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A Mathematical Model for the Computation of Carboxyhaemoglobin in Human Blood as a Function of Exposure Time

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CONTENTS

SUMMARY

A mathematical model is developed for the carbon monoxide (CO) uptake by the blood by taking into account the molecular diffusion, convection, facilitated diffusion and the non-equilibrium kinetics of CO with haemoglobin. The overall rate for the combination of CO with haemoglobin is derived by including the dissociation of CO from carboxyhaemoglobin (COHb). The resulting coupled system of nonlinear partial differential equation with physiologically relevant initial, entrance and boundary conditions is solved numerically. A fixed point iterative technique is used to deal with nonlinearities. The concentration of COHb in the blood is computed as a function of exposure time and ambient CO concentration.

The COHb levels computed from our model are in good agreement with those measured experimentally. Also, results computed from our model give better approximation to the experimental values compared with the results from other models. The time taken by the blood COHb to attain 95% of its equilibrium value is computed. The COHb concentration in the blood increases with the increase in ventilation rate, association rate coefficient of CO with haemoglobin and total haemoglobin content in the blood, and with the decrease in dissociation rate coefficient of CO with haemoglobin and mean capillary blood p_{O_2}.

It is found that the COHb level in the blood is not affected significantly because of endogenous production of CO in the body under normal condition. However, the effect may be significant in the patients with haemolytic anaemia.

1. INTRODUCTION

Owing to increasing vehicular traffic and rapid industrialization, carbon monoxide (CO) is considered as a common atmospheric pollutant that directly affects human health. The adverse effects of relatively small CO exposures, which are normally found in urban, industrial and household air, have been pointed out by Coburn *et al.* (1977) and Laties (1980). Persons may also be exposed accidentally or occupationally to higher concentrations of CO resulting in adverse health effects (Tikuisis *et al.* 1987*a*; Bernard & Duker 1981).

As the affinity of haemoglobin for CO is more than 200 times that for oxygen (O_2), the inhaled CO replaces O_2 from oxyhaemoglobin (O_2Hb) in the red blood cells and forms carboxyhaemoglobin (COHb).

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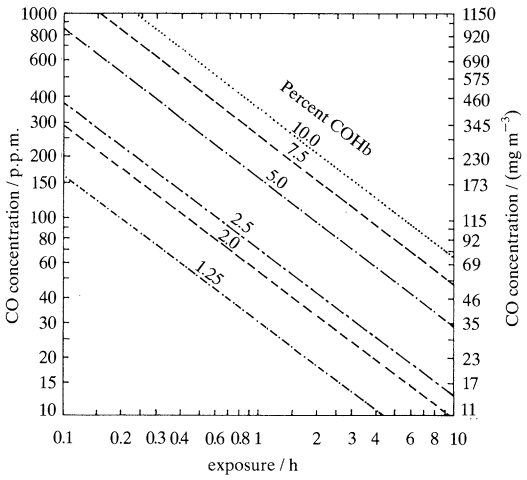

Figure 1. COHb level as a function of exposure time (Air quality criteria for carbon monoxide 1970).

Thus it impairs the O_2 transport that is essential for the survival of the tissue. Persons with any impairment such as cardiac damage, cholesterol build-up in any vascular structure, anaemia or pulmonary function impairment are especially sensitive to CO exposures because of already reduced or marginal O_2 supply. For example, persons with cardiac ailments are at risk to CO exposures sufficient to produce 2.5 to 3.0 % COHb in blood (see Air quality criteria for carbon monoxide 1979). It is also observed that a 3.4 % COHb is sufficient to interfere with safe driving (Wright *et al.* 1973).

For a given concentration of CO in the ambient air, the COHb level in the blood reaches an equilibrium value after a specific time period. Exposure to 10 p.p.m. CO will provide a COHb equilibrium level greater than 2 %, a level that is reported to be the point at which the effect upon the human nervous system becomes apparent. The American carbon monoxide standard of 9 p.p.m. for continuous exposure for 8 h or 35 p.p.m. for 1 h will not exceed COHb levels of 2 % in healthy, non-smoking individuals (figure 1). Individuals exposed to CO levels resulting in more than 2 % of COHb in the blood stream will experience deterioration of reacting time, visual acuity and drowsiness all of which negatively affect the driving task.

The percentage of COHb in the blood is considered as a good index of health effects of CO on humans (Air quality criteria for carbon monoxide 1979) and thus the aim of this study is to develop a mathematical model for the prediction of COHb level in the blood as a function of exposure time and the ambient concentration of CO.

At the beginning of this century, Haldane and his co-workers proposed several basic concepts for the absorption and elimination of CO with haemoglobin (Doughlas *et al.* 1912). Forbes *et al.* (1945) proposed the formulae to compute COHb level in the blood as a function of exposure time by measuring the rate of CO uptake by humans under a wide range of conditions. Attempts have been made by Pace *et al.* (1945) and Lilienthal & Pine (1946) to express mathematically the rate of uptake of CO by the blood. Their formulations reflected the fact that over small ranges the increase in COHb concentration appeared to be nearly proportional to CO concentration and exposure time. Using the data of Forbes *et al.* (1945), Hatch (1952) developed an equation showing explicitly the exponential nature of CO absorption. An equation similar to Hatch (1952) was derived by Goldsmith (1963) to evaluate the COHb concentration due to fluctuating CO exposures. Peterson & Stewart (1970) fitted a log–log function with their experimental data. It appears that this function was used to draw the nomogram (Air quality criteria for carbon monoxide 1970) showing COHb in the blood as a function of exposure time and ambient CO concentration. However, this function does not approximate the values of COHb at equilibrium and for higher exposure time (figure 5). Ott & Mage (1978) and Venkatram & Louch (1979) proposed linear models for COHb. The models mentioned above are empirical and do not appear to be derived from the basic physical principles.

Forster *et al.* (1954) derived an equation containing 14 parameters to predict the COHb level in the blood. Coburn *et al.* (1965) developed a model to derive a relation between blood COHb, rate of CO production and the respiratory CO exchange. In the model, the whole body blood was considered as a well-mixed compartment and the reduced haemoglobin (that is, the haemoglobin that has neither combined with O_2 nor with CO) was ignored. This relation is often known in the literature as the CFK equation. This was linearized assuming a constant concentration of O_2Hb in the blood and solved analytically. Later, Peterson & Stewart (1975) pointed out that the constant value of O_2Hb in the CFK equation led to a significant error in the computation of blood COHb. Then proposed an iterative procedure for accounting the variation of O_2Hb in the CFK equation. Bernard & Duker (1981) solved the nonlinear CFK equation using the fourth-order Runge Kutta method. Tyuma *et al.* (1981) were able to obtain an analytical solution of the CFK equation assuming that haemoglobin is always saturated with O_2 or CO or both. Collier & Goldsmith (1983) solved the CFK equation by taking into consideration the reduced haemoglobin using the analysis proposed by Roughton & Darling (1944). Although the CFK equation was developed to study the endogenous production of CO in the body, it has been widely used to predict blood COHb under different CO exposures (Weir & Viano 1977; Marcus 1980, 1981; Bernard & Duker 1981; Tyuma *et al.* 1981; Coburn & Forman 1987; Tikuisis *et al.* 1987*a*, *b*; Wallace *et al.* 1988).

In the studies mentioned above, the haemoglobin and CO are assumed to be in chemical equilibrium. However, Gutierrez (1986) has shown the importance of non-equilibrium kinetics. Peterson & Stewart (1970) and Tyuma *et al.* (1981) have found that the elimination rate predicted from CFK equation agrees well with the experimental values under normal conditions. However, the predicted values under breathing hyperbaric oxygen do not agree with the experimental values. Recently, Wallace *et al.* (1988)

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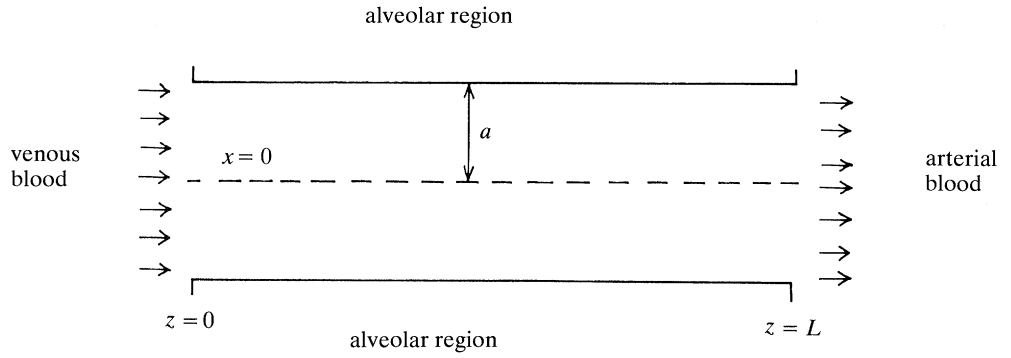

Figure 2. Schematic diagram of the model.

have used the CFK equation to predict the COHb and alveolar CO concentration and have found that the predicted values are not close to those measured experimentally. These differences were attributed to the slower rate of reaction of CO with haemoglobin. Thus the chemical reaction of CO with haemoglobin is important in determining the rate at which CO is taken up or eliminated in the lungs (Forster 1970; Holland 1970).

O_2 and CO are known to undergo a series of chemical reactions in the blood (Roughton 1964). As the combination of O_2 and CO with haemoglobin is very fast and the order of magnitude of association and dissociation rate coefficients in the reaction mechanism (for example, Adair's four-step mechanism) is not known, it is difficult to include all these reactions in the development of realistic models for the transport of O_2 and CO in the blood. The replacement of O_2 from O_2Hb by CO was considered to be a predominant reaction in the pulmonary capillaries (Holland 1970). Gibson & Roughton (1955) have analysed the replacement reaction both theoretically and experimentally. The kinetic studies related to O_2 and CO with haemoglobin have been reviewed extensively in the literature (Roughton 1964; Forster 1964, 1987; Holland 1970; Sharan *et al.* 1989). The kinetics of O_2 and CO with haemoglobin with their association and dissociation rate coefficients for representing the entire O_2 and CO dissociation curves in the mathematical modelling of O_2 and CO transport in the blood flowing through the pulmonary and systemic circulation is not precisely known (Sharan *et al.* 1989). Thus, to begin with, only the replacement reaction of CO has been considered in this study.

When CO reaches the red cell, it has to diffuse across the red cell membrane and diffuse through the substance of the red cell combining at the same time with the available haemoglobin. Roughton *et al.* (1957) and Holland (1969) have observed with *in vitro* experiments that the reaction rate coefficients for cell suspensions are less than those for the haemoglobin solution. They have suggested that the difference was due to resistance exerted by the red cell membrane. However, Coin & Olson (1979) have shown that the rates of CO reaction with haemoglobin in intact cells in a stop–flow rapid-mixing apparatus appeared to be slowed by diffusion of the CO through a stagnant layer of solvent at the surface of the cells. The stagnant layer is not present when the cells are in the capillaries (Forster 1987). Recently, Krawiec *et al.* (1983) and Crapo *et al.* (1989) have measured the rate of CO uptake by the whole blood and found that it depends on p_{O_2} and pH. The process of simultaneous diffusion and chemical reaction is slower than each of the two processes on its own. Britton & Murray (1977) have proposed a model for the transport of O_2 and CO in a layer of haemoglobin solution by considering a single-step kinetics for the uptake of O_2 and CO by haemoglobin and obtained approximate analytical solution using singular perturbation technique. The single-step kinetics of O_2 and CO with haemoglobin leads to hyperbolic O_2 and CO dissociation curves instead of experimentally observed sigmoidial curves (Sharan *et al.* 1989). Britton (1979) has extended the above model for the uptake and release of CO in pulmonary capillaries. In the above study, transport of the species due to convection was not taken into account.

A compartment model has been formulated by Sharan *et al.* (1990) to predict the alveolar partial pressure of CO and blood COHb as a function of exposure time and CO concentration. However, it is assumed that the chemical reactions of CO with haemoglobin are in equilibrium. In this study, we propose a mathematical model for the build up of COHb in the blood by taking into account the transport mechanisms: molecular diffusion, convection and facilitated diffusion and the replacement reaction of CO with O_2Hb.

2. MATHEMATICAL FORMULATION

The blood COHb in the body is determined by the exchange of CO between the pulmonary capillary blood and the ambient air, endogeneous production of CO, dilution of CO in the body tissues and metabolic CO consumption (Coburn & Forman 1987). The ambient air is transported to alveoli by ventilation. The blood absorbs CO from alveoli when it passes through the pulmonary capillaries.

The mechanisms involved in the transport of CO in the pulmonary capillary are the molecular diffusion, convection and the facilitated diffusion of CO due to the presence of haemoglobin as a carrier. We consider the pulmonary capillary as a two-dimensional channel (Sobin *et al.* 1970) of thickness $2a$ surrounded by the alveolar air (figure 2). The venous (deoxygenated) blood enters the pulmonary capillary at $z = 0$ and

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leaves it as arterial (oxygenated) blood at $z = L$. The model is based on the following assumptions.

1. The blood flows through the pulmonary capillary with a uniform speed v in the axial direction.
2. The diffusion of the species in the axial direction is neglected, which can be justified by the scale analysis.
3. Because the molecular mass of CO is much smaller compared with that of haemoglobin, the diffusion coefficients of haemoglobin and COHb are assumed to be the same.
4. The diffusion coefficients of the species are assumed to be constant.
5. The blood is considered to be fully saturated with O_2 in the pulmonary capillary because it is almost fully saturated during most of the time it is in the pulmonary capillary (Holland 1970). The reaction for the replacement of O_2 from O_2Hb by CO is the predominant reaction of CO with haemoglobin (Holland 1970).
6. The concentration of the reduced haemoglobin in the blood is assumed to be negligible and accordingly the sum of the concentrations of O_2Hb and COHb will be equal to the total haemoglobin content in the blood.

The replacement of O_2 from O_2Hb by CO occurs through an overall reversible reaction (Gibson & Roughton 1955):

$$O_2Hb + CO \underset{m}{\overset{m'}{\rightleftharpoons}} COHb + O_2, \tag{1}$$

where m' and m are associated and dissociation rate coefficients. In the unsteady state, the mass balance principle for the species CO, COHb and O_2Hb leads to the following system of partial differential equations:

$$(\partial C_1/\partial t) + v(\partial C_1/\partial z) = D_C(\partial^2 C_1/\partial x^2) - \xi, \tag{2}$$

$$(\partial C_2/\partial t) + v(\partial C_2/\partial z) = D_H(\partial^2 C_2/\partial x^2) + \xi, \tag{3}$$

$$C_2 + C_3 = H, \tag{4}$$

where C_1, C_2 and C_3 are the concentrations of CO, COHb and O_2Hb in the blood, respectively, D_C and D_H are the diffusion coefficients of CO and COHb in the blood, H is the total haemoglobin concentration in the blood and ξ describes the rate of combination of CO in the equation (1). Here x and z are transverse and axial coordinates.

(*a*) *The chemical kinetics of CO with haemoglobin*

The carbon monoxide diffused from the ambient air into the blood combines with the haemoglobin inside the red blood cells to form COHb. Also, because of the higher affinity of haemoglobin for CO over O_2, CO displaces O_2 from O_2Hb and forms COHb. The net rate (ξ) at which CO combines in the red cells is mainly due to the replacement reaction and it is given by Gibson & Roughton (1955):

$$\xi = (m'C_1C_3/[O_2]) - mC_2, \tag{5}$$

where $[O_2]$ is the concentration of O_2 in the blood.

Gibson & Roughton (1955) have shown that m is not independent of the concentration of O_2 and CO. They pointed out that if the reduced haemoglobin is negligible, there should be no appreciable amount of haemoglobin present with less than three gas-binding sites combined with O_2 or CO or both in the Adair's intermediate compound hypothesis (Adair 1925). The various chemical reactions occurring in the blood have been described by Gibson & Roughton (1955):

$$\left.\begin{aligned} Hb_4O_8 &\underset{k'_4}{\overset{k_4}{\rightleftharpoons}} Hb_4O_6 + O_2 \\ Hb_4O_6 + CO &\underset{l_{31}}{\overset{l'_{31}}{\rightleftharpoons}} Hb_4O_6(CO) \end{aligned}\right\} \tag{6a}$$

$$\left.\begin{aligned} Hb_4O_6(CO) &\underset{k'_{31}}{\overset{k_{31}}{\rightleftharpoons}} Hb_4O_4(CO) + O_2 \\ Hb_4O_4(CO) + CO &\underset{l_{22}}{\overset{l'_{22}}{\rightleftharpoons}} Hb_4O_4(CO)_2 \end{aligned}\right\} \tag{6b}$$

$$\left.\begin{aligned} Hb_4O_4(CO)_2 &\underset{k'_{22}}{\overset{k_{22}}{\rightleftharpoons}} Hb_4O_2(CO)_2 + O_2 \\ Hb_4O_2(CO)_2 + CO &\underset{l_{13}}{\overset{l'_{13}}{\rightleftharpoons}} Hb_4O_2(CO)_3 \end{aligned}\right\} \tag{6c}$$

$$\left.\begin{aligned} Hb_4O_2(CO)_3 &\underset{k'_{13}}{\overset{k_{13}}{\rightleftharpoons}} Hb_4(CO)_3 + O_2 \\ Hb_4(CO)_3 + CO &\underset{l_4}{\overset{l'_4}{\rightleftharpoons}} Hb_4(CO)_4 \end{aligned}\right\} \tag{6d}$$

where k_{rs} and k'_{rs} are the dissociation and association velocity coefficients for O_2 and l_{rs} and l'_{rs} are the corresponding coefficients for CO. The sum of the subscripts r and s is always equal to 4. If one of them is already 4, the other assumes zero value, and is omitted.

During the earliest stage of displacement of O_2 by CO, a pair of reactions (6*a*) occurs and applying the law of mass action to the equation (6*a*), we get:

$$\begin{aligned} d[Hb_4O_6]/dt = {} & k_4[Hb_4O_8] - k'_4[O_2]\,[Hb_4O_6] \\ & - l'_{31}[CO]\,[Hb_4O_6] + l_{31}[Hb_4O_6(CO)]. \end{aligned} \tag{7}$$

As $[Hb_4O_6]$ is throughout very small, its variation with time is negligible (Gibson & Roughton 1955) and thus

$$[Hb_4O_6] = \frac{k_4[Hb_4O_8] + l_{31}[Hb_4O_6(CO)]}{k'_4[O_2] + l'_{31}[CO]}. \tag{8}$$

Again applying the law of mass action to (6*a*) and using equation (8), we get

$$\begin{aligned} \frac{d[Hb_4O_6(CO)]}{dt} = {} & \frac{l'_{31}k_4[Hb_4O_8]\,[CO]}{k'_4[O_2] + l'_{31}[CO]} \\ & - \left\{1 - \frac{l'_{31}[CO]}{k'_4[O_2] + l'_{31}[CO]}\right\} l_{31}[Hb_4O_6(CO)]. \end{aligned} \tag{9}$$

Gibson & Roughton (1955) have proposed that the velocity constant for the dissociation of an O_2 or CO molecule is proportional to the total number of combined O_2 or CO molecules in the dissociating complex, whereas the velocity constant for combination of an O_2 or CO with the one vacant haem group in the molecule is independent of the distribution of the

other three combined haem groups between O_2 and CO. Based on the above assumptions, the following relations are obtained:

$$\left.\begin{aligned} &k_4 : k_{31} : k_{22} : k_{13} :: 4:3:2:1 \\ &l_4 : l_{13} : l_{22} : l_{31} :: 4:3:2:1 \\ &k'_4 = k'_{31} = k'_{22} = k'_{13} \\ &l'_4 = l'_{13} = l'_{22} = l'_{31}. \end{aligned}\right\} \quad (10)$$

During the earliest stage of the reaction, the rate of decrease of CO in the blood is

$$-\frac{\mathrm{d}[\mathrm{CO}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{Hb} + \mathrm{CO} \rightarrow \mathrm{COHb}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{Hb_4O_6} + \mathrm{CO} \rightarrow \mathrm{Hb_4O_6(CO)}]}{\mathrm{d}t}, \quad (11)$$

because the unit increase of COHb by the process $Hb + CO \rightarrow COHb$ or the unit increase of $Hb_4O_6(CO)$ by the process $Hb_4O_6 + CO \rightarrow Hb_4O_6(CO)$ both lead to a unit decrease in the number of dissolved CO molecules. In the initial stage of the reaction all the oxygen combined with haemoglobin is in the form of Hb_4O_8, and the CO combined with the haemoglobin after displacing one molecule of O_2 is in the form $Hb_4O_6(CO)$ (Gibson & Roughton 1955). Accordingly, we have

$$\left.\begin{aligned} &[\mathrm{O_2Hb}] = 4[\mathrm{Hb_4O_8}] \\ &\text{and} \\ &[\mathrm{COHb}] = [\mathrm{Hb_4O_6(CO)}]. \end{aligned}\right\} \quad (12)$$

Using the relations (10–12) in the equation (9), we have

$$-\frac{\mathrm{d}[\mathrm{CO}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{COHb}]}{\mathrm{d}t} = \frac{l'_4 k_4 [\mathrm{O_2Hb}][\mathrm{CO}]}{4\{k'_4[\mathrm{O_2}] + l'_4[\mathrm{CO}]\}} - \left\{1 - \frac{l'_4[\mathrm{CO}]}{k'_4[\mathrm{O_2}] + l_4[\mathrm{CO}]}\right\}\frac{l_4}{4}[\mathrm{COHb}]. \quad (13)$$

In each pair of the reactions (equation (6)), one molecule of O_2 is displaced by one molecule of CO. It is easy to show that if the relations given in equation (10) are valid, equation (13) must likewise hold good during all the later stages of the reactions. It should be noted that in the above derivation we have taken into account the back reaction which was neglected by Gibson & Roughton (1955).

Comparing equation (13) with equation (5) in which ξ denotes $\mathrm{d}[\mathrm{COHb}]/\mathrm{d}t$, we get

$$m' = \frac{k_4 l'_4}{4k'_4\{1 + (l'_4[\mathrm{CO}]/k'_4[\mathrm{O_2}])\}} \quad (14)$$

and

$$m = \left\{1 - \frac{l'_4[\mathrm{CO}]/k'_4[\mathrm{O_2}]}{1 + l'_4[\mathrm{CO}]/k'_4[\mathrm{O_2}]}\right\}\frac{l_4}{4}. \quad (15)$$

It is apparent from the above equation that m' and m are not independent of the concentrations of the gases present. At very low concentrations of CO, such as occur in lung function testing, the expressions for m' and m become

$$m' = k_4 l'_4 / 4k'_4 \quad (16)$$

and

$$m = l_4/4. \quad (17)$$

At equilibrium, i.e. $\xi = 0$, we find from equation (5),

$$[\mathrm{COHb}]_\mathrm{e}/[\mathrm{O_2Hb}]_\mathrm{e} = C_{2\mathrm{e}}/C_{3\mathrm{e}} = M(p_{\mathrm{CO}}/p_{\mathrm{O_2}}) \quad (18)$$

where

$$M = \frac{k_4 l'_4 \alpha\mathrm{CO}}{l_4 k'_4 \alpha\mathrm{O_2}} = \frac{m'\alpha\mathrm{CO}}{m\alpha\mathrm{O_2}}, \quad (19)$$

in which the subscript 'e' denotes the quantities at equilibrium, αCO and αO_2 are the solubilities of CO and O_2, respectively, in the blood, p_{CO} and $p_{\mathrm{O_2}}$ are the partial pressures of CO and O_2 in the blood and M is a constant representing the affinity of haemoglobin for CO over O_2. Equation (18) is equivalent to the well-known Haldane's equation. At equilibrium, the p_{CO} in the blood will be the same as that in the inspired air.

(*b*) *Initial, entrance and boundary conditions*

Equations (2) and (3) are subject to the following initial, entrance and boundary conditions.

1. The concentrations of the species in the blood are prescribed initially, i.e.

$$\text{at } t = 0, \quad \begin{cases} C_1 = C_{1\mathrm{I}} \\ C_2 = C_{2\mathrm{I}} \end{cases} (0 \leqslant z \leqslant L), \quad (0 \leqslant x \leqslant a), \quad (20a)$$

where $C_{1\mathrm{I}}$ and $C_{2\mathrm{I}}$ are the initial concentrations of CO and COHb in the blood, respectively.

2. At the entry, the concentration of each of the species is the same as the corresponding value in the venous blood, i.e.

$$\text{at } z = 0, \quad C_l = C_{l\mathrm{ven}}, \quad (0 \leqslant x \leqslant a), \quad t > 0, \quad l = 1, 2. \quad (20b)$$

3. Owing to symmetry

$$\text{at } x = 0, \quad \partial C_l/\partial x = 0, \quad (0 < z \leqslant L), \quad t > 0, \quad l = 1, 2. \quad (20c)$$

4. (*a*) Because the haemoglobin molecule cannot penetrate through the capillary wall, there is no flux of COHb across the wall and accordingly

$$\text{at } x = a, \quad \partial C_2/\partial x = 0, \quad (0 < z \leqslant L), \quad t > 0. \quad (20d)$$

(*b*) Because the pulmonary capillary membrane is extremely thin, its diffusion resistance to CO is relatively unimportant (Forster 1987). The partial pressure of CO at the wall is taken to be the same as the corresponding partial pressure in the alveolar air, i.e.

$$\text{at } x = a, \quad C_1 = \alpha\mathrm{CO}\, p_{1\mathrm{alv}}, \ (0 < z \leqslant L), \quad t > 0, \quad (20e)$$

where $p_{1\mathrm{alv}}$ is the partial pressure of CO in the alveolar air and αCO is the solubility of CO in the blood.

(*c*) *Recirculation of blood*

The blood entering the pulmonary capillary traverses its length in the transit time, T, and leaves as

the arterial blood. During this time, the blood absorbs O_2 and CO in the pulmonary capillary. The arterial blood enters the systemic circulatory system where it unloads the oxygen to tissue and it returns to the pulmonary circulatory system as venous blood after completing one cycle for absorbing more O_2. In this study, one cycle means the transit of a unit volume of blood around the entire systemic and pulmonary circuit (Roughton 1945*b*). The endogenous production of CO in the body, dilution of CO in the body tissues and metabolic CO consumption are negligible compared with the amount of CO exchanged in the lungs. Thus, under these circumstances, the concentration of COHb in the arterial blood will remain constant when it passes through the systemic circulation. When a person is exposed to air containing CO, the concentration of CO in the venous blood is assumed to be zero initially (i.e. for the first cycle) in a non-smoker under normal conditions. The initial value of CO may be non-zero if the individual's blood already has a COHb concentration.

For the second cycle, the input (i.e. venous blood) concentration of CO and COHb will be the same as the corresponding concentration of CO and COHb in the arterial blood at the exit of the capillary during first cycle. In this way the input conditions are assigned for the subsequent cycles. For pth cycle,

$$C_{l\text{ven}}^{p} = C_{l\text{art}}^{p-1}, \quad l = 1, 2. \tag{21}$$

(*d*) *Alveolar partial pressure*

To solve this problem, the partial pressure of CO in the alveolar air is required. However, in practice, the partial pressure of CO is measured in the ambient/inspired air and the corresponding pressure in the alveoli is not known *a priori* (Forster 1964). Unlike the alveolar partial pressures of O_2 and CO_2, the mean partial pressure of CO in the alveoli ($p_{A,CO}$) is not constant. For a measured partial pressure of CO in the ambient air, the partial pressure of CO in the alveoli can be computed using a mathematical model developed by Sharan *et al.* (1990). This model accounts for the ventilation rate and the uptake–release of CO by the blood in the lungs. Because the alveolar partial pressure of CO depends on the degree of uptake of CO by the blood and vice versa, it is necessary to develop a coupled distributed model for predicting the COHb and $p_{A,CO}$ taking into account the reaction kinetics and diffusion mechanisms. The development of such a model does not seem to be feasible at this stage because of the non-availability of data regarding the alveolar region and the complex nature of the mechanisms involved. In this study, we use the following iterative procedure to calculate the $p_{A,CO}$ and blood COHb level in which the uptake of CO by the blood and the $p_{A,CO}$ are dependent on each other.

In the first cycle, the $p_{A,CO}$ is initialized using the compartmental model (Sharan *et al.* 1990). The resulting COHb in the arterial blood is computed by solving equations (2) and (3). Using the computed arterial blood COHb, the improved value of $p_{A,CO}$ is calculated from the equation:

$$p_{A,CO} = [Q_A a_a p_{I,CO} + Q_B(C_v - C_a)]/Q_A a_a, \tag{22}$$

where C_a and C_v are the total CO content of arterial and venous blood, respectively, Q_B is the blood flow rate, Q_A is ventilation rate under standard temperature, pressure, dry conditions (STPD), $p_{I,CO}$ is the inspired p_{CO} and $a_a = 1/(P_B - P_{H_2O})$ in which P_B and P_{H_2O} are the barometric and water vapour pressures, respectively. Equation (22) is based on the material balance of the CO between blood flowing through the pulmonary capillary and the alveolar air in the lungs (Sharan *et al.* 1990). The improved value of $p_{A,CO}$ calculated from equation (22) is again used to compute arterial blood COHb concentration. This procedure is repeated for each cycle until:

$$|p_{A,CO}^{i+1} - p_{A,CO}^{i}| < \epsilon_1, \tag{23}$$

where the index 'i' indicates the ith iteration and ϵ_1 is the tolerance error.

(*e*) *Average concentration*

The average concentration of the species at any cross section of the capillary is defined by

$$\langle C_l(t) \rangle = 1/a \int_0^a C_l(t, x)\, dx, \quad l = 1, 2. \tag{24}$$

3. TRANSFORMATION AND NON-DIMENSIONALIZATION

Using the transformation

$$\tau = \tfrac{1}{2}(t + (z/v)), \tag{25}$$

the equations (2) and (3) can be expressed in dimensionless form as:

$$\partial C_1/\partial \tau = D_1(\partial^2 C_1/\partial x^2) - M_1 C_1(1 - C_2) + M_2 C_2 \tag{26}$$

$$\partial C_2/\partial \tau = D_2(\partial^2 C_2/\partial x^2) + K_1 C_1(1 - C_2) - K_2 C_2, \tag{27}$$

where

$$\left.\begin{aligned} D_1 &= D_C T/a^2; & D_2 &= D_H T/a^2 \\ M_1 &= m' HT/[O_2]; & M_2 &= mHT/\alpha CO\, p_c \\ K_1 &= m' \alpha CO\, p_C T/[O_2]; & K_2 &= mT \end{aligned}\right\} \tag{28}$$

are dimensionless constants. Here p_C is the characteristic partial pressure of CO. In the dimensionless scheme we have referred C_1 to $\alpha CO\, p_C$, C_2 to H, x to a and τ to T.

The initial and boundary conditions become:

$$\text{(i)} \quad \text{at } \tau = 0, \quad \begin{cases} C_1 = C_{1i}/\alpha CO\, p_C \\ C_2 = C_{2i}/H, \quad (0 \leqslant x \leqslant 1) \end{cases} \tag{29a}$$

$$\text{(ii)} \quad \text{at } x = 0, \quad \partial C_l/\partial x = 0, \quad \tau > 0, \quad l = 1, 2 \tag{29b}$$

$$\text{(iii)} \quad \text{at } x = 1, \quad \begin{cases} \partial C_2/\partial x = 0 \\ C_1(x, \tau) = p_{1alv}/p_C, \quad \tau > 0. \end{cases} \tag{29c}$$

The dimensionless average concentration of each of the species is given by

$$\langle C_l(t) \rangle = \int_0^1 C_l(t)\, dx, \quad l = 1, 2. \tag{30}$$

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4. NUMERICAL SCHEME

The coupled system of nonlinear parabolic partial differential equations (26) and (27) with physiologically relevant initial and boundary conditions (29) is solved numerically. We use a four-point implicit scheme because it is unconditionally stable.

For the finite difference scheme, we divide the domain of interest into different meshes of net size h and k in x and τ directions, respectively. Any node of the mesh can be represented as

$$x = ih \quad \text{and} \quad \tau = jk,$$

with

$$i = 0, 1, \ldots, n \quad \text{and} \quad j = 1, 2, \ldots, J,$$

where $nh = 1$. As the equations are parabolic, there is no bound in τ direction. However, the solutions are required to be computed only up to $\tau = 1$ (i.e. non-dimensional transit time) at each cycle. Thus we choose J levels in the direction of τ such that $Jk = 1$.

In the implicit scheme, the first-order derivative in τ is replaced by backward difference formula and the second-order derivative in x is approximated by central difference formula at $(j = 1)$th level (i.e. unknown level) instead of jth level.

The finite difference approximation for the equations (26) and (27) is

$$-D_1\mu C^{j+1}_{1,i-1} + \{2D_1\mu - M_1(1 - C^{j+1}_{2,i})\,k + 1\}\,C^{j+1}_{1,i} - D_1\mu C^{j+1}_{1,i+1} = C^{j}_{1,i} + M_2 k C^{j+1}_{2,i}, \quad (31)$$

$$-D_2\mu C^{j+1}_{2,i-1} + \{2D_2\mu - (K_1 C^{j+1}_{1,i} + K_2)\,k + 1\}\,C^{j+1}_{2,i} - D_2\mu C^{j+1}_{2,i+1} = C^{j}_{2,i} + K_1 k C^{j+1}_{1,i}, \quad i = 0, 1, 2, \ldots, n, j = 1, 2, \ldots, J, \quad (32)$$

where

$$\mu = k/h^2.$$

The equations (31) and (32) can be modified at the boundary points by using the difference approximations of the boundary conditions (29). The finite difference scheme has the truncation error of the order $O(k + h^2)$.

The equations (31) and (32) form a non-homogeneous system of nonlinear algebraic equations for each level of j which requires an iterative technique for the solution. This system can be solved directly using Gauss elimination method coupled with an iterative procedure for a given j. However, it requires large space and computation time because the system of equations does not have the tridiagonal form. Here, the system of equations is solved iteratively by first setting $F(C^{j+1}_{l,i}) = F(C^{j}_{l,i})$ where F indicates any nonlinear term. This linearizes the equations. The linearized algebraic equations are solved for $C^{j+1}_{l,i}$ and this is substituted in $F(C^{j+1}_{l,i})$ which is again solved for $C^{j+1}_{l,i}$. As C_2 in equation (31) is known from previous iteration, this can be solved directly for C_1. The calculated value of C_1 is now used in the second equation (i.e. equation (32)) of the same iterative cycle to compute C_2.

The iteration is continued at a given level j until

$$\sum_{i=1}^{n}\sum_{l=1}^{2} |C^{j+1,\,r+1}_{l,i} - C^{j+1,\,r}_{l,i}| < \epsilon_2, \quad (33)$$

where ϵ_2 is the error of tolerance and taken to be $2n \times 10^{-6}$ and r denotes the rth iteration.

The average concentration of the species are computed by evaluating the integral (30) using Simpson's rule. We continue the above procedure for computing the concentrations of CO and COHb in the capillary at all levels up to $j = J$. The values at the level $j = J$ (i.e. $\tau = 1$) will represent the corresponding concentrations in the arterial blood.

It may be noted that the above method gives the concentrations of CO and COHb in the blood for a given cycle and it is repeated for subsequent cycles until

$$\left|\frac{\langle C_l^{J,\,p}\rangle - \langle C_l^{J,\,p-1}\rangle}{\langle C_l^{J,\,p}\rangle}\right| < \epsilon_3, \quad (34)$$

where ϵ_3 is the error of tolerance taken to be 0.001 and p denotes the pth cycle. When the condition (34) is satisfied, blood COHb and CO are in equilibrium with ambient CO.

5. PARAMETERS OF THE MODEL

For the computation of the COHb levels in the blood, the following values of the parameters have been used: diffusion coefficient of CO in the blood $(D_{\mathrm{C}}) = 3.0 \times 10^{-5}$ cm^2 s^{-1}; diffusion coefficient of COHb in the blood $(D_{\mathrm{H}}) = 2.5 \times 10^{-7}$ cm^2 s^{-1} (Murray & Wyman 1971) solubility of CO in the blood $(\alpha\mathrm{CO}) = 1.07 \times 10^{-9}$ mol ml^{-1} mmHg^{-1}† (Forster 1987); solubility of O_2 in the blood $(\alpha O_2) = 1.4 \times 10^{-9}$ mol ml^{-1} mmHg^{-1} (Forster 1987); association rate (m') and dissociation rate (m) coefficients are 18.8 s^{-1} and 0.062 s^{-1}, respectively (Holland 1970); radius of the pulmonary capillary $(a) = 4 \times 10^{-4}$ cm (Guyton 1981); total haemoglobin concentration $(H) = 9.302 \times 10^{-6}$ mol ml^{-1} equivalent to 15 g per 100 ml of blood. Because the blood is almost fully saturated in the pulmonary capillary (Holland 1970), the partial pressure of O_2 is taken to be 100 mmHg (Peterson & Stewart 1970) and the pulmonary capillary transit time $(T) = 0.75$ s (Roughton 1945).

The normal human body contains 5000 ml of blood and cardiac output is 5000 ml min^{-1} at rest (Thews & Vaupel 1985). The average circulation time, i.e. the time taken by the blood to traverse the entire pulmonary and systemic circuit, is taken as the ratio of total volume of blood in the body to the cardiac output (Roughton 1945). Thus the circulation time is equal to 1 min (Forbes *et al.* 1945), which corresponds to one cycle in the present analysis. The ventilation rate is chosen to be 6000 ml min^{-1} in the resting condition (Peterson & Stewart 1970).

6. RESULTS AND DISCUSSION

The values of θ_{CO} (the rate at which one millilitre of whole blood will take up CO in STPD per minute per millimetre of mercury of partial pressure) can be computed from the relation (Roughton & Forster 1957):

$$1/D_{\mathrm{L,\,CO}} = (1/D_{m,\,\mathrm{CO}}) + (1/\theta_{\mathrm{CO}}\,V_{\mathrm{C}}), \quad (35)$$

† 1 mmHg ≈ 133.32 Pa.

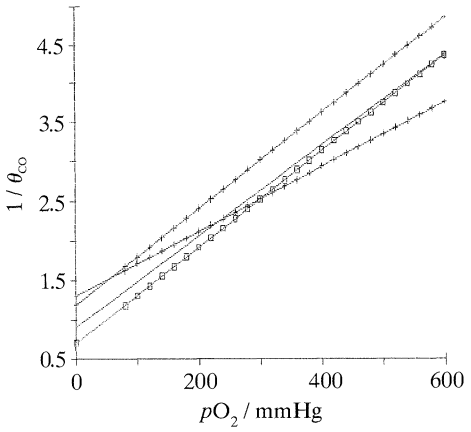

Figure 3. Comparison of $1/\theta_{CO}$ computed from our model (——) and with experimentally measured values: (—┼┼┼—) Krawicz *et al.* (1983); (—□—□—□—) Roughton & Forster (1957).

where $D_{L,CO}$ is the diffusing capacity of whole lung, V_C is the volume of blood in the pulmonary capillaries and $D_{m,CO}$ is the diffusing capacity of the alveolar membrane alone. Because we have assumed that the resistance offered by alveolar–capillary membrane to CO is negligible, $1/D_{m,CO}$ will be zero. $D_{L,CO}$ is defined as (Forster 1964):

$$D_{L,CO} = Q_B(C_a - C_v)/(p_{A,CO} - p_{C,CO}), \quad (36)$$

where $p_{C,CO}$ is the mean capillary p_{CO} that is in equilibrium with COHb. The values of C_a, C_v, $p_{A,CO}$ and $p_{C,CO}$ are known from our model. From these values, $D_{L,CO}$ can be computed from equation (36).

Several values of $D_{L,CO}$ have been reported in the literature (Cerretelli & Prambero 1987). The difference between the $D_{L,CO}$ estimates based on different methods used by various authors may be in part attributed to the effects of lung volume and the functional inhomogeneity (Meyer *et al.* 1981). Piiper & Scheid (1980) have reported an average value of $D_{L,CO}$ of 34 ± 8 ml min^{-1} mmHg^{-1} (based on 45 references) measured by various investigators using the breath-holding technique. Recently, Borland & Higenbottam (1989) have measured a $D_{L,CO}$ of 39 ml min^{-1} mmHg^{-1} under normal conditions. The $D_{L,CO}$ calculated from our model is 42.9 ml min^{-1} mmHg^{-1} (with mean capillary p_{O_2} of 100 mmHg). The $D_{L,CO}$ measured by Power & Bradford (1969) with mean capillary p_{O_2} of 191 and 591 mmHg are 28.5 and 17.4 ml min^{-1} mmHg^{-1}, respectively, and the corresponding values of $D_{L,CO}$ computed from our model are 29.8 and 13.9 ml min^{-1} mmHg. Thus the $D_{L,CO}$ values predicted from our model are reasonably close to those measured experimentally. The slight deviation may be due to the fact that the functional inhomogeneity of the lungs has not been considered in the model.

As $V_C = Q_B \times T$ (Q_B is the blood flow rate and T is the transit time), the values of θ_{CO} can be readily obtained from equation (35) using the predicted value of $D_{L,CO}$ from the model. As $D_{L,CO}$ depends on the mean values of p_{O_2}, θ_{CO} are calculated from various values of p_{O_2}. The regression equation for the $1/\theta_{CO}$ values computed from the model is obtained as

$$1/\theta_{CO} = 0.905\,26 + 0.006\,14 * p_{O_2} \quad (r = 0.999). \quad (37)$$

Table 1. *Comparison of COHb levels computed from our model with the experimental values*

ambient CO concentration/p.p.m.	exposure time/min	percentage COHb: our model	percentage COHb: experimental
25.4	120	1.78	1.50
39.6	60	1.69	1.80
44.7	120	2.71	2.48
46.0	180	3.54	3.86
48.0	240	4.33	5.07
50.3	480	6.27	5.60
51.2	180	3.88	3.75
51.6	60	2.00	2.12
87.9	60	2.96	2.90
91.9	180	6.56	6.61
93.2	360	9.89	10.75
93.5	60	3.11	3.37
94.0	480	11.23	12.08
96.4	120	5.20	5.10
98.1	180	6.97	7.23
98.4	240	8.37	7.34
98.7	180	7.01	6.36
99.2	180	7.04	7.02
100.0	45	2.69	3.05
100.2	480	11.91	12.87
101.0	360	10.65	11.38
101.5	360	10.70	11.27
102.0	30	2.10	2.10
103.2	420	11.63	10.59
196.9	120	9.98	10.08
198.4	180	13.41	13.83
199.5	240	16.16	15.97
200.8	30	3.47	3.43
200.8	60	5.93	5.93
502.0	15	4.27	5.25
502.0	90	19.19	18.40
506.0	60	13.85	13.70
507.0	114	23.24	24.80
510.9	105	22.00	23.75
512.0	60	14.00	16.55
512.0	80	17.78	19.80
523.0	30	7.89	8.15

The standard error of the estimate for the constant is ± 0.035 and for regression coefficient (r) is $\pm 0.000\,043$. The values of $1/\theta_{CO}$ are plotted against p_{O_2} in figure 3. The values of $1/\theta_{CO}$ measured experimentally (Roughton & Forster 1957; Krawiec *et al.* 1983) under different physiological conditions are also plotted in the figure. It can be seen that the $1/\theta_{CO}$ values computed from our model lie well within the range of experimental measurement. This reveals that the calculated rates of CO uptake for a haemoglobin solution in the capillary are not far from experimental rates in red cells.

Table 1 represents the COHb levels computed from our model and those measured experimentally (Peterson & Stewart 1970) with the ambient CO concentration and exposure time. In the table, columns 1, 2 and 4 represent the exposure time, ambient CO concentration and experimentally measured COHb levels in the blood, respectively, and are taken from Peterson & Stewart (1970). For the computation, we

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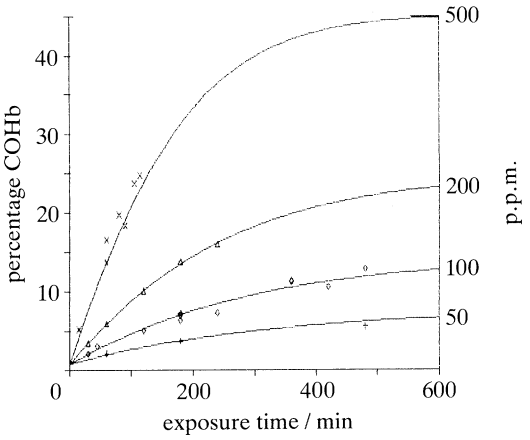

Figure 4. Comparison of COHb levels in the blood computed from our model (——) with experimentally measured values: +, 50 p.p.m.; ◇, 100 p.p.m.; △, 200 p.p.m.; ×, 500 p.p.m..

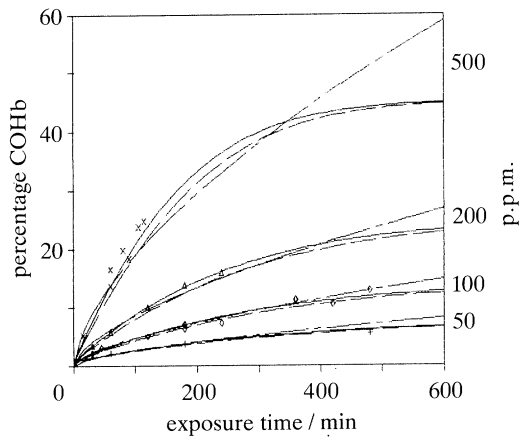

Figure 5. Comparison of COHb levels computed from our model (——), one based on CFK equation (– – –) and nomogram (— — — — —) with experimentally measured values: +, 50 p.p.m.; ◇, 100 p.p.m.; △, 200 p.p.m.; ×, 500 p.p.m.

have taken the initial concentration of COHb in the blood to be 0.76 % corresponding to the experimental conditions.

Figure 4 shows the time course of increase of COHb in human subjects exposed to air containing 50, 100, 200 and 500 p.p.m. of CO, respectively. It is clear from table 1 and figure 4 that the results predicted from our model are in good agreement with those measured experimentally.

Figure 5 represents the COHb concentration in the blood as a function of exposure time computed from our model, CFK equation (Coburn *et al.* 1965) and nomogram (Air quality criteria for carbon monoxide 1970). Experimentally measured values of COHb (Peterson & Stewart 1970) are also displayed in the graph. We have solved the CFK equation using the method outlined by Peterson & Stewart (1975). These authors fitted their experimental data to a log–log function. It appears that the nomogram drawn (Air quality criteria for carbon monoxide 1970) is based on this empirical relation.

The values predicted from our model are closer (figure 5) to the experimental values compared with other models. We point out that the results computed from our model and the CFK equation tend to the same equilibrium value.

Figure 5 also reveals that the COHb level in the blood increases as exposure time increases. This increases further with the increase in ambient CO concentration.

The standard error (s.e.) between the values predicted from different models and the experimentally measured values are calculated using the formula (Peterson & Stewart 1975):

$$\mathrm{SE} = \left[\sum_{i=1}^{N} (Y_i - \hat{Y}_i)^2/(N-2)\right]^{\frac{1}{2}}, \tag{38}$$

where Y_is are the experimentally measured values, $\hat{Y}_i$s are the predicted values and N is the total number of values. The standard errors for our model, CFK equation and nomogram are 0.848, 1.31 and 1.56, respectively. The standard errors of CFK equation and nomogram differ significantly (at 5 % level) from our model. The low value of the error reveals the fact that our model predictions are more accurate than other models.

As $\tau \to \infty$ in equations (26) and (27), the species will attain the equilibrium through the process of their chemical combination, i.e. at equilibrium $\xi = 0$. This condition yields the Haldane's first law (equation (18)). It is found that the numerical solution obtained by solving the nonlinear partial differential equations (26) and (27) approaches the equilibrium solution (equation (18)). Note that the concentration of COHb predicted at equilibrium from the empirical relation (Peterson & Stewart 1970) or nomogram deviates from the equilibrium value calculated from the Haldane first law (equation (18)) for a given inspired CO concentration. The deviation increases (figure 5) as the concentration of CO in the ambient air increases. This is, presumably, because of the fact that the fitted formula may not be valid beyond the range of experimental values used in the curve fitting. Thus the empirical relation (Peterson & Stewart 1970) is not suitable for calculating the equilibrium COHb level.

The concentration of CO in the blood and in the air will reach equilibrium after more than 6 h of continuous exposure (figures 4 and 5). The time required to reach 95 % of equilibrium value of COHb is calculated as 847, 777, 640 and 399 min for 50, 100, 200 and 500 p.p.m. CO exposure, respectively.

(*a*) *Sensitivity analysis*

The model depends on various parameters such as ventilation rate, blood flow, total haemoglobin concentration, mean capillary p_{O_2}, association and dissociation rate coefficients of CO with haemoglobin. We now study the effect of these parameters on the build-up of COHb in the blood as a function of exposure time. In the following, the concentration of CO in the ambient air is taken to be 100 p.p.m.

Figure 6 represents the variation of COHb levels in the blood as a function of exposure time for different ventilation rates. The ventilation rate is used in the model to compute alveolar partial pressure of CO

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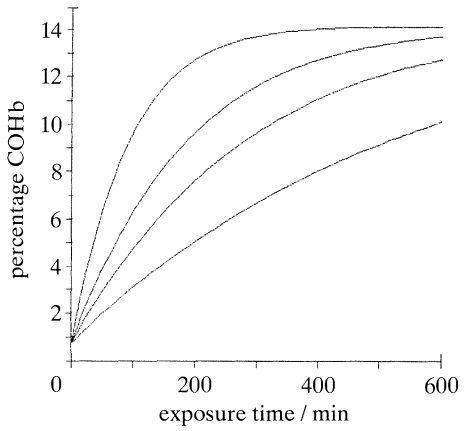

Figure 6. Variation of COHb levels with exposure time for different ventilation rates. The curves from top to bottom correspond to ventilation rates 30000, 10000, 6000 and 3000 ml min^{-1}, respectively.

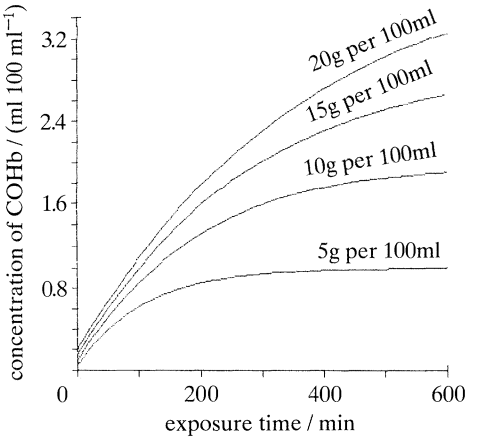

Figure 7. Variation of COHb concentration with exposure time for different total haemoglobin content in the blood.

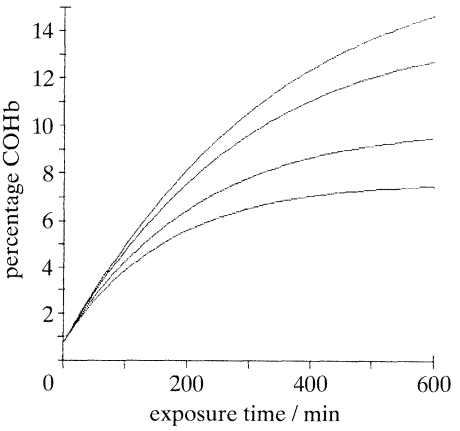

Figure 8. Variation of COHb levels with exposure time for different mean values of p_{O_2} in the capillary. The curves from top to bottom correspond to p_{O_2} of 80, 100, 150 and 200 mmHg.

(equation 22). The concentration of COHb increases with increase in ventilation rate (figure 6). Also the time required to achieve equilibrium decreases with increase in ventilation rate. For example the equilibrium time (i.e. the time necessary to reach 95 % of C_{2e}) is reduced from 777 to 262 min when the ventilation rate is increased fivefold from 6000 to 30000 ml min^{-1}. Similarly, the equilibrium time is increased from 777 to 1271 min with a decrease in the ventilation rate from 6000 to 3000 ml min^{-1}.

The amount of CO carried by the blood depends upon the total haemoglobin concentration which can change significantly in anaemia and polycythemia (Hudak *et al.* 1986). Figure 7 shows the predicted COHb concentration in the blood as a function of exposure time for haemoglobin concentration in the range 5 to 20 g per 100 ml of blood. Blood COHb increases as H increases. This is expected because with increase in total haemoglobin content, the blood will absorb a larger amount of CO. If one plots the percentage COHb in place of the COHb concentration, the percentage COHb is found to increase with a decrease in H.

The equilibrium time is decreased by approximately 475 min from 777 min when the haemoglobin in the blood falls from 15 to 5 g per 100 ml of blood, and when the haemoglobin concentration rises from 15 to 20 g per 100 ml, the equilibrium time increases by 177 min.

Figure 8 shows that the blood COHb level decreases as the mean capillary p_{O_2} increases. This is due to the fact that the increase of mean capillary p_{O_2} decelerates the rate of uptake of CO by haemoglobin. When p_{O_2} is raised from 100 to 150 mmHg, the COHb level after 10 h of exposure time is reduced to 9.49 % from 12.8 %. The blood COHb rises from 12.8 % to 14.7 % when p_{O_2} is reduced from 100 to 80 mmHg. Thus the effect of p_{O_2} on the build up of COHb is relatively high with lower p_{O_2}. The equilibrium value of COHb is observed to decrease with an increase in the mean capillary p_{O_2} which can be explained in the light of Haldane's first law.

Different values for the kinetic parameters (m' and m) are quoted in the literature (Holland 1970). These parameters are related to the equilibrium constant M by equation (19). For practical purposes, M can be considered to be constant over the range of [COHb] + [O_2Hb] that is found in normal and CO-poisoned humans and animals (see Rodkey *et al.* 1974). There appears to be significant variation in M in blood from different humans (see Rodkey *et al.* 1974). In abnormal human haemoglobin, M can be markedly different. As expected from different characteristics of CO and O_2 binding to haemoglobin, M is markedly altered by temperature and pH (Joels & Pugh 1958). Blood COHb level will be affected by two factors: (i) varying m' and m independently, implying variation in M; and (ii) varying m' and m such that M remains constant. COHb increases as m' increases (figure 9*a*) or m decreases (figure 9*b*). This is justifiable because an increase in m' or a decrease in m will increase the affinity of haemoglobin for CO over O_2, so augmenting the formation of COHb. Equation (19) shows that for a constant M, any change in m' will imply the corresponding change in m. It is observed that the changes in blood COHb with constant M are not significant. This is because the increase in m' augments the uptake of CO by the blood whereas the corresponding increase in m to keep M constant would inhibit the uptake of CO by releasing CO from COHb.

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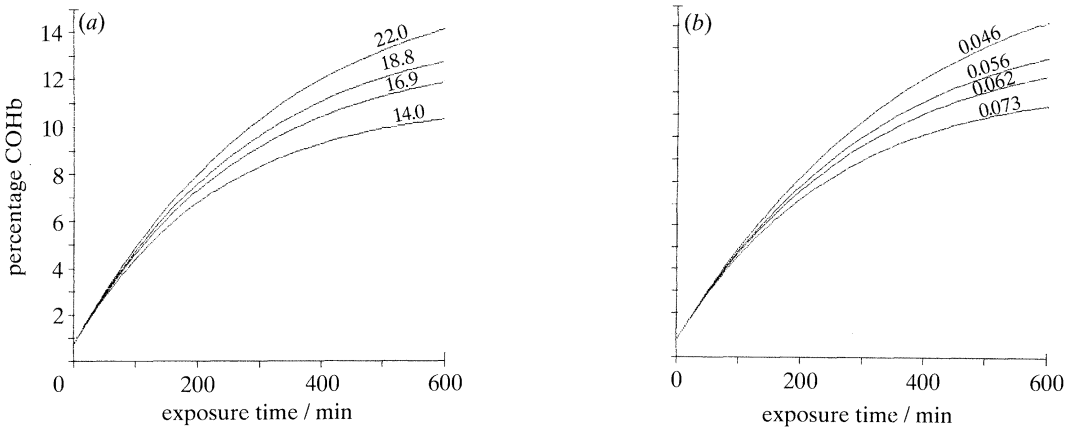

Figure 9. (*a*) Variation of COHb levels with exposure time for different values of association rate coefficient (m'). (*b*) Variation of COHb levels with exposure time for different values of dissociation rate coefficient (m).

It is clear from figure 9*a*, *b* that the increase in m' and m will have the opposite effect on the formation of blood COHb.

In this study, we have neglected the endogenous production of CO in the body. However, in normal conditions, about 0.007 ml min^{-1} of CO is produced endogenously in the whole body, and this may increase several fold in patients with haemolytic anaemia (Coburn *et al.* 1966). It may be recalled that in the model, the concentrations of CO and COHb in the venous blood at each cycle are taken to be the same as the corresponding concentrations in the arterial blood. The entrance condition in the model can be modified by taking into consideration the endogenous production of CO. The amount of CO produced endogenously in the body increases the concentration of CO dissolved physically in the plasma and in combination with haemoglobin. The effective amount of CO added to the unit volume of blood in each cycle is $[CO]_{en}$ = amount of CO produced per unit time in the whole body/blood flow rate. Because the amount of CO dissolved in the plasma is negligibly small, the increase in COHb concentration due to endogenous CO production will be $[CO]_{en}$. The modified COHb concentration in the venous blood is the sum of the concentration of COHb in the arterial blood and $[CO]_{en}$.

Figure 10 shows the variation of COHb levels as a function of exposure time for different rates of endogenous production of CO in the body. The equilibrium times are calculated as 777, 766, 651 and 540 min for the endogenous production rates of CO of 0.0, 0.007, 0.014 and 0.021 ml min^{-1}, respectively, in the whole body. The comparison of the results (figure 10) shows that the COHb level in the blood is not significantly affected because of endogenous production of CO under normal conditions. However, the effects may be significant in patients with haemolytic anaemia.

In our study, p_{O_2} in the capillary is assumed to be constant. However, O_2, CO_2 and CO undergo a series of reactions with haemoglobin in the blood. Because the order of magnitude of association and dissociation rate coefficients of the reactions are not known, it is not feasible to develop a model by considering all the species as independent variables. However, an attempt has been made (Selvakumar *et al.* 1991) to develop a model for the simultaneous transport of O_2, CO_2 and CO by assuming chemical equilibrium of the gases in the blood. It is observed that when p_{O_2} in the capillary is taken as constant (mean value) all along the capillary instead of varying p_{O_2} in the model, it does not appreciably affect the COHb level in the arterial blood.

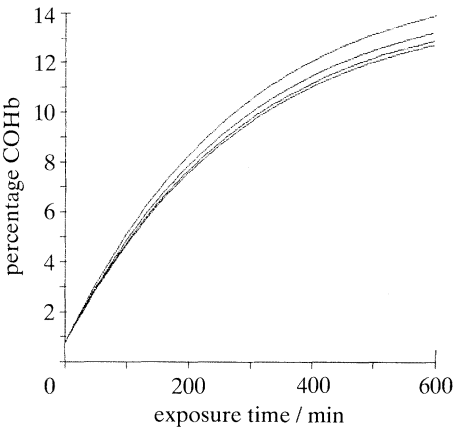

Figure 10. Variation of COHb levels with exposure time for different rates of endogenous production of CO in the body. The curves from top to bottom correspond to endogenous production of CO in the whole body 0.05, 0.021, 0.007 and 0.0 ml min^{-1}, respectively.

7. CONCLUSIONS

In this study, we have formulated a mathematical model to predict the COHb level in the blood as a function of exposure time and inspired CO concentration. The displacement of O_2 from O_2Hb by CO has been considered to be the predominant reaction of CO with haemoglobin. The overall rate at which CO combines with haemoglobin has been derived by accounting the dissociation of CO from COHb by taking into consideration the non-equilibrium chemical kinetics of CO in the model. The resulting system of nonlinear partial differential equations is solved numerically with physiologically relevant boundary, entrance and initial conditions.

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The COHb levels predicted from our model are in good agreement with those measured experimentally (Peterson & Stewart 1970). The time taken by COHb to reach 95 % its equilibrium value has been computed. The COHb level in the blood increases with the increase in ventilation rate, haemoglobin content and association rate coefficient of CO with haemoglobin and decrease in dissociation rate coefficient of CO.

In this study, the transport of O_2 and CO_2 in the pulmonary capillary is neglected. However, it is important because under hypoxic conditions, the blood in the pulmonary capillary is not always fully saturated with O_2 or CO or both. Further,the amount of reduced haemoglobin is not negligible (Collier & Goldsmith 1983). Thus the model can be improved by taking into account (i) the transport of O_2 and CO_2 in the pulmonary capillary, (ii) the amount of reduced haemoglobin, (iii) the interactions of the gases in the blood and (iv) transport of the gases in the blood flowing through the systemic capillaries and the surrounding tissue. The computation of the model should be checked with the experimental measurements as and when they become available.

REFERENCES

Adair, G. S. 1925 The oxygen dissociation curve of haemoglobin. *J. biol. Chem.* **63**, 529–545.

Air quality criteria for carbon monoxide 1970 National Air Pollution Control Administration, AP-62, Washington, D.C.: HEW.

Air quality criteria for carbon monoxide 1979 EPA-600/8-79-022, Environmental Criteria and Assessment Office, Research Triangle Park, NC 27711.

Bernard, T. E. & Duker, J. 1981 Modelling of carbon monoxide uptake during work. *Am. ind. Hyg. Ass. J.* **42**, 361–364.

Borland, C. D. R. & Higenbottam, T. W. 1989 A simultaneous single breath measurement of pulmonary diffusing capacity with nitric oxide and carbon monoxide. *Eur. Respir. J.* **2**, 56–63.

Britton, N. F. & Murray, J. D. 1977 The effects of carbon monoxide on haem-facilitated oxygen diffusion. *Biophy. Chem.* **7**, 159–167.

Britton, N. F. 1979 A mathematical model for carbon monoxide poisoning in man. *Nonlin. Anal.: Theor. Meth. Applic.* **3**, 361–377.

Cerretelli, P. & Prampero, P. E. D. 1987 Gas exchange in exercise. In *Handbook of physiology*, section 3, vol. IV, (*The respiratory system*), chapter 16, 297, Bethesda: American Physiological Society.

Coburn, F. F. & Forman, H. J. 1987 Carbon monoxide toxicity. In *Handbook of physiology*, section 3, vol. 4 (*The respiratory system*), Bethesda: American Physiological Society.

Coburn, R. F., Forster, R. E. & Kane, P. B. 1965 Consideration of the physiological variables that determine the blood carboxyhaemoglobin concentration in man. *J. clin. Invest.* **44**, 1899–1910.

Coburn, R. F., Williams, E. J. & Kahn, P. B. 1966 Endogeneous carbon monoxide production in patients with haemolytic anaemia. *J. clin. Invest.* **45**, 460–468.

Coburn, R. F., Allen, E. R., Ayers, S., Bartlett Jr, D., Horvath, S. M., Kuller, L. H., Laties, V., Longo, L. D. & Radford Jr, E. P. 1977 *Carbon monoxide*. Washington D.C.: National Academy of Sciences.

Coin, J. T. & Olson, J. S. 1979 The rate of oxygen uptake by human red blood cells. *J. biol. Chem.* **254**, 1178–1190.

Collier, C. R. & Goldsmith, J. R. 1983 Interactions of carbon monoxide and haemoglobin at high altitude. *Atmos. Envir.* **17**, 723–728.

Crapo, R. O., Bitterman, N., Berlin, S. L. & Forster, R. E. 1989 Rate of CO uptake by canine erythrocytes as a function of p_{O_2}. *J. appl. Physiol.* **67**, 2265–2268.

Douglas, C. G., Haldane, J. S. & Haldane, J. B. S. 1912 The laws of combination of haemoglobin with carbon monoxide and oxygen. *J. Physiol., Lond.* **44**, 275–304.

Forbes, W. H., Sargent, F. & Roughton, F. J. W. 1945 The rate of carbon monoxide uptake by normal men. *Am. J. Physiol.* **143**, 594–608.

Forster, R. E. 1964 Diffusion of gases. In *Handbook of physiology*, section 3, vol. 1 (*Respiration*), chapter 33. Washington D.C.: American Physiological Society.

Forster, R. E. 1970 Carbon monoxide and the partial pressure of oxygen in tissue. *Ann. N.Y. Acad. Sci.* **174**, 233–241.

Forster, R. E. 1987 Diffusion of gases across the alveolar membrane. In *Handbook of physiology*, section 3, vol. 4 (*The respiratory system*), chapter 5. Bethesda: American Physiological Society.

Forster, R. E., Fowler, W. S. & Bates, D. V. 1954 Considerations on the uptake of carbon monoxide by the lungs. *J. clin. Invest.* **33**, 1128–1134.

Gibson, Q. H. & Roughton, F. J. W. 1955 The kinetics of dissociation of the first oxygen molecule from fully saturated oxyhaemoglobin in sheep blood solution. *Proc. R. Soc. Lond.* B **143**, 310–334.

Goldsmith, S. R., Terzahi, J. & Hackney, J. D. 1963 Evaluation of fluctuating carbon monoxide exposures. *Arch. envir. Hlth* **7**, 647–663.

Gutierrez, G. 1986 The rate of oxygen release and its effect on capillary O_2 tension: a mathematical analysis. *Resp. Physiol.* **63**, 79–96.

Guyton, A. C. 1981 *Textbook of medical physiology*. W. B. Saunders.

Hatch, T. F. 1952 Carbon monoxide uptake in relation to pulmonary performance. *Arch. indust. hyg. occup. Med.* **6**, 1–8.

Holland, R. A. B. 1969 Rate at which CO replaces O_2 from O_2Hb in red cells of different species. *Resp. Physiol.* **7**, 43–63.

Holland, R. A. B. 1970 Reaction rates of carbon monoxide and haemoglobin. *Ann. N.Y. Acad. Sci.* **174**, 154–171.

Holland, R. A. B. 1981 Kinetics of O_2 and CO reactions in blood. *Prog. resp. Res.* **16**, 152–157.

Hudak, M. L., Koehler, R. C., Rosenberg, A. A., Traystman, R. J. & Jones Jr, M. D. 1986 Effect of haemotocrit on cerebral blood flow. *Am. J. Physiol.* **251**, H63–H70.

Joels, N. & Pugh, L. G. C. E. 1958 The carbon monoxide dissociation curve of human blood. *J. Physiol., Lond.* **143**, 63–77.

Krawiec, J. A., Forster, R. E., Gottliebsen, T. W. & Fish, D. 1983 Rate of CO uptake by human red blood cells. (Abstract.) *Fedn Proc. Fedn Am. Socs exp. Biol.* **42**, 993.

Laties, V. 1980 Carbon monoxide and behavior. *Arch. Neural.* **167**, 68–126.

Lilienthal Jr, J. T. & Pine, M. B. 1946 The effect of oxygen pressure on the uptake of carbon monoxide by man at sea level and at altitude. *Am. J. Physiol.* **145**, 346–350.

Marcus, A. H. 1980 Mathematical models for carboxyhaemoglobin. *Atmos. Envir.* **14**, 841–844.

Marcus, A. H. 1981 Mathematical models for carboxyhaemoglobin. *Atmos. Envir.* **15**, 1776–1781.

Meyer, M., Scheid, P., Riepl, C., Wagner, H. J. & Piiper, J. 1981 Pulmonary diffusing capacity for O_2 and CO

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measured by a rebreathing technique. *J. appl. Physiol.* **51**, 1643–1650.

Murray, J. D. & Wyman, Y. 1971 Facilitated diffusion: In case of carbon monoxide. *J. biol. Chem.* **246**, 5903–5906.

Ott, W. & Mage, D. 1978 Interpreting urban carbon monoxide concentrations by means of a computerized blood COHb model. *J. Air Pollut. Control Ass.* **28**, 911–916.

Pace, N., Consolazio, W. V. & White, W. A. 1946 Formulation of the principal factors affecting the rate of uptake of carbon monoxide by man. *J. Physiol.* **144**, 352–359.

Peterson, J. E. & Stewart, R. D. 1970 Absorption and elimination of carbon monoxide by inactive young men. *Arch. envir. Hlth* **21**, 165–170.

Peterson, J. E. & Stewart, R. D. 1975 Predicting the carboxyhaemoglobin levels resulting from carbon monoxide exposures. *J. appl. Physiol.* **39**, 633–638.

Piiper, J. & Scheid, P. 1980 Model for capillary alveolar equilibrium with special reference to O_2 uptake in hypoxia. *Resp. Physiol.* **46**, 193–208.

Piiper, J. 1981 Blood-gas equilibration in lungs and pulmonary diffusing capacity. *Prog. resp. Res.* **16**, 115–125.

Power, G. G. & Bradford, W. C. 1969 Measurement of pulmonary diffusing capacity during blood-to-gas exchange in humans. *J. appl. Physiol.* **27**, 61–66.

Rodkey, F. L., O'Neal, J. D., Collison, H. A. & Uddin, D. A. 1974 Relative affinity of haemoglobin S and haemoglobin A for carbon monoxide and oxygen. *Clin. Chem.* **20**, 83–84.

Roughton, F. J. W. 1945 the average time spent by the blood in human lung capillary and its relation to the rates of CO uptake and elimination in man. *Am. J. Physiol.* **143**, 621–633.

Roughton, F. J. W. 1964 Transport of oxygen and carbon dioxide. In *Handbook of physiology*, section 3, vol. 1 (*Respiration*), pp. 767–825. Washington, D.C.: American Physiological Society.

Roughton, F. J. W. & Darling, R. C. 1944 The effect of carbon monoxide on the oxyhaemoglobin dissociation curve. *Am. J. Physiol.* **141**, 17–31.

Roughton, F. J. W. & Forster, R. E. 1957 Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in human lung, with reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. *J. appl. Physiol.* **11**, 290–302.

Roughton, F. J. W., Forster, R. E. & Cander, L. 1957 Rate at which carbon monoxide replaces oxygen from combination with human haemoglobin in solution and in the red cell. *J. appl. Physiol.* **11**, 267–276.

Selvakumar, S., Maithili Sharan & Singh, M. P. 1991 A mathematical model for the exchange of gases in the lungs with special reference to carbon monoxide. *Med. Biol. Engng Comput.* (In the press.)

Sharan, Maithili, Singh, M. P. & Aminataei, A. 1989 A mathematical formulation for the computation of oxygen dissociation curve in the human blood. *BioSystems* **22**, 249–260.

Sharan, Maithili, Selvakumar, S. & Singh, M. P. 1990 Mathematical model for the computation of alveolar partial pressure of carbon monoxide. *Int. J. biomed. Comput.* **26**, 135–147.

Sobin, S. S., Tremer, H. M. & Fung, Y. C. 1970 The morphometric basis of the sheet-flow concept of the pulmonary alveolar microcirculation in the cat. *Circ. Res.* **26**, 397–414.

Thews, G. & Vaupel, P. 1985 *Automatic functions in human physiology*. Springer-Verlag.

Tikuisis, P., Madill, H. D., Gill, B. J., Lewis, W. F., Cox, K. M. & Kane, D. M. 1987*a* A critical analysis of the use of the CFK equation in predicting COHb formation. *Am. ind. Hyg. Ass. J.* **48**, 208–213.

Tikuisis, P., Buick, F. & Kane, D. M. 1987*b* Percent carboxyhaemoglobin in resting humans exposed repeatedly to 1500 and 7500 p.p.m. CO. *J. appl. Physiol.* **63**, 820–827.

Tyuma, I., Ueda, Y., Imaizumi, K. & Kosaka, H. 1981 Prediction of the carbonmonoxyhaemoglobin levels during and after carbon monoxide exposures in various animal species. *Jap. J. Physiol.* **31**, 131–143.

Vekatram, A. & Louch, R. 1979 Evaluation of CO air quality criteria using a COHb model. *Atmos. Envir.* **13**, 869–872.

Wallace, L., Thomas, J., Mage, D. & Ott, W. 1988 Comparison of breath CO, CO exposure and Coburn model predictions in US EPA Washington–Denver (CO) study. *Atmos. Envir.* **22**, 2183–2193.

Weir, F. W. & Viano, D. C. 1977 Prediction of carboxyhaemoglobin concentration from transient carbon monoxide exposure. *Aviat. Space envir. Med.* **48**, 1076–1080.

Wright, G., Randell, P. & Shephard, R. J. 1973 Carbon monoxide and driving skills. *Arch. envir. Hlth* **27**, 349–354.

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