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PHYSIO-MATHEMATICAL ASPECTS OF BLOOD OXYGENATION IN LUNG CAPILLARIES

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A mathematical model for the oxygenation of blood is presented by taking into account the main transport mechanisms of molecular diffusion, convection and the facilitated diffusion. The four step kinetics based on the intermediate compound hypothesis of Adair[1] is used for considering the sigmoidial oxyhaemoglobin saturation curve. The rate at which blood gets oxygenated is determined by setting up an appropriate eigenvalue problem. This method eventually leads to a transcendental equation. The smallest root of this determines the rate at which equilibrium is achieved, is obtained numerically by using the method of bisection. A highly skilled multiprecision technique developed by Verma and Sharan[8] is employed to obtain an acceptable solution of this problem. It has been found that the results based on four step kinetics are qualitatively more or less similar to those obtained for one step kinetics[5].

The effects of various physical parameters such as diffusion coefficients of the species, speed of the blood, radius of the capillary, association and dissociation rate constants and partial pressure in alveolar air, on equilibration length have been discussed.

Finally, the effects of these results on some of the physiological situations such as, mediation, muscular excercise, polluted environment, high altitude, fever etc. have been examined.

INTRODUCTION

The studies on the process of gas exchange leading to the oxygenation of blood in lung capillaries have got considerable impetus among the scientists working in multidisciplinary areas due to its applications to the design of extra-corporeal oxygenation equipment. The related work in this direction has recently been reviewed extensively by Sharan[2] and Sharan and Singh[3].

The earlier studies[4,5] are based on one step reversible reaction between oxygen and haemoglobin. However, one step kinetics leads to a hyperbolic, rather than

sigmodial oxyhaemoglobin saturation curve. In view of the structural configuration of haemoglobin the four step scheme, due to Adair[1], seems to be more accurate. One important advantage of the four step kinetics is that the oxygen dissociation curve fits in very well with the one based on experimental data.[6] Besides, the saturation function obtained by earlier investigators[1] does not include the simultaneous effects of CO_2. However, the saturation function obtained by Singh *et al.*[6] includes the simultaneous effect of CO_2. We present here briefly, a mathematical model for the oxygenation of blood in pulmonary capillaries by taking into account the intermediate compound hypothesis of Adair[1].

Mathematical Formulation

Let the venous blood enter the lung capillary at $z = 0$ as shown in Fig. 1 and the length L is sufficiently large in normal situation for equilibrium to be achieved so that arterial (oxygenated) blood leaves the system at $z = L$. we visualize the capillary as a two dimensional channel of thickness $2a$. As the blood enters the capillary, it loses its carbondioxide and gains oxygen. It is clear from the well known structure of haemoglobin that one molecule of haemoglobin contains four molecules of haem attached to one molecule of globin. Further, each haem molecule contains one Fe^{+2} ion. Singh *et al.*[6] pointed out that one molecule of haemoglobin can combine with

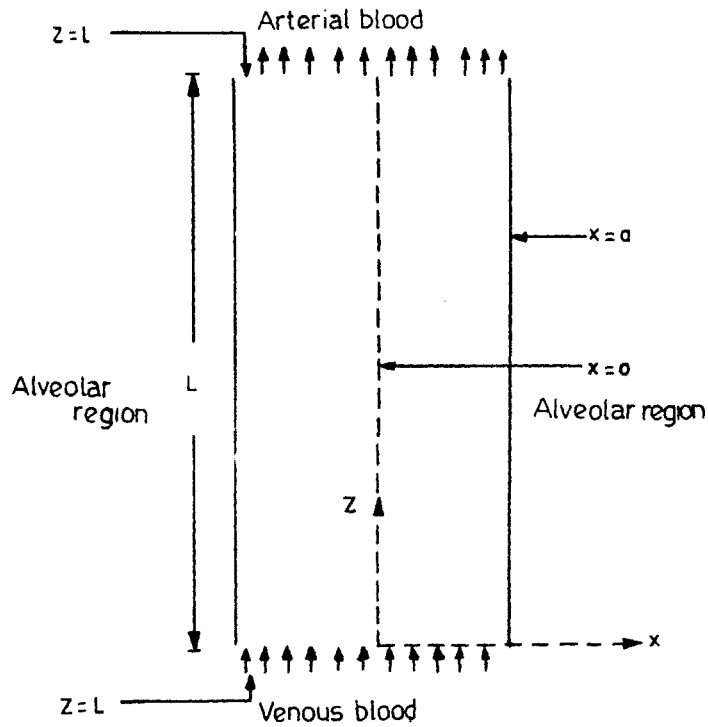

FIG. 1. Sketch of the mathematical model.

both oxygen and carbon dioxide at the same time because one combines with the haem part while the other with the globin part. More precisely, a single haemoglobin molecule can combine with four molecules of oxygen bound reversibly with the ferrous ion in the four haem groups and with one molecule of CO_2 bound reversibly with the globin part. According to Adair[1] intermediate compound hypothesis the reversible reaction of the haemoglobin molecule with four molecules of oxygen actually proceeds in four sequential steps. Therefore, in the present analysis the following reactions according to which the gases, oxygen and carbondioxide, combine reversibly with the haemoglobin are considered :

$$\text{(a)} \quad Hb + O_2 \underset{k_{12}}{\overset{k_{11}}{\rightleftharpoons}} Hb\,O_2,$$

$$\text{(b)} \quad Hb\,O_2 + O_2 \underset{k_{22}}{\overset{k_{21}}{\rightleftharpoons}} Hb\,O_4,$$

$$\text{(c)} \quad Hb\,O_4 + O_2 \underset{k_{32}}{\overset{k_{31}}{\rightleftharpoons}} Hb\,O_6,$$

$$\text{(d)} \quad Hb\,O_6 + O_2 \underset{k_{42}}{\overset{k_{41}}{\rightleftharpoons}} Hb\,O_8,$$

$$\text{(e)} \quad Hb + CO_2 \underset{m_2}{\overset{m_1}{\rightleftharpoons}} Hb\,CO_2, \qquad \ldots(1)$$

in which k_{i1} and m_1 $(i = 1, 2, 3, 4)$ are forward rate constants, and k_{i2} and m_2 $(i = 1, 2, 3, 4)$ are the backward rate constants.

Let y_1, y_2, y_3, y_4, y_5, y_6, y_7 and y_8 be respectively the concentrations, of the species O_2, HbO_2, HbO_4, HbO_6, Hbo_8, CO_2, $HbCO_2$ and Hb in the blood. The diffusion coefficients of haemoglobin and its species are assumed to be same, which is denoted by D_H and treated as a constant quantity here[7]. Likewise, D_0 and D_c represent the diffusion coefficients of oxygen and carbon dioxide and these are also assumed to be constants. Diffusion of the gases occurs only in a single direction perpendicular to the alveolar-capillary membrane which is justifiable because the longitudinal distance is much larger in comparison of the radial distance in the capillary. Furthermore, let the blood flowing with a constant velocity (Q), there is no flow of blood perpendicular to the membrane and the fluctuations from the steady state are neglected for the reason that the time for the exchange of gases is too small and the pulsations are rather slow as they represent the cardic pressure pulse. Also blood is treated as a homogeneous solution in which RBC shrunk to a point.

Basic Equations

On the basis of the above assumptions and established facts, the law of mass action leads to the following system of second order nonlinear partial differential equations :

$$\text{(a)} \quad D_0 \frac{\partial^2 y_1}{\partial x^2} = \rho_1 + \rho_2 + \rho_3 + \rho_4 + Q \frac{\partial y_1}{\partial z},$$

$$\text{(b)} \quad D_H \frac{\partial^2 y_2}{\partial x^2} = \rho_2 - \rho_1 + Q \frac{\partial y_2}{\partial z},$$

$$\text{(c)} \quad D_H \frac{\partial^2 y_3}{\partial x^2} = \rho_3 - \rho_2 + Q \frac{\partial y_3}{\partial z},$$

$$\text{(d)} \quad D_H \frac{\partial^2 y_4}{\partial x^2} = \rho_4 - \rho_3 + Q \frac{\partial y_4}{\partial z},$$

$$\text{(e)} \quad D_H \frac{\partial^2 y_5}{\partial x^2} = -\rho_4 + Q \frac{\partial y_5}{\partial z},$$

$$\text{(f)} \quad D_C \frac{\partial^2 y_6}{\partial x^2} = \rho_5 + Q \frac{\partial y_6}{\partial z},$$

$$\text{(g)} \quad D_H \frac{\partial^2 y_7}{\partial x^2} = -\rho_5 + Q \frac{\partial y_7}{\partial z},$$

$$\text{(h)} \quad D_H \frac{\partial^2 y_8}{\partial x^2} = \rho_1 + \rho_5 + Q \frac{\partial y_8}{\partial z}, \qquad \ldots(2)$$

where

$$\rho_1 = k_{11}\, y_1\, y_8 - k_{12}\, y_2,$$

$$\rho_2 = k_{21}\, y_2\, y_1 - k_{22}\, y_3,$$

$$\rho_3 = k_{31}\, y_3\, y_1 - k_{32}\, y_4,$$

$$\rho_4 = k_{41}\, y_4\, y_1 - k_{42}\, y_5,$$

$$\rho_5 = m_1\, y_6\, y_8 - m_2\, y_7 \qquad \ldots(3)$$

and first and the last terms of each equation are respectively the contributions due to molecular diffusion and convection whereas the remaining terms represent the effect of chemical combination of the gases with haemoglobin.

The above system of equations is to be solved under the following conditions :

I. Boundary Conditions

(a) At $x = 0$, due to symmetry the flux of the species will be zero, i. e.,

$$\frac{\partial y_i}{\partial x} = 0, \text{ at } x = 0, \; i = 1, \ldots, 8. \qquad \ldots(4a)$$

(b) Since the thickness of the membrane is infinitesimally small, it is reasonable to assume that the concentration of the gases at the wall, $x = \pm a$, is the same as in the alveolar region.

In view of the larger size of haemoglobin molecule in comparison to oxygen and carbondioxide molecules, the haemoglobin and its species can not penetrate across the wall and hence there will be no flux of these species across the wall of the capillary.

Accordingly,

$$\text{at } x = a, \begin{cases} y_1 = y_{1alv}, \\ y_6 = y_{6alv}, \\ \dfrac{\partial y_i}{\partial x} = 0, \; i = 2, 3, 4, 5, 7, 8 \end{cases} \qquad \ldots(4b)$$

II. Entrance Conditions

Concentrations of the species at the entry are equal to corresponding concentrations in venous blood, i.e.,

$$y_i = y_{iven}, \text{ at } z = 0, \; i = 1, 2, \ldots, 8. \qquad \ldots(4c)$$

For solving the above system, Singh *et al.*[6] have first determine the equilibrium solution, concentrations of the species in the arterial blood, by letting $z \to \infty$ which amounts to neglect the convective effect.

We would now like to determine the distance traversed by the blood in lung capillary to achieve equilibration and the effects of the various parameters on the rate of equilibration. Also we know that at equilibration

$$y_i \to y_{iart} \text{ as } z \to \infty \qquad \ldots(5)$$

where (y_{iart}, $i = 1, 2, \ldots, 8$) are the concentrations of the species in the arterial blood and their values are computed by Singh *et al.*[6] We set

$$y_i = y_{iart} + f_i(x)\, e^{-kz} \qquad \ldots(6)$$

where k essentially determines the rate of equilibration. The amount of total haemoglobin at every value of z will still be constant (same as in equilibrium case), because there is no flux of the haemoglobin across the wall of the capillary, i.e.,

$$y_2 + y_3 + y_4 + y_5 + y_7 + y_8 = H. \qquad ...(7)$$

Mathematically, this result can be obtained in a similar manner as given in Singh *et al.*[5]

We have, therefore,

$$f_2(x) + f_3(x) + f_4(x) + f_5(x) + f_7(x) + f_8(x) = 0. \qquad ...(8)$$

Clearly, we are now going to get an eigen-value problem and the lowest value of the eigenvalue k will essentially determine the rate at which equilibration is reached. Since we are primarily interested in the lowest eigenvalue, it would be adequate if we substitute (6) into (2) and consider the equations obtained by equating the coefficients of e^{kz} in each of the eight equations in (2). The derivatives with respect to x are denoted by primes, accordingly, we obtain

(a) $$D_0 f_1'' = k_{11}[f_1 y_{8art} + f_8 y_{1alv}] - k_{12} f_2 + k_{21} (f_1 y_{2art} + f_2 y_{1alv}] - k_{22} f_3 + k_{31}[f_1 y_{3art} + f_3 y_{1alv}] - k_{32} f_4 + k_{41} (f_1 y_{4art} + f_4 y_{1alv}) - k_{42} f_5 - kQ f_1$$

(b) $$D_H f_2'' = k_{21}(f_1 y_{2art} + f_2 y_{1alv}) - k_{22} f_3 - k_{11} (f_1 y_{8art} + f_8 y_{1alv}) + k_{12} f_2 - kQ f_2$$

(c) $$D_H f_3'' = k_{31}(f_1 y_{3art} + f_3 y_{1alv}) - k_{32} f_4 - k_{21} (f_1 y_{2art} + f_2 y_{1alv}) + k_{22} f_3 - kQ f_3$$

(d) $$D_H f_4'' = k_{41}(f_1 y_{4art} + f_4 y_{1alv}) - k_{42} f_5 - k_{31} (f_1 y_{3art} + f_3 y_{1alv}) + k_{32} f_4 - kQ f_4$$

(e) $$D_H f_5'' = -k_{41}(f_1 y_{4art} + f_4 y_{1alv}) + k_{42} f_5 - kQ f_5$$

(f) $$D_C f_6'' = m_1(f_6 y_{8art} + f_8 y_{6alv}) - m_2 f_7 - kQ f_6$$

(g) $$D_H f_7'' = -m_1 (f_6 y_{8art} + f_8 y_{6alv}) + m_2 f_7 - kQ f_7$$

(h) $$D_H f_8'' = k_{11} (f_1 y_{8art} + f_8 y_{1alv}) - k_{12} f_2 + m_1$$

$$(f_6 y_{8art} + f_8 y_{6alv}) - m_2 f_7 - kQ f_8. \qquad \ldots(9)$$

The boundary conditions (4a and b) become :

(a) at $x = 0$, $f_i' = = 0$, $i = 1, \ldots\ldots, 8$

(b) at $x = a, f_1 = f_6 = f_2' = f_3' = f_4' = f_5' = f_7' = f_8' = 0.$

$\ldots(10)$

In view of (8), (9h) is automatically satisfied and so is not required.

In order to compare the order of magnitude of the various terms, we now non-dimensionalize the variables as follows :

$$F_1 = \frac{f_1}{y_{1alv}}, \; F_6 = \frac{f_6}{y_{6alv}}, \; F_i = \frac{f_i}{H} \; (i = 2, 3, 4, 5, 7, 8)$$

and

$$X = x/a. \qquad \ldots(11)$$

On substituting (11) in (9), we obtained a system of second order ordinary differential equations in the variables F_i's ($i = 1, 2, \ldots, 7$). Their general solution has been expressed in a straightforward manner interms of the arbitrary constants A_i and B_i ($i = 1, 2, \ldots, 7$) and eigenvalue k in the form of

$$\sum_{i=1}^{7} A_i \cosh \sqrt{R_i}\, x + \sum_{i=1}^{7} B_i \sinh \sqrt{R_i}\, x. \qquad \ldots(12)$$

On application of boundary conditions, it is found that the one set of constants B_i's is equal to zero and would yield a system of linear homogeneous algebraic equations interms of A's and the equilibration rate k. For a nontrivial solution the determinant formed by the coefficients of A's must vanish and this condition leads to a transcedental equation interms of k. The smallest root of this transcedental equation, that determines the rate at which the equilibration is achieved, is obtained numerically by using the method of bisection.

It is noteworthy that the intermediate terms occurring in computation are of higher orders. From the convergence point of view, the solution of the transcendental equation requires much more significant places than are normally available on the computers. Hence a highly skilled multiprecision technique, developed by Verma and Sharan[8], has been employed to obtain an acceptable solution of this physical problem.

The technique helps to run a programme with one hundred twenty significant digits.

By using the experimental values of the parameters the least value of k is given as

$$k \approx O(10^4)\ cm^{-1} \qquad \ldots(13)$$

and corresponding order of magnitude of the functions F_i's relative to F_1 are obtained as

$$F_1 \sim O(1)\ ,\ F_4 \sim O(10^{-3})\ ,\ F_7 \sim O(10^{-11}).$$

$$F_2 \sim O(10^{-3})\ ,\ F_5 \sim O(10^{-1})$$

$$F_3 \sim O(10^{-3})\ ,\ F_6 \sim O(10^{-9}). \qquad \ldots(14)$$

It would be convenient to express the results in the following form :

$$y_1 = y_{1alv}\,(1 + e^{-kz}),\ y_{1alv} \sim O(10^{-7})$$

$$y_2 = H\left(\frac{y_{2art}}{H} + 10^{-3}\,e^{-kz}\right),\ \frac{y_{2art}}{H} \sim O(10^{-2})$$

$$y_3 = H\left(\frac{y_{3art}}{H} + 10^{-3}\,e^{-kz}\right),\ \frac{y_{3art}}{H} \sim O(10^{-2})$$

$$y_4 = H\left(\frac{y_{4art}}{H} + 10^{-3}\,e^{-kz}\right),\ \frac{y_{4art}}{H} \sim O(10^{-3})$$

$$y_5 = H\left(\frac{y_{5art}}{H} + 10^{-1}\,e^{-kz}\right),\ \frac{y_{5art}}{H} \sim O(1)$$

$$y_6 = y_{6alv}\,(1 + 10^{-9}\,e^{-kz})\ ,\ \frac{y_{7art}}{H} \sim O(10^{-11})$$

$$y_7 = H\left(\frac{y_{7art}}{H} + 10^{-11}\,e^{-kz}\right). \qquad \ldots(15)$$

The length L of the capillary is generally taken by the physiologists as the sum of the perimeter of three alveoli which amounts to be 100 microns approximately.

Equation (13) shows that the blood has traversed a distance of the order of 10^{-4} cm in the capillary before equilibrium is achieved. It implies that the blood is completely oxygenated well before it leaves the capillary—a well known physiological fact.

Equations (14) and (15) reveal that the dissolved oxygen takes the longest to achieve equilibration, where as carbon dioxide attains equilibration at the fastest rate. This is due to the fact that as soon as $HbCO_2$ dissociates into Hb and CO_2, the gas is almost instantaneously diffused out into the alveoli and the free haemoglobin combines even more rapidly with oxygen due to the stronger affinity. Also the dissociation rate in each of the four reactions eqn. (1) is very small, therefore, oxygen takes longest to achieve equilibration. On the other hand the dissociation rate of $HbCO_2$ is much larger than the rate at which CO_2 combines with Hb. Hence CO_2 attains equilibration at the fastest rate.

Results and Discussions

Thus, it has been found that the blood is oxygenated completely well before it leaves the capillary. Also the dissolved oxygen takes longer to reach equilibration whereas the CO_2 is fastest to attain equilibrium condition. The results are qualitatively same as obtained in Singh *et al.*[5] for one step kinetics model. The transcedental equation in k depends upon various parameters, for example, calibre of the capillary, diffusion coefficients of the species, concentrations of the gases in the alveolar region, amount of haemoglobin in the blood, flow rate and association and dissociation rate constants etc. Their individual effects on equilibration length ($\sim 1/k$) or rate k are computed and inferred as follows:

(a) y_{6alv} and the reaction rate constants m_1 and m_2 for carbamino-haemoglobin do not have significant effect on equilibration rate.

(b) The increase in y_{1alv}, partial pressure of oxygen in the alveolar air, increases the pressure gradient which drives the oxygen into lung capillaries through the membrane. It accelerates the process of diffusion from a region of higher concentration to that of lower concentration which results in decreased equilibration length. On the other hand, y_{1art} increases with the increase in y_{1alv} which implies that the blood will traverse a longer distance in the capillary to achieve larger content of oxygen in the arterial blood. Besides their opposing tendencies our analysis clearly shows the dominance of molecular diffusion resulting in the decrease of equilibration length as the oxygen tension in the alveolar air increases. This may have some relevance in situations arising in masked oxygen breathing in aircraft, artificial breathing and positive pressure in the mines.

(c) Increase in the total amount of haemoglobin increases the equilibration length. Since increase in haemoglobin concentration implies higher oxygen carrying

capacity of the blood, the venous blood will traverse a larger distance in the capillary to absorb more oxygen required for saturation.

(d) Increase in the dissociation rate constant of any step increases the equilibration length. It is justified in the sense that increase in the backward rate constant facilitates the dissociation of oxyhaemoglobin and it results in the venous blood traversing longer distance to achieve equilibration.

(e) Increase in the association rate constant of any step decreases the equilibration length. In fact, it is due to that the increase in the association rate implies stronger affinity of haemoglobin for oxygen, resulting in hastening of oxygenation process.

(f) Increase in the speed of the blood (Q) increases the equilibration length which is due to the fact that the time for the blood to remain in the capillary is substantially reduced because of the increased cardiac output. Hence the oxygenation of the blood suffers resulting in longer distance for the blood to traverse the capillary for achieving equilibration.

(g) Decrease in diffusion coefficient of oxygen (D_0) results in increase of equilibration length which is understandable because the free molecular diffusion of oxygen is inhibited

(h) The equilibration length increases as the calibre increases due to larger distance covered by the gases in diffusion mechanism. This may have some relevance to situations like vasodilations involving increase in the calibre.

(i) Increase in diffusion coefficient of haemoglobin (D_H) decreases the equilibration length due to the enhanced molecular diffusion of haemoglobin.

We will apply these results in various pathological conditions relevant to this investigation :

In the case of anaemia, the deficiency of the red cells results in (i) a decrease in the blood viscosity increasing the equilibration length and (ii) a reduction in the amount of available haemoglobin decreasing equilibration length. Inspite of these opposing tendencies, our study reveals that the equilibration length increases with the rise in flow rate (fall in blood viscosity) as well as the fall in total haemoglobin content. Hence the convection dominates over the facilitated diffusion in anaemic conditions. Likewise, in the case of polycythaemia, the equilibration length tends to decrease and we find the dominance of convection process over facilitated diffusion.

During meditation, the decrease in the speed of the blood flowing through the lungs due to reduction in the heart rate decreases the equilibration length. The reduction in the concentration gradient across the pulmonary membrane increases the equili-

bration length. Inspite of differing effects, our analysis shows that the overall effect in mediation is a decrease in equilibration length and the convection process dominates over diffusion mechanism.

During muscular exercise, (i) an increase in the speed of the blood in comparison to the resting conditions, increases the equilibration length and (ii) a rise in the concentration gradient across the pulmonary membrane in comparison to the resting conditions, results in the decrease of the equilibration length. Inspite of these opposite effects, our analysis shows that the equilibration length will increase in muscular exercise.

In fever, a rise in body temperature results in (i) an increase in the dissociation rate of oxyhaemoglobin increasing the equilibration length and (ii) an increase in the rate of blood flow due to an increase in the pulse rate increases the equilibration length. Thus, the process of blood oxygenation in lungs is affected adversely in fever.

At high altitude, the immediate change is the fall in alveolar PO_2. As discussed earlier, a decrease in alveolar PO_2 increases the equilibration length and decreases the PO_2 in the arterial blood. Thus, not only the amount of oxygen dissolved in arterial blood is reduced at high altitude, but also the increase in equilibration length contributes to the factors responsible for hypoxia.

In certain borderline respiratory disorders, it is known that the PaO_2 and $PaCO_2$ (i.e., arterial blood tensions) are normal in resulting conditions. However, it is observed that if an individual is put to physical exertion, his PaO_2 falls below the normal value but $PaCO_2$ still remains normal. This situation indicates developing respiratory disorders and can be explained in the light of present analysis. The blood is completely oxygenated in the lung capillary in resting condition. However, during exercise, since the equilibration length increases and the oxygen takes longest to achieve equilibration blood is not able to have an adequate supply of oxygen during its passage through the capillary. This shows fall in PaO_2. On the other hand, since CO_2 is fastest to achieve equilibration, it follows that although the equilibration length has exceeded the capillary length during exercise, CO_2 has attained the normal value within the length of the capillary.

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