Numerical Solution of Partial Differential Equation Describing Oxygenation Rate of the Red Blood Cell

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Abstract The non-linear partial differential equation for O\textsubscript{2} diffusion was solved numerically in the three-dimensional red cell model by using the alternating-direction implicit method. The oxygenation rate factor of hemoglobin (\(F_s\)) was assumed to decrease as the O\textsubscript{2} saturation (\(S_{O_2}\)) increases, as given by \(F_s = 2.1 \times (1 - S)^2 \) (sec\(^{-1}\) · (mmHg\(^{-1}\)). The result obtained was compared with the solutions of the equations derived by Thews and Moll and also with those obtained from the sheet model. The oxygenation rate of the red cell largely depended on the diffusivity across the diffusion barrier around the red cell (\(\eta\)). When \(\eta = 2.5 \times 10^{-6} \text{cm} \cdot \text{sec}^{-1} \cdot \text{(mmHg)}^{-1}\) was inserted into the present equation, the numerical solution showed a good correlation with the experimental data. When the sheet model was applied, the \(\eta\) value obtained from the same experimental data was about twice as great as that obtained in the disc model.

One of the characteristic features of the \(S_{O_2}\)-time curves of the red cell was the decrease in steepness at a high \(S_{O_2}\) range, which has been thought to occur due to the decrease in the oxygenation rate of hemoglobin. Therefore, the difference of the actual \(P_{O_2}\) in the red cell from the fictitious, so-called "back-pressure" which is evaluated from the O\textsubscript{2} dissociation curve through the actual \(S_{O_2}\) has been expected to become greater as the \(S_{O_2}\) increases. The result obtained from the present equation revealed that the above \(P_{O_2}\) difference became as great as 20 mmHg at the maximum point. In the solutions obtained from Thews' and Moll's equations, however, the slope of the \(S_{O_2}\)-time curve was not significantly reduced at a high \(S_{O_2}\) range.

Key Words: O\textsubscript{2} diffusion, oxygenation of red blood cell, non-linear differential equation, numerical solution.

The oxygenation rate of the red blood cell was measured for the first time by Hartridge and Roughton (1923) who showed that it was significantly slower than that of hemoglobin molecules. The slowness was theoretically explained.
by ROUGHTON (1932) as being ascribed to the diffusion of oxygen into the red cell. Furthermore, he (1945a, b) demonstrated that the reaction in which CO replaces O₂ combining with hemoglobin was relatively slow in comparison with the transit of the red cell through the lung capillary, and that this reaction rate decreased even further as $P_{O_2}$ increased. Using this measured reaction rate he attempted to estimate the transit time in the pulmonary capillary. Later, Gibson et al. (1955) reported that the oxygenation rate of the red cell, similarly to this CO replacement reaction, was not fast enough to be able to disregard its influence on the oxygen uptake in the lung capillary. MOCHIZUKI and FUKUOKA (1958), on the other hand, calculated the rate of diffusion of O₂ in the red cell and suggested that the rate of oxygenation of hemoglobin should be slower in a high O₂ saturation range, because the concentration of reduced hemoglobin is diminished as the O₂ saturation increases. MOCHIZUKI et al. (1958) further verified experimentally that the oxygenation of the red cell partly limited O₂ uptake in the lung.

The differential equation used by ROUGHTON (1932) and NICOLSON and ROUGHTON (1951) had two components, e.g., the diffusion and chemical reaction components, as given in a one-dimensional model by

$$\frac{\partial P}{\partial t} = \alpha D \frac{\partial^2 P}{\partial z^2} - k' \cdot P \cdot y + k \cdot (1-y),$$

(1)

where $\alpha$ is the O₂ solubility, $D$ the diffusion coefficient, $y$ the concentration of reduced hemoglobin, and $k'$ and $k$ are the forward and backward reaction rate constants of oxygenation. In order to simplify the two terms in the chemical reaction in Eq. (1), MOCHIZUKI and FUKUOKA (1958) used the following treatment: in an equilibrium state the reduced Hb concentration, $y$, can be expressed by the O₂ dissociation curve. Along this curve the relation between $P_{O_2}$ and $(1-y)$ is roughly given by

$$k' \cdot P^* \cdot y = k \cdot (1-y),$$

(2)

where $P^*$ is the $P_{O_2}$ equilibrated with the O₂ saturation, $(1-y)$. Inserting Eq. (2) into Eq. (1), the following relation is obtained:

$$\frac{\partial P}{\partial t} = \alpha D \frac{\partial^2 P}{\partial z^2} - k' \cdot y \cdot (P - P^*).$$

(3)

The $P_{O_2}$ of hemoglobin, $P^*$, is a function of $(1-y)$, and $y$ decreases as the reaction proceeds. Therefore, $P^*$ is, in a strict sense, a function of position ($z$), time ($t$), and the O₂ saturation $(1-y)$. However, because it was impossible to solve analytically such a non-linear differential equation, Mochizuki and Fukuoka solved Eq. (3) by assuming $P^*$ to be a function of $z$ and $t$, but independent of the O₂ saturation, at least for a short period. THEWS (1961), however, pointed out that such an approximation was not permissible, because the rate of oxygenation of hemoglobin is so fast that the $P_{O_2}$ difference, $P - P^*$, in the second term of Eq. (3) becomes so small that it should be neglected. He proposed a new equation:
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\[ \alpha' \frac{\partial P}{\partial t} = \alpha D \frac{\partial^2 P}{\partial z^2}, \]

where \( \alpha' \) is the slope of the \( O_2 \) dissociation curve.

As shown by the second term of Eq. (3), the rate of oxygenation of hemoglobin depends on the concentration of reduced hemoglobin, \( y \). Equation (4) may certainly hold, insofar as \( y \) is still large enough to keep the chemical reaction rate at a high level, but in a physiological \( S_{O_2} \) range of 70 to 95\%, it becomes invalid. MOCHIZUKI (1966a) measured the oxygenation rate of the red cell using a rapid flow method and found that it actually decreased as the \( S_{O_2} \) increased. Moreover, according to the experimental data on the rate factor of hemoglobin and the red cell, MOCHIZUKI (1966b) reported that the process of oxygenation of hemoglobin inside the red cell was given by

\[ \frac{dS}{dt} = \frac{2.09}{N} (1 - S)^{2.02} (P - P^*) , \]

where \( S \) is the fractional \( O_2 \) saturation of hemoglobin and \( N \), the \( O_2 \) capacity of 1 ml red cells. MOLL (1969), on the other hand, derived differently a differential equation for a sheet model from Eq. (1). He made \( k' = 2.08/N \) sec\(^{-1}\)·(mmHg)\(^{-1}\) according to the data of GIBSON et al. (1955), and assumed the following relation according to the findings of MOCHIZUKI and FUKUOKA (1958): \( k = (P^* · (1 - S)/S) · k' \). Thus, the chemical reaction term was given by,

\[ \frac{dS}{dt} = \frac{2.08}{N} (1 - S) · (P - P^*) . \]

The above \( k' \) value is converted to \( 3.5 \times 10^6 \) mol\(^{-1}\)·sec\(^{-1}\) by changing its dimension, that is, by dividing it by \( \alpha/22.4 \) mol·(mmHg)\(^{-1}\). The coefficients of the right hand side of Eqs. (5) and (6), i.e., \( (2.09/N)(1 - S)^{2.02} \) and \( (2.08/N)(1 - S) \), are comparable near \( S = 0 \), but as the \( S_{O_2} \) rises, the former becomes significantly smaller than the latter. Therefore, the oxygenation rate of the red cell calculated through Eqs. (3) and (5) has been expected to be smaller at a high \( S_{O_2} \) than that obtained from Eqs. (3) and (6).

Basically, the hypothesis that the chemical reaction rate is given by the 2nd and 3rd terms of Eq. (1) assumes that the \( O_2 \) dissociation curve is hyperbolic. Recently, KUTCHAI (1975) and COIN and OLSON (1979) computed the oxygenation rate in a sheet model using Eq. (1). The rate constants used were \( k' = 3.5 \times 10^6 \) mol\(^{-1}\)·sec\(^{-1}\) and \( k = 40 \) sec\(^{-1}\). From these values, the \( P_{50} \) of the \( O_2 \) dissociation curve is about 10 mmHg, while that of the actual \( O_2 \) dissociation curve about 27 mmHg. For obtaining the reaction rate at a high \( S_{O_2} \) range, where it falls rapidly as the \( S_{O_2} \) increases, the discrepancy of the relation between \( P_{50} \) and \( S_{O_2} \) from that given by the \( O_2 \) dissociation curve seems to be serious. The interaction between the \( O_2 \) and \( CO_2 \) exchange, as observed in the Bohr and Haldane effect, has been defined by the \( O_2 \) and \( CO_2 \) dissociation curve. Thus, the use of the \( O_2 \)
dissociation curve is important for computing the oxygenation rate, though the $P^*$, i.e., the $P_{O_2}$ on the curve may certainly be fictitious during the course of the oxygenation. Furthermore, the use of the $P^*$ becomes even more advantageous when the relationship between the oxygenation and the pulmonary diffusing capacity is discussed. This is because the diffusing capacity is calculated by dividing the $O_2$ uptake by the difference between alveolar $P_{O_2}$ and the time average of the $P^*$ in the pulmonary capillary.

In order to evaluate the effect of the diffusion on the red cell oxygenation as accurately as possible, an attempt was made to obtain the numerical solution in a three-dimensional disc model by using the $O_2$ dissociation curve and the oxygenation rate factor of hemoglobin obtained from the experimental data of MOCHIZUKI et al. (1966).

**PROGRAMMING OF THE NUMERICAL SOLUTION**

The following partial differential equation was solved in a disc model of thickness 1.6 $\mu$m and radius 3.5 $\mu$m:

\[
\alpha \frac{\partial P}{\partial t} = \alpha D \left( \frac{\partial^2 P}{\partial r^2} + \frac{1}{r} \frac{\partial P}{\partial r} + \frac{\partial^2 P}{\partial z^2} \right) - F_s \cdot (P - P^*),
\]

where $F_s$ is the rate factor of the oxygenation of Hb molecules inside the cell as given by

\[
F_s = 2.09 \times (1 - S)^{1.02}.
\]

The back-pressure $P^*$ was given from the Hill’s equation of the $O_2$ dissociation curve by

\[
P^* = \frac{S}{K(1 - S)^{1/n}},
\]

where $n$ is 2.5 and $K = 0.32 \times 10^{-3}$. In order to check the validity of the numerical solution of Eq. (7), two equations were solved: one was Thews’ equation and the other Moll’s equation. Thews’ equation states:

\[
\alpha' \frac{\partial P}{\partial t} = \alpha D \left( \frac{\partial^2 P}{\partial r^2} + \frac{1}{r} \frac{\partial P}{\partial r} + \frac{\partial^2 P}{\partial z^2} \right),
\]

where $\alpha'$ is given from the $O_2$ dissociation curve by

\[
\frac{\alpha'}{\alpha} = \frac{1 + K \cdot N \cdot P^{(n-1)}}{\alpha (1 + KP^*)^2}.
\]

Moll’s equation is identical with Eq. (7), except that the following $F_s$ value is used instead of Eq. (8):

\[
F_s = 2.08 \times (1 - S).
\]

**Initial conditions.** The $P_{O_2}$ in the surrounding medium was changed abruptly from $P_o$ to $P_p$, that is,
Boundary conditions. Because of the symmetricity of radial and vertical diffusion, the \(P_o\) gradient at \(r=0\) and \(z=0\) becomes zero, that is,

\[
(\partial P/\partial r)_{r=0} = 0,
\]

and

\[
(\partial P/\partial z)_{z=0} = 0.
\]

The diffusion rate across the fixed boundary layer including the red cell membrane was expressed by the transfer coefficient, \(\eta\). Let the distances of the radial and upper and lower boundaries from the origin be \(r=c\), and \(z=\pm d\), respectively. The boundary conditions are given by

\[
\alpha D (\partial P/\partial r)_{r=c} = \eta(P_{r=c} - P_p),
\]

and

\[
\alpha D (\partial P/\partial z)_{z=\pm d} = \eta(P_{z=\pm d} - P_p).
\]

Fig. 1. A flow chart for solving the differential equation of diffusion for the oxygenation process in the red cell disc model. An alternating-direction implicit method was adopted.
Programming. The differential equation was converted to the difference forms, and then computed by using the alternating-direction implicit method which was developed and elaborated by DOUGLAS and RACHFORD (1956). The computation procedure and an example of the program are shown in Appendix. The summarized flow chart is shown in Fig. 1. The solution of Eq. (7) was compared with that of the sheet model which was solved by use of the Crank-Nicolson technique (VON ROSENBERG, 1969). The sheet thickness was 1.6 μm and other parameter values are the same as used in the disc model.

Parameter values.
- RBC radius, $c = 3.5 \text{ μm}$,
- RBC thickness, $2d = 1.6 \text{ μm}$,
- $O_2$ solubility in RBC, $\alpha = 0.31 \times 10^{-4} (\text{mmHg})^{-1}$,
- $O_2$ diffusion coefficient in RBC, $D = 0.46 \times 10^{-5} \text{cm}^2\cdot\text{sec}^{-1}$,
- $O_2$ capacity of RBC, $N = 0.43$,
- $K$ value of $O_2$ dissociation curve, $= 0.32 \times 10^{-3}$,
- $n$ value of the $O_2$ dissociation curve, $= 2.5$.

RESULTS

First, the oxygenation process was computed by varying the $\eta$ value, where the initial and boundary conditions were given according to the experimental data (MOCHIZUKI, 1966a). In Fig. 2 are shown 5 $S_{O_2}$-time curves calculated by varying the $\eta$ values from $1.5 \times 10^{-6}$ to $3.5 \times 10^{-6} \text{cm}\cdot\text{sec}^{-1}\cdot(\text{mmHg})^{-1}$. The initial $P_{O_2}$ was 11.26 mmHg and the $P_{O_2}$ outside the red cell was 100 mmHg, the $O_2$ saturation increasing thereby from 12 to about 95%. The increase in $S_{O_2}$ was fairly sensitive to the $\eta$ value, and the half-time varied from 80 to 40 msec as the $\eta$ value was increased.

The $S_{O_2}$-time curve calculated by use of $\eta = 2.5 \times 10^{-6} \text{cm}\cdot\text{sec}^{-1}\cdot(\text{mmHg})^{-1}$ coincided well with the experimental data, as shown in Fig. 3. The upper curve thereof was calculated when the initial $P_{O_2}$ was 23 mmHg and the $P_{O_2}$ in the outer medium was 114 mmHg. The $S_{O_2}$ rose from 45% and the half-time was about 35 msec, showing good agreement with the experimental data. Both of the calculated curves agreed well with respective experimental data. Assuming the $O_2$ solubility in the boundary layer around the red cell to be equal to that of the plasma, namely, to $0.31 \times 10^{-4} (\text{mmHg})^{-1}$ and the diffusion coefficient equal to $0.32 \times 10^{-5} \text{cm}^2\cdot\text{sec}^{-1}$ according to the data obtained in a saline solution by GERTZ and LOESCHCKE (1954), the layer thickness is estimated to be 4 μm. Therefore, the diffusivity across the red cell membrane appears fairly low compared with that of the saline solution. The $\eta$ value which was previously estimated from the same experimental data by using an analytical solution obtained from a one-dimensional sheet model with a thickness of 1.6 μm was $3.3 \times 10^{-6} \text{cm}\cdot\text{sec}^{-1}\cdot(\text{mmHg})^{-1}$ (MOCHIZUKI, 1966b). That is, a great difference was observed between...
the previous and present \( \gamma \) values. In order to reconfirm the difference between those two models, the \( S_{O_2} \)-time curves were also computed numerically in the sheet model by using the Crank-Nicolson technique. The results are shown in Fig. 4, where the half-time of the disc model with the \( \gamma \) of \( 2.5 \times 10^{-6} \text{ cm sec}^{-1} \text{(mmHg)}^{-1} \) coincided with that of the sheet model with the \( \gamma \) of \( 5.0 \times 10^{-6} \text{ cm sec}^{-1} \text{(mmHg)}^{-1} \). In other words, the \( \gamma \) value of the sheet model was twice as great as that of the disc model. Since the oxygenation rate of the sheet model was slower than that of the disc model, a higher transfer coefficient was needed to attain the same reaction rate. Thus, it is imperative to use the disc model to estimate the transfer coefficient from the experimental \( S_{O_2} \)-time curve in view of the structural analogy.

Figure 5 shows three \( S_{O_2} \)-time curves obtained from Thews' and Moll's equations and the present differential equation, using the disc model with the \( \gamma \) value of \( 2.5 \times 10^{-6} \text{ cm sec}^{-1} \text{(mmHg)}^{-1} \). They resemble each other in shape, except for the part above 70% \( S_{O_2} \). Both of the curves obtained from Thews' and Moll's equations showed a rapid increase even in the upper \( S_{O_2} \) region, but the present equation showed a comparatively slower increase. Such a difference was demon-
Fig. 3. $S_{O_2}$-time curves (two solid lines) calculated in the disc model with the $\gamma$ of $2.5 \times 10^{-6}$ cm·sec$^{-1}$·(mmHg)$^{-1}$ and the experimental data (open circles) obtained by MOCHIZUKI (1966a), using a rapid flow method. The initial and boundary $P_{O_2}$'s of the upper curve were 23 and 114 mmHg, and those of the lower, 11.3 and 100 mmHg, respectively.

The cause of the above difference lies in the difference between $P(t)$ and $P^*(t)$. Figure 7 shows the relation between those two $P_{O_2}$'s. The Thews' equation showed no difference, as expected from Eq. (10). Moll's equation showed some difference, but this was only a few mmHg in magnitude. In contrast, the present equation yielded a difference up to 20 mmHg at the widest part of the reaction.

This value is useful for describing the relation between the oxygenation rate of the red cell and the pulmonary diffusing capacity for $O_2$. When the $F_c$ value is multiplied by the product of the volume of red cells flowing through the total pulmonary capillaries in 1 min and the contact time, the resulting product becomes the diffusing capacity (MOCHIZUKI, 1975). That is, $D_{LO_2} = \dot{Q} \cdot Ht \cdot F_c \cdot t_c$, where $\dot{Q}$ is the cardiac output, $Ht$, the hematocrit, and $t_c$, the contact time. In Fig. 6 the $F_c$ values are plotted against the $O_2$ saturation. Only the present curve shows decay similar to that found in the experimental data as the $S_{O_2}$ increases, while the other two curves show a fairly flat curve.

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DISCUSSION

In Fig. 2 it was revealed that the rate of oxygenation of the red cell depends largely on the diffusivity across the barrier around the cell. ROUGHTON and FORSTER (1957) expressed the above diffusivity by a term, \( \lambda \alpha D/d \), where \( \alpha \) is the \( O_2 \) solubility in the red cell, \( D \), the diffusion coefficient, \( d \), the thickness of the one-dimensional sheet model and \( \lambda \), the ratio of \( (\alpha D)/d \) of the diffusion barrier to that of the red cell interior. Such an expression can be applied to the sheet model, but not to other models. In contrast to their method, MOCHIZUKI and FUKUOKA (1958) used the transfer coefficient, \( \gamma \), which had usually been used for heat transfer. The \( \gamma \) value has the same dimension as \( \alpha D/d \) and, in addition, it can be used for the three-dimensional model as given by Eqs. (16) and (17).

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Fig. 5. \( S_{\text{O}_2} \)-time curves computed from Thews', Moll's, and the present (Mochizuki's) equations. The \( \eta \) value of \( 2.5 \times 10^{-8} \text{ cm sec}^{-1} \text{ (mmHg)}^{-1} \) was used.

Fig. 6. The rate factors of oxygenation, \( F_c \) of Eq. (18), obtained from Thews', Moll's, and Mochizuki's equations.
Fig. 7. The differences between the actual $P_{O_2}$ in the red cell ($P$), and the back-pressure ($P^*$) are shown against the reaction time. The above difference in $P_{O_2}$ is based upon three equations; Thews', Moll's, and Mochizuki's equations.

As shown in Fig. 4 the diffusivity, or the transfer coefficient, estimated by using the three-dimensional disc model, was about half that obtained by use of the sheet model. Taking the structural resemblance of the model to the red cell into account, it seems to be of great advantage to express the diffusivity of the barrier by the $\eta$ value of the disc model.

Another rate-limiting factor of red cell oxygenation is the rate of oxygenation of hemoglobin itself inside the red cell. In the measurement of oxygenation of hemoglobin in a saline solution (Mochizuki et al., 1966), it was clarified that the rate factor, $F_s$, diminished much more strongly than had so far been expected from Eq. (1), as the $S_{O_2}$ increased. Using the above $F_s$ value and the oxygenation rate measured in a red cell suspension, Mochizuki (1966b) evaluated the $F_s$ value in the red cell by using the analytical solution obtained in a linearized sheet model. Fortunately, the $S_{O_2}$-time curve as well as the $F_c$, both calculated using this $F_s$ value which is given by Eq. (8), coincided well with the experimental data, though the $\eta$ value showed a significant difference between the previous analytical and the present numerical solutions. In other words, the $F_c$ value in the present equation
decreased as the $S_o_2$ approached 100\% while in the other equations such as Thews’ and Moll’s it was kept almost constant regardless of the $S_o_2$. Previously, MOCHIZUKI et al. (1958) demonstrated that the pulmonary diffusing capacity for O$_2$ showed a similar decline against the $S_o_2$, thus supporting the theoretical evidence of Fig. 6. The direct cause of the decline has been ascribed to the difference between the actual $P_o_2$ and the back-pressure, whereas no quantitative data have been available as yet. In Fig. 7 a surprisingly great difference is observed between the actual $P_o_2$ and the back-pressure, $P^\ast$.

In order to analyze the pulmonary diffusing capacity for CO ($D_{Lco}$), ROUGHTON and FORSTER (1957) subdivided it into two components of red cell and alveolar membrane. Generally speaking, however, it is fairly difficult, practically, to separate the diffusion component across the alveolar membrane from that across the red cell membrane and the fixed boundary layer. Thus, MOCHIZUKI et al. (1972) proposed to express the overall diffusion component around the red cell by the unique transfer coefficient, i.e., the $\gamma$ value. The keys for determining the $\gamma$ value for CO along the lung capillary are, (1) to know the rate factor of the reaction of CO with hemoglobin inside the red cell and, (2) to adopt the best fitting model for the flowing red cell. FUKUI and MOCHIZUKI (1972) attempted to measure the CO reaction in a diluted Hb solution and found that the $F_{SCO}$ value was so widely dispersed that they could not determine a definite value. They ascribed the cause of such a wide dispersion to the dissociation of the hemoglobin molecule into its subunits, and estimated the $F_{SCO}$ inversely from the measured $F_{CCO}$ by using the analytical solution of the disc model, where the $\gamma$ value used was $3 \times 10^{-6}$ cm·sec$^{-1}$·(mmHg)$^{-1}$. In the present study, however, the value for O$_2$ in the red cell suspension was estimated to be about $2.5 \times 10^{-6}$ cm·sec$^{-1}$·(mmHg)$^{-1}$, as shown in Fig. 3. Hence, the $\gamma$ value for CO in the red cell suspension is now estimated from the ratio of $(\alpha D)_{CO}/(\alpha D)_{O_2} = 0.8$ to be $2 \times 10^{-6}$ cm·sec$^{-1}$·(mmHg)$^{-1}$. The $F_{SCO}$ value recalculated from both the $F_{CCO}$ value measured and the analytical solution obtained on the disc model by using this new $\gamma_{CO}$ value was given by

$$F_{SCO} = 5.1/(P_{O_2} - 38) \quad (\text{cm} \cdot \text{sec}^{-1} \cdot \text{(mmHg)}^{-1})$$

(19)

Regarding the shape of the red cell flowing through the capillary, MOCHIZUKI (1975) used a cylindrical model, referring to the experimental observation made by MIYAMOTO and MOLL (1971). The size of the model was 4.44 µm in thickness and 4.2 µm in diameter. Thus, by using the same model with the same $F_{SCO}$ as given by Eq. (19) and by varying the $\gamma_{CO}$ value, the $F_{CCO}$ was recalculated. Figure 8 shows the $F_{CCO}$ plotted against the $P_{O_2}$, where the $\gamma_{CO}$ value varied from $0.3 \times 10^{-6}$ to $2.4 \times 10^{-6}$ cm·sec$^{-1}$·(mmHg)$^{-1}$. The $\gamma_{CO}$ values in Fig. 8 were in general smaller than the previous values (MOCHIZUKI et al., 1972) at the same $F_{CCO}$. The relation between the $D_{LCO}$ measured previously in 7 normal subjects at various $P_{O_2}$ levels and the $F_{CCO}$ is shown in Fig. 9, where the $F_{CCO}$ was calculated by using
Fig. 8. The rate factors of the reaction of CO with the red cell, $F_{c_{CO}}$, obtained by putting $F_{s_{CO}}$ of Eq. (19) into the analytical solution with various transfer coefficients.

Fig. 9. Pulmonary diffusing capacity for CO ($D_{LCO}$) plotted against the $F_{c_{CO}}$ calculated under $\gamma=1.2 \times 10^{-6} \, \text{cm} \cdot \text{sec}^{-1} \cdot \text{(mmHg)}^{-1}$ by referring to the alveolar $P_{O_2}$ at which the $D_{LCO}$ was measured. The experimental data of Fukui and Mochizuki (1972) and Mochizuki et al. (1972) were used for the calculation.

both the $\gamma_{CO}$ value of $1.2 \times 10^{-6} \, \text{cm} \cdot \text{sec}^{-1} \cdot \text{(mmHg)}^{-1}$ and the $P_{O_2}$'s determined in the experiment. Considering that the regression line intersects the origin of the graph, the $\gamma_{CO}$ value in the lung capillary is conjectured to be about 60% of that
in the red cell suspension, \(2 \times 10^{-6} \text{ cm} \cdot \text{sec}^{-1} \cdot (\text{mmHg})^{-1}\). This value may become an important criterion for estimating diffusion impairment in pulmonary diseases in the near future.

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**APPENDIX**

The computation procedure. The use of a symmetrical system greatly simplified the construction of a gridwork for the numerical solution. As seen in Fig. 10, the gridwork at cross-sections from \(r=0\) to \(r=c\), from \(z=0\) to \(z=d\), and from \(t=0\) to \(t=t_o\) completely describes the red cell system. Since the term \(1/r\) appears in Eqs. (7) and (10), special attention was paid to the point \(r=0\). For eliminating this difficulty we adopted a fictitious boundary method according to RENEAU et al. (1967). With the use of the boundary conditions of Eqs. (14) and (15), the following equations are valid.

\[
\begin{align*}
P_{1,1,k} &= P_{2,1,k} \\
P_{1,2,k} &= P_{2,2,k} \\
& \vdots \\
P_{1,j,k} &= P_{2,j,k} \\
P_{1,1,k} &= P_{1,2,k} \\
P_{1,2,k} &= P_{1,j,k} \\
& \vdots \\
P_{1,j,k} &= P_{1,j,k}
\end{align*}
\]

(20)

The differential equations were solved by applying an alternating-direction implicit method (DOUGLAS and RACHFORD, 1956). In the alternating-implicit method the analogs to \(\partial^2 P/\partial r^2\) and \((1/r) \partial P/\partial r\) were written at the new time level, \(t_{k+1}\), and the analog to the \(z\)-derivative, \(\partial^2 P/\partial z^2\) was written at the old time level. The resulting finite difference equation was processed in the following three ways.

A) Present differential equation: Rewriting Eq. (7) by the difference form, the following equation is obtained:

\[
\begin{align*}
\frac{1}{k} & (P_{i,j,k+1} - P_{i,j,k}) = \frac{D}{h^2} (P_{i,j+1,k} - 2P_{i,j,k} + P_{i,j-1,k}) \\
& + \frac{D}{2hr_j} (P_{i,j+1,k} - P_{i,j-1,k+1}) + \frac{D}{g^2} (P_{i+1,j,k} - 2P_{i,j,k} + P_{i-1,j,k}) \\
& - \frac{F_{i,j,k}}{\alpha} (P_{i,j,k+1} - P_{*,i,j,k}) \ .
\end{align*}
\]

(21)

The derivatives in the \(r\)-direction in Eq. (21) are written with the backward analog and those in the \(z\)-direction are written with the forward analog. That is, the
terms in the $r$-direction are implicit and explicit in the $z$-direction. The finite difference equation for any $j$-row on which the $i$-value is constant forms a tridiagonal coefficient matrix and their solution can readily be obtained by using the Thomas algorithm (VON ROSENBERG, 1969). For the next time step, from $t_k$ to $t_{k+2}$, an equation which is explicit in the $r$-direction and implicit in the $z$-direction was used with the same size of $k$. The equation is:

$$\frac{1}{k}(P_{i,j,k+2} - P_{i,j,k+1}) = \frac{D}{h^2}(P_{i,j+1,k+1} - 2 \cdot P_{i,j,k+1} + P_{i,j-1,k+1})$$

$$+ \frac{D}{2hr_i}(P_{i,j+1,k+1} - P_{i,j-1,k+1}) + \frac{D}{g_z}(P_{i+1,j,k+2} - 2 \cdot P_{i,j,k+2} + P_{i-1,j,k+2})$$

$$- \frac{F_{st,i,j,k+1}}{\alpha}(P_{i,j,k+2} - P_{i,j,k+1}). \quad (22)$$

Equation (22) contains three unknown values of $P$, that is, $P_{i+1,j,k+1}$, $P_{i,j,k+2}$, and $P_{i-1,j,k+2}$, which are arranged along the $z$-direction. The finite difference equations resulting from Eq. (22) for a constant $j$-value form a tridiagonal coefficient matrix, so their solution can be obtained from the Thomas algorithm.

Collecting and rearranging terms, the differenced equation, Eq. (21) assumes the following algebraic form:

$$F_jP_{i,j+1,k+1} + G_jP_{i,j,k+1} + H_jP_{i,j-1,k+1} = Z_j,$$  \quad (23)$$

where

$$i=2, 3, 4, \cdots, I-1,$$

$$j=2, 3, 4, \cdots, J.$$
The first term of the Zj-equation includes Pi+1,j,k. Since i+1 cannot exceed the maximum of i, I, the number i in this equation is limited within I-1, i.e., 2 ≤ i ≤ I-1. Thus, from the above computation the PI,j,k+1 which is indispensable for the implicit calculation of the next time step cannot be evaluated. For obtaining PI,j,k+1, then, we adopted the boundary conditions given by Eq. (17) as follows:

\[ P_{i,j,k+1} = \frac{\alpha D}{\alpha D + \eta} P_{i-1,j,k+1} + \frac{\eta}{\alpha D + \eta} P_d. \]  

In other words, after computation of Eq. (23) according to the Thomas algorithm, \( P_{i,j,k+1} \) was calculated by using \( P_{i-1,j,k+1} \) from Eq. (24).

Collecting terms and rearranging, Eq. (22) assumes the following algebraic form:

\[ F_j P_{i+1,j,k+2} + G_j P_{i,j,k+2} + H_j P_{i-1,j,k+2} = Z_j. \]  

where

\[ i = 2, 3, 4, \ldots, I, \]
\[ j = 2, 3, 4, \ldots, J-1, \]
\[ F_j = D / g^2, \]
\[ G_j = -2D / g^2 - 1/k - F_{S_t,j,k+1} / \alpha, \]
\[ H_j = D / g^2, \]
\[ Z_j = -\frac{\alpha D}{h^2 + \eta} P_{t-1,j,k+1} + \frac{\eta}{\alpha D + \eta} P_d. \]

In this calculation, too, the j-increment is limited within the following range: 2 ≤ j ≤ J-1. Therefore, the \( P_{i,j,k+1} \) which becomes necessary for the implicit calculation of the next step was evaluated after the computation of Eq. (25) by using \( P_{i,j,k+2} \) as follows:

\[ P_{i,j,k+1} = \frac{\alpha D}{\alpha D + \eta} P_{i,j-1,k} + \frac{\eta}{\alpha D + \eta} P_d. \]

The non-linear terms, \( F_{S_t,j,k} \) and \( P_{i,j,k}^* \) were obtained as follows: First, the fractional O2 saturation, \( S_{t,j,k} \) was calculated by adding the change of \( S_{t,j,k} \) to the \( S_{t,j,k-1} \) as given by

\[ S_{t,j,k} = S_{t,j,k-1} + (F_{S_t,j,k-1} \cdot \Delta t / N) (P_{t,j,k} - P_{t,j,k-1}). \]

Next, by putting \( S_{t,j,k} \) into Eqs. (8) and (9), \( F_{S_t,j,k} \) and \( P_{i,j,k}^* \) were obtained. The same calculation was repeated in each time step.

B) Thews' equation: Thews' equation (10) was converted to the differenced
form analogous to Eq. (21) as given by
\[
\frac{E_{i,j,k}}{k} (P_{i,j,k+1} - P_{i,j,k}) = \frac{D}{h^2} (P_{i,j+1,k} + P_{i,-j,k+1} - 2P_{i,j,k+1})
\]
\[
+ \frac{D}{2hr_j} (P_{i,j+1,k+1} - P_{i,j-1,k+1}) + \frac{D}{g}(P_{i+1,j,k} - 2P_{i,j,k} + P_{i-1,j,k}) ,
\]
where \( E_{i,j,k} = \alpha_i,j,k/\alpha \). The non-linear \( E \) term was determined by putting \( P_{i,j,k} \) into Eq. (11). After collecting and rearranging terms, the difference equation (28) was solved by using the method similar to that shown in Eq. (23).

C) Moll’s equation: The computation of this equation was carried out in the same way as that of the present equation, except for the non-linear term of \( F_{si,j,k} \). That is, the chemical reaction terms were expressed by \( F_s = 2.08 \times (1 - S) \) instead of Eq. (8).

Adaptation of boundary conditions. The boundary conditions used for the Thomas algorithm were derived from Eqs. (16) and (17) for the time step of \( k+1 \) and \( k+2 \), respectively. The equations were written in the difference forms as:
\[
\frac{\alpha D}{h} (P_{i,j,k+1} - P_{i,j,k+1}) = \gamma (P_{i,j,k+1} - P_{i,j,k+1}) ,
\]
\[
\frac{\alpha D}{g} (P_{i,j+1,k} - P_{i,j-1,k}) = \gamma (P_{i,j,k+1} - P_{i,j,k+1}) .
\]
For computational purposes it was preferred to place the interface equation in the same forms as Eqs. (23) and (25). Rearranging Eq. (28) to fit the necessary form gives
\[
G_j P_{i,j,k+1} + H_j P_{i,j,k+1} = Z_j ,
\]
\[
G_j P_{i,j,k+1} + H_j P_{i,j,k+1} = Z_j .
\]
where
\[
G_j = \gamma + \alpha D/h , \hspace{1cm} H_j = -\alpha D/g , \hspace{1cm} Z_j = \gamma P_{i,j} .
\]

Solution by the method of Thomas. When the boundary conditions were applied, the system of \( n \) equations with \( n \) unknowns established by Eq. (23) or Eq. (25) forms the tridiagonal coefficient matrix and is solved by the method of Thomas. Applying the boundary conditions, the equations for each \( j \)-row become:
\[
(H_j + G_j) P_{i,j,k+1} + F_j P_{i,j,k+1} = Z_j , \hspace{1cm} j = 2 ,
\]
\[
H_j P_{i,j,k+1} + G_j P_{i,j,k+1} = Z_j , \hspace{1cm} 3 \leq j \leq J - 1 ,
\]
\[
H_j P_{i,j,k+1} + G_j P_{i,j,k+1} = Z_j , \hspace{1cm} j = J .
\]
The components of these equations form a matrix as follows:

\[
\begin{bmatrix}
(H_2 + G_2) & F_2 \\
H_0 & G_0 & F_3 \\
\vdots & \vdots & \vdots \\
H_{j-1} & G_{j-1} & F_{j-1} \\
H_j & G_j & \vdots
\end{bmatrix}
\begin{bmatrix}
P_2 \\
P_3 \\
\vdots \\
P_{j-1} \\
P_j
\end{bmatrix} =
\begin{bmatrix}
Z_2 \\
Z_3 \\
\vdots \\
Z_{j-1} \\
Z_j
\end{bmatrix}
\]

A similar matrix is also shown for the z-direction. According to Thomas, the unknowns in the matrix of the above form are quickly solved in a straight manner. Let

\[
W_j = G_x + H_x, \quad j = 2, \\
(SV)_{j-1} = F_{j-1}/W_{j-1}, \quad 3 \leq j \leq J, \\
W_j = G_j - H_j F_{j-1}/W_{j-1}, \quad 3 \leq j \leq J, \\
U_j = Z_j/W_j, \quad j = 2, \\
U_j = (Z_j - H_j U_{j-1})/W_j, \quad 3 \leq j \leq J.
\]

If the \( W_j \) and \( U_j \) are calculated in the sequence of increasing \( j \), all the values of \( P \) may be calculated by putting

\[
P_j = U_j,
\]

and

\[
P_j = U_j - (SV)_j \cdot P_{j+1}, \quad 2 \leq j \leq J - 1.
\]

After computation of \( P_{t,j,k+1} \), the change in \( S_{t_2} \) was calculated from Eq. (27). Furthermore, \( P^*_{t,j,k+1} \) was calculated from Eqs. (9) and (27). In the time step of \( k+2 \), a similar computation was repeated with respect to the z-direction.

**Space average of \( P_{t_2} \) and \( S_{t_2} \) in the red cell.** After the computation of \( S_{t,j,k} \) and \( P_{t,j,k} \), the space averages of \( P \), \( P^* \), and \( S \) were calculated. First, the average at each \( j \)-row was obtained as follows:

\[
\overline{P}_t = (1/r_j^2) \sum_{j} \left( r_{j}^2 - r_{j-1}^2 \right) P_{t,j}.
\]

Then, the total average was calculated as:

\[
\bar{P} = \frac{1}{2(I-2)} \left( \overline{P}_2 + 2 \overline{P}_3 + 2 \overline{P}_4 + \cdots + 2 \overline{P}_{J-1} + \overline{P}_J \right)
\]

**Examples of the program.** An example of the program is shown in Fig. 11A and B.
OXYGENATION RATE OF THE RED BLOOD CELL

10 DIM P(6,6),P8(6,6),S(6,6),U(6,6),V(6,6),W(6,6)
15 DIM X(6,6),XI(6,6),X2(6,6),X3(6,6)
20 REM PARAMETERS SET
25 R1=7.77800E-05 \ R0=3.50000E-04 \ Z1=2.00000E-05
30 A=3.10000E-05 \ D=4.60000E-06
35 K=5.20000E-04 \ E=2.50000E-06
40 E1=E*R1/(A+D) \ E2=E*Z1/(A+D)
45 P0=11.2673 \ P8=P0 \ S0=-12 \ P1=100
50 REM INITIAL CONDITIONS
55 FOR I=1 TO 6
60 FOR J=1 TO 6 \ P(I,J)=P0 \ P8(I,J)=P8 \ S(I,J)=S0 \ NEXT J
65 NEXT I
70 PRINT "(SEC)","P-02","S-02","P*02"
75 PRINT T,P0,S0,P8
80 M=0
90 REM
95 REM CALCULATION
100 FOR M=1 TO 150
105 M=M+1
110 T=T+2*M*T1
115 FOR I=2 TO 6 \ GOSUB 800 \ NEXT I
120 FOR I=2 TO 5 \ GOSUB 700 \ NEXT I
125 FOR J=2 TO 6 \ P(I,J)=(P(S,J)*E2+P1)/(1+E2) \ NEXT J
130 FOR J=2 TO 5 \ GOSUB 300 \ NEXT J
135 FOR J=2 TO 5 \ GOSUB 900 \ NEXT J
140 FOR J=2 TO 5 \ GOSUB 750 \ NEXT J
145 FOR J=2 TO 6 \ P(I,J)=(P(I,5)+E1*P1)/(1+E1) \ NEXT I
150 FOR I=2 TO 6 \ P(1,6)=P(3,6)
155 GOSUB 300
160 FOR I=2 TO 6 \ FOR J=2 TO 6 \ X(I,J)=P(I,J) \ NEXT J \ NEXT I
165 GOSUB 400 \ P2=X
170 FOR I=2 TO 6 \ FOR J=2 TO 6 \ X(I,J)=S(I,J) \ NEXT J \ NEXT I
175 GOSUB 400 \ S2=X
180 FOR I=2 TO 6 \ FOR J=2 TO 6 \ X(I,J)=P8(I,J) \ NEXT J \ NEXT I
185 GOSUB 400 \ P3=X
190 IF M<5 THEN 190
195 M=M+1
199 PRINT T,P2,S2,P3
200 NEXT M
205 CLOSE #1
210 STOP
215 REM
220 REM CALCULATION OF S-02, P-02
225 FOR I=2 TO 6 \ FOR J=2 TO 6
230 FI=2.89*(X(I,J)-2.02
235 S1=FI*(P(I,J)-P8(I,J))*T1/N
240 S2=(S1,J)*N1)
245 NEXT J
249 NEXT I
250 RETURN
255 REM
260 REM SPACE AVERAGES OF P-02, S-02, P*02
265 FOR I=2 TO 6
270 X3(I)=(X(1,2)+3*X(I,3)+5*X(I,4)+8*X(1,5)+3.1875*X(I,6))/20.25
275 NEXT I
280 X=X3(2)+2*X3(3)+2*X3(4)+2*X3(5)+X3(6))/8
285 RETURN

Fig. 11A. An example of the computer program, where BASIC for MINC-11 was used.
Fig. 11B. Continuation of the computer program.
OXYGENATION RATE OF THE RED BLOOD CELL

REFERENCES


ROUGHTON, F. J. W. (1945a) The kinetics of the reaction $\text{CO} + \text{O}_2\text{Hb} = \text{O}_2 + \text{COHb}$ in human


