A MATHEMATICAL MODEL FOR THE PROCESS OF GAS EXCHANGE IN LUNG CAPILLARIES USING nTH ORDER ONE-STEP KINETICS OF OXYGEN UPTAKE BY HAEMOGLOBIN

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Abstract

A mathematical model is developed for the process of gas exchange in lung capillaries, taking into account the transport mechanisms of molecular diffusion and the facilitated diffusion of the species due to haemoglobin. We have assumed here equilibrium conditions which enable us to neglect advection effects. The nth order one-step kinetics of oxygen uptake by haemoglobin, proposed by Sharan and Singh [8], have been incorporated. The solution of this coupled nonlinear facilitated diffusion-reaction problem together with the physiologically-relevant boundary conditions is obtained in the closed form.

It is found that about 97.15% of total haemoglobin has combined with oxygen and 2.85% free pigment is left, which is present as carbaminohaemoglobin, met haemoglobin, carboxy haemoglobin etc. It is also shown that the percentage of free haemoglobin at a given PO_2 and PCO_2 is independent of total haemoglobin content present in the blood.

The well-known Hill's empirical relation is deduced from our solution. The results obtained from our model, based on physical formulation, are in good agreement with the documented data [6] and those computed from the Kelman [3] empirical relation.

1. Introduction

The process of gas exchange between the blood flowing through the lung capillaries and the surrounding alveolar air has been a subject of considerable interest

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in recent years. The related work has been reviewed extensively by Sharan and Singh [7].

Murray [4] has discussed the transport of O_2 through a layer of haemoglobin solution. An approximate solution has been obtained by singular perturbation methods. Singh et al. [13] have considered the simultaneous transport of O_2 and CO_2 for studying the facilitated diffusion of O_2 and CO_2 in the presence of haemoglobin, and they have found an approximate solution of the governing equations by an asymptotic approach. With a slight modification in the boundary conditions, the model has been used in the lung capillaries [12]. Recently, Singh et al. [11] and Sharan and Singh [9] have developed a mathematical model for the oxygenation of blood in lung capillaries by taking into account the main transport mechanisms of molecular diffusion, convection and the facilitated diffusion due to the presence of haemoglobin as a carrier of the gases. These studies are based on first-order one-step kinetics of oxygen uptake by haemoglobin. However, first-order one-step kinetics lead to a hyperbolic curve rather than the experimentally observed sigmoidal oxygen dissociation curve [8]. The curve obtained from one-step kinetics is not compatible with the one based on experimental data. The four-step kinetics suggested by Adair [1] lead to the saturation function [10] which fits in very well with the one based on experimental data [6]. Since the order of magnitude of each of the association and dissociation rate constants of the corresponding reaction in the four-step mechanism is not known, it is difficult to formulate a realistic mathematical model for the blood oxygenation in the lungs. Further, Adair's hypothesis is not valid in the physiological range [5]. Hill [2] has developed an empirical relation for the O_2 saturation function which provides a fairly good approximation to the experimental data in the physiological range [5]. However, Hill's formula does not depend explicitly on the CO_2 concentration and is not suitable in dealing with the simultaneous transport of O_2 and CO_2 in the lung capillaries [8].

Recently, Sharan and Singh [8] have shown an equivalence between one-step kinetics and Hill's equation. A modified form of one-step kinetics of oxygen uptake by haemoglobin has been proposed by taking the association rate of oxygen with haemoglobin as a function of oxygen concentration. It has been suggested that the modified one-step kinetics are more appropriate in dealing with the simultaneous transport of O_2 and CO_2 in the lungs.

The earlier studies [9, 11] on the process of gas exchange in the lungs are based on first-order one-step kinetics of oxygen uptake by haemoglobin. In the present study, we describe a mathematical model for analysing the process of gas exchange in the blood flowing through the lung capillaries using the nth order one-step kinetics of oxygen uptake by haemoglobin. The model takes into account the transport of gases by molecular diffusion and the facilitated diffusion due to haemoglobin as a carrier of the gases. The solution of the governing

equations with the physiologically relevant boundary conditions is obtained in a closed form. The solution found here is the far-downstream solution of the equations (2) of Sharan and Singh [9] for a two-dimensional channel, with a revised form for the chemical kinetics of oxygen with haemoglobin.

2. Mathematical formulation

Let the deoxygenated blood enter the capillary at $z = 0$ and leave it as fully oxygenated blood after traversing a length L (Figure 1). The capillary is assumed to be an axisymmetric straight tube. In the capillary, oxygen diffuses from the alveolar air to the blood and CO_2 is diffused out from the blood simultaneously. We assume that equilibration of gases has taken place so that the convective effects due to the motion of the blood will not be important. In the blood, O_2 and CO_2 combine with Hb according to following reversible reactions:

$$Hb + O_2 \overset{k_1'}{\underset{k_2}{\rightleftharpoons}} HbO_2 \tag{1}$$

$$Hb + CO_2 \overset{m_1}{\underset{m_2}{\rightleftharpoons}} HbCO_2 \tag{2}$$

where k_1', k_2, m_1 and m_2 are the reaction rate coefficients.

Let c_1, c_2, c_3, c_4 and c_5 represent the concentrations of O_2, HbO_2, CO_2, $HbCO_2$ and Hb respectively. By using the first-order one-step kinetics, the analysis and treatment are simplified. If the combination of oxygen with haemoglobin in (1) is of order one, the first-order one-step kinetics lead to a hyperbolic curve rather than the sigmoidal oxygen dissociation curve [11]. In other words, the curve obtained from first-order one-step kinetics is not compatible with the one obtained from the experimental data.
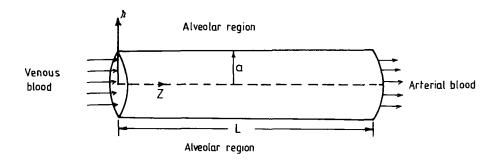

FIGURE 1. Sketch of the mathematical model.

According to modified one-step kinetics, proposed by Sharan and Singh [8], we assume that the combination of oxygen with haemoglobin in (1) is of order n.

The transport of O_2 and CO_2 in the blood mainly depends on molecular diffusion and the facilitated diffusion due to Hb. The material balance of each of the species in the blood leads to the following system of second-order nonlinear ordinary differential equations:

$$\frac{D_0}{r} \frac{d}{dr}\left(r\frac{dc_1}{dr}\right) = k_1' c_1^n c_5 - k_2 c_2 \tag{3a}$$

$$\frac{D_H}{r} \frac{d}{dr}\left(r\frac{dc_2}{dr}\right) = -k_1' c_1^n c_5 + k_2 c_2 \tag{3b}$$

$$\frac{D_C}{r} \frac{d}{dr}\left(r\frac{dc_3}{dr}\right) = m_1 c_3 c_5 - m_2 c_4 \tag{3c}$$

$$\frac{D_H}{r} \frac{d}{dr}\left(r\frac{dc_4}{dr}\right) = -m_1 c_3 c_5 + m_2 c_4 \tag{3d}$$

$$\frac{D_H}{r} \frac{d}{dr}\left(r\frac{dc_5}{dr}\right) = k_1' c_1^n c_5 - k_2 c_2 + m_1 c_3 c_5 - m_2 c_4 \tag{3e}$$

where D_0 and D_C are respectively the diffusion coefficients of O_2 and CO_2, D_H is the diffusion coefficient (assumed to be the same) for Hb, HbO_2 and $HbCO_2$ [14]. The reaction rate coefficients k_1', k_2, m_1 and m_2 are assumed to be constant. The detailed description of the model is given in Singh et al [10, 11] and Sharan and Singh [9]. In (3), the left-hand terms represent the molecular diffusion whereas terms on the right-hand side represent the effect of chemical combination of the gases with haemoglobin. Thus, (3) provides the balance between the molecular diffusion and the facilitated diffusion.

The system (3) is subject to the following physiologically-relevant boundary conditions:

(a) At $r = 0$, due to symmetry, the flux of the species will be zero, that is,

$$\frac{dc_i}{dr} = 0, \quad \text{at } r = 0, \ i = 1, 2, \ldots, 5. \tag{4}$$

(b) (i) Since the thickness of the membrane is small, we shall assume that the concentration of the gases at the wall $r = a$ is the same as in the alveolar region, that is,

$$\text{at } r = a, \quad \begin{cases} c_1 = c_{1\text{alv}} \\ c_3 = c_{3\text{alv}} \end{cases} \tag{5}$$

where the suffix "alv" corresponds to the quantities in the alveolar air.
(ii) Since the haemoglobin molecule is much larger in comparison to the oxygen and cardon dioxide molecules, Hb, HbO_2, and $HbCO_2$ cannot

penetrate across the membrane wall and hence there will be no flux of these species across the capillary wall. Accordingly, we have:

$$\frac{dc_2}{dr} = \frac{dc_4}{dr} = \frac{dc_5}{dr} = 0, \quad \text{at } r = a. \tag{6}$$

The coupled system of differential equations (3) is nonlinear where n can have any positive value, not necessarily integral.

3. Solution

Adding (3b), (3d) and (3e) and integrating twice, using the boundary conditions (4) and (6), we obtain

$$c_2 + c_4 + c_5 = H \tag{7}$$

where H is a constant and known from the physiological data. Equation (7) states that haemoglobin content remains constant. This is understandable because there is no flux of the haemoglobin and its species across the wall.

Adding (3a) and (3b) and integrating once, we obtain

$$D_0 \left(r\frac{dc_1}{dr} \right) + D_H \left(r\frac{dc_2}{dr} \right) = F, \tag{8}$$

where F is a constant. Using the boundary condition (4), we get

$$F = 0. \tag{9}$$

In view of the boundary conditions (5) and (6), there is, at equilibrium, no flux of oxygen at the capillary wall, which implies that the oxygen concentration is constant, that is,

$$c_1 = c_{1\text{alv}}. \tag{10}$$

A similar result will hold for CO_2, that is,

$$c_3 = c_{3\text{alv}}. \tag{11}$$

By considering (3a), (3c) and (7), we find the following constant-valued solution:

$$c_2 = \frac{kc_{1\text{alv}}^n H}{1 + kc_{1\text{alv}}^n + mc_{3\text{alv}}} \tag{12a}$$

$$c_4 = \frac{mc_{3\text{alv}} H}{1 + kc_{1\text{alv}}^n + mc_{3\text{alv}}} \tag{12b}$$

$$c_5 = \frac{H}{1 + kc_{1\text{alv}}^n + mc_{3\text{alv}}} \tag{12c}$$

where $k = k_1'/k_2$ and $m = m_1/m_2$.

4. Results and discussion

We have found that the nonlinear system of ordinary differential equations (3), together with the boundary conditions (4)–(6), has a constant-valued solution. In fact, the solution obtained here is the far-downstream solution of the equations (2) for a two dimensional channel of Sharan and Singh [9], with the modified form of one-step kinetics of oxygen uptake by haemoglobin.

It is just a coincidence that the form of the solution (12) derived here is the same as obtained by Sharan and Singh [8], where the role played by transport mechanisms has not been considered. It may be noted that we are able to obtain here the solution of a nonlinear facilitated diffusion-reaction problem in a closed form.

The percentage saturation (s) of O_2 is defined as:

$$\frac{s}{100} = \frac{c_2}{H} = \frac{kc_{1alv}^n}{1 + kc_{1alv}^n + mc_{3alv}}. \tag{13}$$

If $m = 0$, (13) reduces to the well-known Hill's equation [2]:

$$\frac{s}{100} = \frac{kc_{1alv}^n}{1 + kc_{1alv}^n}. \tag{14}$$

Equation (13) is the modified form of Hill's equation which shows an explicit dependence of the O_2 saturation function on the concentration of CO_2. Similarly, the function for the saturation of Hb with CO_2 (12b) depends explicitly on the concentration of O_2. Also, we are able to establish Hill's empirical relation (14) on the basis of formulated physical principles.

Equation (12a) shows that the O_2 saturation (c_2) increases as the concentration of $O_2(c_{1alv})$ increases or the concentration of $CO_2(c_{3alv})$ decreases. The concentration of $HbCO_2$ decreases with the increase in c_{1alv} and vice-versa (12b). Likewise, the saturation function for O_2 decreases as c_{3alv} increases and vice-versa (13). Thus, the solution given by (12a) and (12b) is consistent with the well known Bohr's and Haldane's effects. In fact, they are confirmed mathematically as:

$$\frac{\partial c_2}{\partial c_{3alv}} < 0 \tag{15}$$

and

$$\frac{\partial c_4}{\partial c_{1alv}} < 0. \tag{16}$$

By fitting the solution (13) with the experimental data for the O_2 dissociation curve, the following values of the parameters have been obtained [8]:

$$k = 7.52455 \times 10^{19} \ (mole. \ cm^{-3})^{-n}$$
$$m = 2.983574 \times 10^6 \ mole.^{-1}cm^3$$
$$n = 2.6478. \tag{17}$$

Using the following physiological data:

$$c_{1alv} = 1.43 \times 10^{-7} mole.\ cm^{-3} \text{ (equivalent to 100 mm } Hg)$$
$$c_{3alv} = 2.216 \times 10^{-7} mole.\ cm^{-3} \text{ (equivalent to 40 mm } Hg) \qquad (18)$$

and

$$H = 2.3 \times 10^{-6}\ mole.\ cm^{-3}$$

it is found that:

$$c_1 = 1.43 \times 10^{-7} mole.\ cm^{-3}$$
$$c_2 = 2.2345 \times 10^{-6} mole.\ cm^{-3}$$
$$c_3 = 2.216 \times 10^{-7} mole.\ cm^{-3}$$
$$c_4 = 2.608 \times 10^{-8} mole.\ cm^{-3}$$
$$c_4 = 3.9446 \times 10^{-8} mole.\ cm^{-3}. \qquad (19)$$

Equation (19) shows that in arterial blood, about 97.15% haemoglobin has combined with oxygen and about 2.85% free haemoglobin (the amount of Hb not combining with O_2 or CO_2) is left free, out of which $HbCO_2$ is about 1.134%.
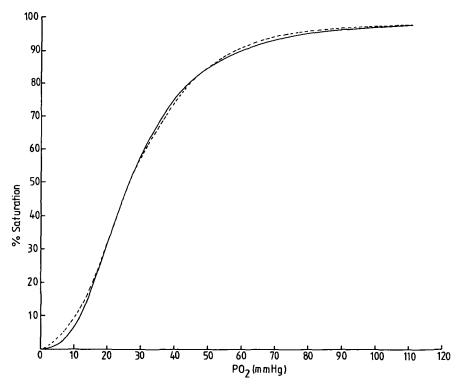

FIGURE 2. Comparison of oxygen dissociation curve obtained from our solution (13) (——) with the one based on documented data of Severinghaus [6] (-----) ($PCO_2 = 40$ mm Hg).

Figure 2 represents the O_2 saturation computed from (13) using (17) for different values of O_2, with $c_{3alv} = 2.216 \times 10^{-7} mole. \, cm^{-3}$ (equivalent to $PCO_2 = 40$ mm Hg). The graph shows that the oxygen dissociation curve is fairly close to the one based on documented data [6]. Table 1 shows that the values of haemoglobin saturation with O_2 computed from (13) for various values of PO_2 (i.e., the partial pressure of O_2) and PCO_2 are in good agreement with those calculated from Kelman's equation [3] within the limits of the computational accuracy. Thus, the modified form of Hill's equation (13) provides a good approximation for representing the oxygen dissociation curve at different PCO_2.

TABLE 1. Results computed from equation (13) and Kelman's equation [3]

$PO_{2_{mmHg}}$ $PCO_{2_{mmHg}}$	39	40	41	42	43	44	45
120	98.24	98.223	98.205	98.188	98.171	98.153	98.136
120*	98.297	98.292	98.287	98.282	98.277	98.272	98.267
100	97.179	97.151	97.124	97.096	97.069	97.041	97.014
100*	97.498	97.49	97.48	97.474	97.466	97.459	97.451
85	95.726	95.685	95.644	95.603	95.562	95.521	95.480
85*	96.388	96.375	96.362	96.35	96.338	96.325	96.314
75	94.145	94.09	94.035	93.979	93.924	93.869	93.814
75*	95.097	95.078	95.06	95.042	95.024	95.007	94.989
65	91.673	91.596	91.52	91.443	91.367	91.291	91.215
65*	92.858	92.828	92.799	92.771	92.743	92.716	92.689
55	87.614	87.505	87.396	87.288	87.18	87.072	86.964
55*	88.639	88.591	88.543	88.497	88.452	88.407	88.363
40	75.272	75.085	74.90	74.715	74.531	74.348	74.166
40*	74.202	74.116	74.031	73.948	73.868	73.789	73.712
30	58,697	58.454	58.214	57.975	57.738	57.503	57.270
30*	56.799	56.706	56.616	56.528	56.442	56.358	56.275

*Computed from Kelman's equation [3]

Figure 3 shows that the concentration of free haemoglobin increases with the decrease in PO_2. Also, the percentage of free haemoglobin at a given PO_2 is independent of the total haemoglobin content in the blood. Figure 4 shows that the percentage of $HbCO_2$ increases as PCO_2 increases or PO_2 decreases. Equation (12a) indicates theoretically how in the anaemic condition, the total amount of oxyhaemoglobin is reduced. Similarly, it shows how at high altitude, where PO_2 is reduced, not only the dissolved oxygen in the arterial blood but also the oxyhaemoglobin is reduced. Similar qualitative information can be obtained in the polycythaemic patient and deep-sea environment.
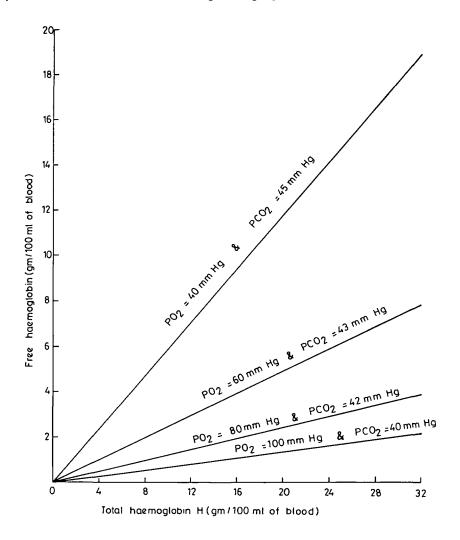
FIGURE 3. Variation of free haemoglobin concentration with total haemoglobin content in the blood for different PO_2 and PCO_2.
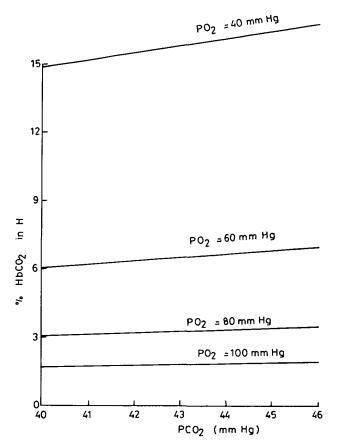
FIGURE 4. Variation of percentage $HbCO_2$ in total haemoglobin content with PCO_2 at different PO_2.

Acknowledgement

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