

$$\frac{\partial P_{\text{re}}}{\partial \xi} = B_i y (P_{\text{bi}} - P_{\text{re}}) \text{ at } \xi = 1$$

where

$$\xi = \frac{y}{b}, \quad \Delta x = \frac{t}{b \alpha \sqrt{\eta}}, \quad P_{\text{re}} = \frac{P_{\text{re}}}{P_{\text{ai}}}$$

$$B_i = \frac{\eta b}{D_{\text{re}}} \left( \frac{\alpha_2}{\alpha_1} \right) \left( \frac{b}{D_{\text{re}}} \right)$$

The mass transfer coefficient remains practically the same, even in the presence of nonlinear kinetics.

APPENDIX C

Spatial Averaging of Convection-Diffusion-Reaction Equation in the RBC

The simplified diffusion-reaction equation (in Lagrangian coordinates) for dissolved O2 and HbO2 concentrations in the RBC is given by

$$\frac{\partial P_{\text{re}}}{\partial t} = D_{\text{E}} \nabla^2 P_{\text{re}}$$

with initial and boundary conditions being given by Eqs. 9, 11, and 12, where $D_{\text{E}}$ is given by

$$D_{\text{E}} = \frac{D_{\text{bi}} + D_{\text{rec}}[HbO2]}{1 + [HbO2]} \frac{\beta}{\alpha_E}$$

We first illustrate the averaging process for an infinite slab geometry and then generalize it for other shapes of RBCs. Equations 9, 11, 12, and 19 for the case of a thin disc of thickness $2b$ are written in terms of dimensionless coordinates and numbers as

$$\frac{\partial P_{\text{re}}}{\partial \xi} = B_i \frac{\partial P_{\text{re}}}{\partial t'}$$

with

$$P_{\text{re}} = p_{\text{O}2} \text{ at } t' = 0$$

$$\frac{\partial P_{\text{re}}}{\partial \xi} = 0 \text{ at } \xi = 0$$

$$\frac{\partial P_{\text{re}}}{\partial \xi} = B_i y (P_{\text{bi}} - P_{\text{re}}) \text{ at } \xi = 1$$

and $P_{\text{ai}}$ is the alveolar partial pressure of O2. Here, $B_i$ is the ratio of external mass transfer resistance in the stagnant layer to the internal mass transfer resistance in the RBC and is given by

$$B_i = \frac{\eta b}{D_{\text{E}}} \left( \frac{\alpha_2}{\alpha_1} \right) \left( \frac{b}{D_{\text{E}}} \right)$$

Fig. 13. Stagnant plasma layer around the RBC.
The time scale for mass transfer across the unstirred layer (\(t_{\text{trans-bl}}\)) in the RBC, local diffusional equilibrium exists and \(p_{\text{rbc}} = \langle p_{\text{rbc}} \rangle \) everywhere inside the RBC. Mathematically speaking, for \(Bi = 0\), Eqs. 103–106 have a zero eigenvalue with a constant eigenfunction. For \(Bi > 0\) (i.e., \(Bi\) is small but finite), diffusional gradients exist inside the RBC, and we express the dimensionless partial pressure of O\(_2\) in the RBC (which now depends both on the transverse coordinates and time) as
\[
p_{\text{rbc}}(\xi, t) = \langle p_{\text{rbc}} \rangle(t') + p'_{\text{rbc}}(\xi, t')
\]
where \(\langle p_{\text{rbc}} \rangle\) is the spatially averaged partial pressure of O\(_2\) in the RBC and \(p_{\text{rbc}}\) is a fluctuation about this average such that it satisfies the solvability criterion
\[
\langle p_{\text{rbc}} \rangle = \int_{-b}^{b} p_{\text{rbc}} d\xi = 0
\]
The fluctuation \(p_{\text{rbc}}(\xi, t)\) is solved by substituting Eq. 109 in Eq. 103, which gives
\[
\frac{\partial^2 p_{\text{rbc}}}{\partial \xi^2} = Bi \left[ \frac{\partial p_{\text{rbc}}}{\partial t'} + \frac{\partial p'_{\text{rbc}}}{\partial t'} \right]
\]
with boundary conditions
\[
\left. \frac{\partial p_{\text{rbc}}}{\partial \xi} \right|_{\xi = 0} = 0
\]
and
\[
\frac{\partial p'_{\text{rbc}}}{\partial \xi} = Bi \gamma (\langle p_{\text{rbc}} \rangle - p_{\text{rbc}}) \quad \text{at} \quad \xi = 1
\]
Equation 103 on being averaged (or integrated) over the thickness \(2b\) of the RBC gives
\[
\frac{d(p_{\text{rbc}})}{dt} = \gamma (\langle p_{\text{rbc}} \rangle - p_{\text{rbc}})
\]
where \(\langle p \rangle = \int_{-b}^{b} p(\xi) d\xi\), and \(p_{\text{rbc,s}} = p_{\text{rbc}}(\xi = 1.0)\), which could be obtained by evaluating the local fluctuation \(p_{\text{rbc}}\) by solving Eqs. 110–113 and using the relation
\[
p_{\text{rbc}}(t) = \langle p_{\text{rbc}} \rangle(t) + p_{\text{rbc}}(\xi = 1.0)
\]
This is achieved by subtracting Eq. 114 from Eq. 111 and using Eq. 115, which gives
\[
\frac{\partial^2 p_{\text{rbc}}}{\partial \xi^2} = Bi \left[ \frac{\partial p'_{\text{rbc}}}{\partial t'} + \gamma (\langle p_{\text{rbc}} \rangle - p_{\text{rbc}}) - p'_{\text{rbc}}(\xi =-1.0) \right]
\]
Equation 116 is solved along with Eqs. 110, 112, and 113 by using perturbation expansion of the fluctuation as
\[
p'_{\text{rbc}} = \sum_{j=1}^{N} Bi^j p_j
\]
Equation 114 is called the “global equation.” Eq. 116 is called the “local equation,” and the averaging technique illustrated above by using the simple example of diffusion and reaction in a flat plate is called “spatial averaging by the Liapunov-Schmidt method.” This averaging technique can be applied to any diffusion-convection-reaction or diffusion-reaction system in which diffusion is dominant at the small scale and at diffusion-equilibrium the system has a zero eigenvalue with a constant eigenfunction. In such cases, the above method can be used to eliminate spatial degrees of freedom near zero eigenvalues by averaging over the small scale and yet retain all the important physics of the small scale in the averaged equations. Further details of spatial averaging by Liapunov-Schmidt method could be obtained from related publications (1, 5).

The spatially averaged equations (following the solution of Eq. 116) for the above example are given by
\[
\frac{d(p_{\text{rbc}})}{dt} = \gamma (\langle p_{\text{rbc}} \rangle - p_{\text{rbc}})
\]
and
\[
\frac{p_{\text{rbc}} - \langle p_{\text{rbc}} \rangle}{Bi} = \frac{\gamma \eta}{Sh} (p_{\text{rbc}} - \langle p_{\text{rbc}} \rangle)
\]
where \(\langle p_{\text{rbc}} \rangle\) and \(p_{\text{rbc}}\) are the spatially averaged partial pressures of O\(_2\) in the RBC and the plasma, respectively, and \(p_{\text{rbc}}\) is the O\(_2\) partial pressure in the RBC membrane. The averaged equations (Eqs. 118 and 119) could be written as a simple equation by eliminating the partial pressure of O\(_2\) at the red cell membrane, \(p_{\text{rbc,s}}\), and the single averaged equation is given in dimensional form by
\[
\frac{d(P_{\text{rbc}})}{dt} = \frac{\gamma \eta}{b_{\text{rbc}}} (\langle P_{\text{rbc}} \rangle - \langle P_{\text{rbc}} \rangle)
\]
where \(P_{\text{rbc}}\) and \(\langle P_{\text{rbc}} \rangle\) are the (dimensional) average partial pressures of O\(_2\) in the RBC and the plasma, respectively, and other symbols retain their usual meanings. As is obvious, the averaged equations (Eqs. 118 and 119) retain information about the size and shape of the RBC, and the thickness of the unstirred layer in terms of \(Bi\) and \(Sh\), as well as internal and external diffusional gradients of the RBC in terms of differences between the different O\(_2\) partial pressures, namely, \(P_{\text{rbc}}, P_{\text{rbc,s}},\) and \(P_{\text{rbc}}\).

Although the above formulation has been derived in Lagrangian (or moving) frame of reference, it could easily be transformed into Eulerian (or fixed) coordinates by replacing the total derivative \(d/dt\) in Eq. 120 by the substantive derivative \(D/Dr = d/dr + \gamma x/dx\), and the averaged equation for the RBC is given by
\[
\frac{D(P_{\text{rbc}})}{Dr} = \frac{\gamma \eta}{b_{\text{rbc}}} (\langle P_{\text{rbc}} \rangle - \langle P_{\text{rbc}} \rangle)
\]
i.e.,
\[
\frac{\partial (P_{\text{rbc}})}{\partial t} + v_{\text{rbc}} \frac{\partial (P_{\text{rbc}})}{\partial x} = \frac{\gamma \eta}{b_{\text{rbc}}} (\langle P_{\text{rbc}} \rangle - \langle P_{\text{rbc}} \rangle)
\]
with the initial condition
\[
\langle P_{\text{rbc}} \rangle = P_{\text{V}O_2} \text{ at } t = 0
\]
where \(v_{\text{rbc}}\) is the velocity of the RBC and \(x\) is the axial coordinate along the length of the capillary. The advantage of an Eulerian description is that the slip between the RBC and the plasma could easily be accounted for by allowing the velocity of RBC \(v_{\text{rbc}}\) to be different from that of the plasma \(v_{\text{pl}}\).

It must be mentioned that the spatial averaging procedure illustrated above is independent of the shape and/or geometry of the RBC, and the averaged equations (Eqs. 118 and 119) remain the same irrespective of the shape of the RBC. The shape of the RBC is accounted for in the averaged models through the (dimensionless) internal mass transfer coefficient, \(Sh\), (in Eq. 119), which is obtained for different shapes of the RBC by inverting the Laplacian \(\nabla^2 P_{\text{rbc}}\) in Eq. 7 for different geometries, or, in other words, by solving the following local equation instead of Eq. 116:
\[ \nabla^2 \phi_{rbc} = Bi \left[ \frac{\partial \phi_{rbc}}{\partial t} + \langle \phi_{rbc} \rangle - \langle \phi_{rbc} \rangle - \phi_{rbc} \right] \] (123)

Table 1 shows the shape factors (Shi) for different shapes of RBCs, obtained by solving Eq. 123 for different geometries. For a finite cylinder of height H and diameter D (as shown in Fig. 2), the internal mass transfer coefficient is given as a function of H/D by (from unpublished notes of V. Balakotaiah)

\[ \frac{1}{Sh_i} = \frac{1}{3} \left(1 + 2\lambda^2\right) - \frac{128\lambda(1 + 2\lambda^2)}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{(2n - 1)^2} I_0(v_n) \] (124)

where

\[ \lambda = \frac{H}{D} \] (125)

\[ v_n = \frac{(2n - 1)\pi}{2\lambda} \] (126)

and \( I_0 \) and \( I_1 \) are modified Bessel functions. Figure 3 uses Eq. 124 to plot the variation of Shi with D/H, obtained for different geometries, and Table 1 shows the shape factors (Shi) for different shapes of RBCs, with the initial condition \( \langle \phi_{rbc} \rangle = Prbc \), \( v_{rbc} = 0.2 \), and therefore (from Fig. 3) have Shi = 0.2.

The averaged model (Eq. 122) for an RBC of any shape is given by

\[ \alpha_{\phi} \left( \frac{\partial \langle \phi_{rbc} \rangle}{\partial t} + v_{rbc} \frac{\partial \langle \phi_{rbc} \rangle}{\partial x} \right) = \frac{S}{V_{rbc}} \frac{\gamma}{D_{rbc}} \] (127)

with the initial condition

\[ \langle \phi_{rbc} \rangle = P_{\text{Vo}_{2}} \] at \( t = 0 \),

where \( (S/V)_{rbc} \) is the surface area-to-volume ratio of a single RBC, Shi is the dimensionless internal mass transfer coefficient of the RBC (listed in Table 1 for different geometries), and

\[ \eta = \frac{\alpha_{\phi} D_{bi}}{\delta} \] (128)

\[ Bi = \frac{\eta}{\alpha_{\phi} DE} \left( \frac{V}{S}_{rbc} \right) \] (129)

\[ \frac{D_{bi}}{\delta_{DE}} \left( \frac{V}{S}_{rbc} \right) \] (130)

\[ \gamma = \frac{DE}{D_{rbc}} \] (131)

In dimensional form, Eq. 127 is given by

\[ \alpha_{\phi} + [Hb]_e \beta \left( \frac{\partial \langle \phi_{rbc} \rangle}{\partial t} + v_{rbc} \frac{\partial \langle \phi_{rbc} \rangle}{\partial x} \right) \] (132)

\[ \quad = \alpha_{\phi} \left( \frac{S}{V}_{rbc} \right) \left( 1 + \frac{1}{\delta_{DE}} \frac{[Hb]}{\alpha_{\phi}} + \frac{1}{Sh_i D_{rbc}} \left( \frac{V}{S}_{rbc} \right) \right) \langle \phi_{rbc} \rangle \]

ACKNOWLEDGMENTS

We thank the reviewers for helpful comments.

GRANTS

The work of V. Balakotaiah and S. Chakraborty was supported by the University of Houston through a Moore Professorship. The work of A. Bidani and S. Chakraborty was supported by National Heart, Lung, and Blood Institute Grant HL-51241.

REFERENCES


28. Holland RAB. Rate at which CO replaces O\textsubscript{2} from O\textsubscript{2}Hb in red cells of different species. Respir Physiol 7: 43–63, 1969.


31. Hughes JMB and Bates DV. Some factors affecting the red cell.


