A MATHEMATICAL MODEL FOR TRANSFER OF O_2 AND CO_2 IN A MEMBRANE ARTIFICIAL LUNG*

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An analysis of oxygen absorption and carbon dioxide desorption in a film of blood through a gas-permeable membrane is presented. The mathematical analysis treats blood as a homogeneous, non-Newtonian fluid, in which the system p_{O_2}, p_{CO_2} hemoglobin, pH is always in equilibrium due to the reaction rate in the erythrocites.

Influence of flow rate, hematocrit and gas composition on blood saturation are studied, and the possibility of calculating an optimal membrane length is found.

Introduction

Cardiac surgery using an artificial lung for the by-pass of the human heart was first successfully performed in 1953. In recent years researchers aimed at making perfusion equipments more compact, more reliable, and less traumatic to the blood. Today the total body perfusion has become a routine hospital procedure.

The transfer surface needed may be created by dispersion of gas in a blood pool, as in the bubble artificial lung, or by spreading a thin layer of blood in a gas atmosphere, as in the screen or disc lung machines. Another possibility is spreading the blood film between plastic membranes, as in the membrane artificial lung.

The membrane artificial lung may achieve longer perfusions with minimum blood trauma, during more complex and time-consuming operations. The role of the membrane is twofold: (a) it limits the volume expansion of the extracorporeal blood compartment, thus simplifying the control of blood volume in the perfused organism, (b) it prevents blood damage by avoiding a direct blood-gas interface.

Some attempts have been made at applying the principles of mass transfer and chemical reactor design to the design of membrane artificial lungs[2,23,24]. In general, not enough attention has been paid to carbon dioxide removal and its influence on the overall oxygen mass transfer rate. Indeed, artificial lungs are usually called oxygenators, as if their only task were blood oxygenation. We are now going to consider simultaneous oxygen and carbon dioxide mass transfer in a membrane lung machine.

The Mathematical Model

A thin film of blood flowing between a solid surface and a gas-permeable membrane is shown in **Fig. 1**. Blood enters the system at $z=0$ with uniform concentration of oxygen and carbon dioxide. The flow is supposed to be fully developed. At the other side of the membrane there is a gas atmosphere rich in oxygen. It is assumed that:

·The flow profiles are given by Eqs.(7)–(9).
·The transversal section is rectangular and uniform over all the length.
·The velocity of blood does not change along the axis.
·Temperature is constant.
·Metabolic consumption of oxygen is negligible.
·Diffusion occurs perpendicularly to the membrane.
·Axial diffusion is negligible.
·Gas composition is constant.
·Steady state exists.

The process may be represented by two partial differential equations.

$$V_z \nabla C_{O_2} = D_{O_2} \nabla^2 C_{O_2} - R_{O_2} \tag{1}$$

$$V_z \nabla C_{CO_2} = D_{CO_2} \nabla^2 C_{CO_2} + R_{CO_2} \tag{2}$$

Analysis of Eqs.(1) and (2) shows that for their integration we need the following items:
(a) Blood rheology to obtain V_z, the velocity profiles of the blood film, (b) Diffusion coefficients of O_2 and CO_2 in blood, and (c) Chemical reactions of CO_2 and O_2 with blood components.

Blood Rheology

Blood is a suspension of particulates in a viscous fluid.

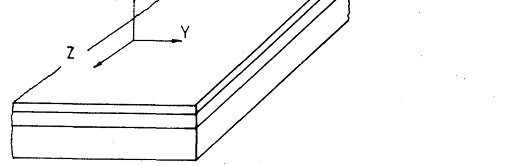

Fig. 1 Schematic diagram

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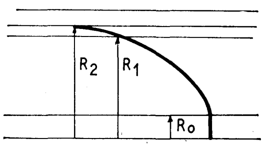

Fig. 2 Velocity profile

It consists of erythrocytes or red corpuscles, leukocytes or white corpuscles and thrombocytes or platelets. It is well known that at shear stresses below 40–50 dynes/cm^2, blood behaves like a pseudoplastic fluid; above these values, it behaves like a Newtonian fluid.

As blood flows through a conduit, a thin film of plasma without red cells is formed near the wall; the width of this film is of a couple of microns. Its presence may be due to the displacement of red cells towards the axis of the conduit. Such a displacement may appear in any suspension of particles in laminar flow when asymmetrical flow around the particle occurs and the relative velocity of the particle is not null[17].

Benis[1] demonstrated that the rheological behaviour of blood is well represented by Casson's equation.

$$T^{1/2}=B+M\left(\frac{dv}{dn}\right)^{1/2} \tag{3}$$

He obtained the velocity of blood in a tube as a function of the radial position from Eq.(3). Sevilla Larrea[19] determined Casson's constants as a function of blood hematocrit and obtained the velocity for three separate zones: a thin layer near the wall of width δ, where only plasma flows; a zone around the axis where plug flow may be accepted; and an intermediate zone. His results were:

$$B=0.05+0.0375H\,[\mathrm{dynes}^{1/2}/\mathrm{cm}] \tag{4}$$

$$M=0.12+0.002H\,[(\mathrm{dynes/sec})^{1/2}/\mathrm{cm}] \tag{5}$$

$$\delta=68.4(H)^{-0.824} \tag{6}$$

The velocity profiles for flux in a tube are for the three zones (**Fig. 2**).

For $0\leq r\leq R_0$

$$V_z=V_{\max} \tag{7}$$

$$V_{\max}=V_z|_{r=R_0} \tag{8}$$

being V_z given by Eq.(9)

For $R_0\leq r\leq R_1$

$$\begin{aligned}V_z=&0.5\,T_w(R_1/R_2)(R_1/M^2)\{1-(r/R_1)^2\}\\&-0.75BT_w^{0.5}(R_1/R_2)^{0.5}(R_1/M^2)\{1-(r/R_1)^{1.5}\}\\&+B^2(R_1/M^2)\{1-(r/R_1)\}+V_0\end{aligned} \tag{9}$$

$$V_0=V_z|_{r=R_1} \tag{10}$$

being V_z given by Eq.(11).

For $R_1\leq r\leq R_2$, where pure serum flows and the mechanism for the diffusion of O_2 and CO_2 is physical, without chemical reaction:

$$\begin{aligned}V_z=&0.5\,T_w(R_2/M_p^2)\{1-(r/R_2)^2\}\\&-0.75B_pT_w^{0.5}(R_2/M_p^2)\{1-(r/R_2)^{1.5}\}\\&+B_p^2(R_2/M_p^2)\{1-(r/R_2)\}\end{aligned} \tag{11}$$

where

$$R_1=R_2-\delta \tag{12}$$

R_0 is the value of r where

$$T=B^2 \tag{13}$$

B_p and M_p are the constants of Casson's equation for plasma and are obtained making $H=0$ in Eqs.(4) and (5).

To obtain the velocity profile along x by using Eqs.(7) to (13), the following steps must be taken into account: (a) equal velocity for every value of y must be assumed (Fig. 1), (b) r replaced by x, (c) R_2 replaced by b (half the width of the blood film), (d) the origin of x should be placed at the axis of flow.

Diffusivity of O_2 and CO_2 in blood

Oxygen must diffuse through the membrane, then through the blood serum; the resistance to the passage of oxygen into the erythrocyte imposed by the cell membrane is still a matter of dispute. When inside the erythrocyte, oxygen simultaneously diffuses and reacts in the hemoglobin solution. "Facilitated diffusion" of oxygen in hemoglobin solutions is a topic widely treated[5,7,18,25]; nevertheless, the value of diffusivity of O_2 in blood plasma will be used in Eq.(1). This procedure will be understood in terms of the chemical reactions involved. The same is valid for CO_2 diffusivity.

The chemical reaction between O_2 and hemoglobin

This chemical reaction may be written as

$$\mathrm{Hb}+4\mathrm{O}_2 \underset{k'}{\overset{k}{\rightleftarrows}} \mathrm{Hb(O_2)_4}$$

As each molecule of hemoglobin fixes four O_2 molecules, one in each heme group, four pairs of velocity constants are needed in order to describe the reaction rate rigorously. Because of the size of the hemoglobin molecule, however, it is usually assumed that each heme group reacts independently of the other three:

$$\mathrm{Hb}+\mathrm{O}_2 \underset{k'}{\overset{k}{\rightleftarrows}} \mathrm{HbO_2}$$

Available data of k and k'[6,8,15,16] show that k is much greater than k'.

Buckles[2] assumed a pseudo first order chemical reaction based on oxygen partial pressure on the cell membrane. Using Dankwert's solution for diffusion accompanied by first-order irreversible reaction, the importance of the reaction rate was evaluated.

It was found that the reaction rate so determined is several orders of magnitude greater than the diffusion parameters, thus showing that diffusion of oxygen in serum is the rate-controlling step. It can be concluded that the chemical reaction between oxygen and hemoglobin reaches equilibrium instantaneously.

Equilibrium conditions will be assumed in the present case. Reaction terms will be dropped in Eqs.(1) and (2). The same procedure was followed by other researchers[1,20,23,24].

The chemical reaction of CO_2

Carbon dioxide and bicarbonate are part of the most important buffer systems in blood. Carbon dioxide may appear in blood either as CO_2 or as CO_3H^-, dissolved either inside the erythrocyte or in the blood serum[13,21].

The formation of carbamic compounds seems to be represented by[14]

$$\text{Hb NH}_3^+ \rightleftharpoons \text{Hb NH}_2 + \text{H}^+$$

$$\text{Hb NH}_2 + \text{CO}_2 \rightleftharpoons \text{HbNHCOO}^- + \text{H}^+$$

These reactions are very rapid and, as in the case of oxygen, equilibrium is reached almost instantaneously.

The Coupling of the Two Mass-Transfer Equations

Including the assumption of chemical equilibrium in Eqs.(1) and (2), these can be written

$$V_z \partial C_{O_2}/\partial z = D_{O_2} \partial^2 C_{O_2}/\partial x^2 \quad (14)$$

$$V_z \partial C_{CO_2}/\partial z = D_{CO_2} \partial^2 C_{CO_2}/\partial x^2 \quad (15)$$

Diffusion occurs due to a concentration partial pressure gradient, and only the gas dissolved in serum appears in the diffusive term. The convective term, however, must account both for the dissolved gas and for the gas that is chemically combined with blood components and does not contribute directly to partial pressure.

In the case of the O_2, the convective term will be

$$V_z \partial C_{O_2}/\partial z = V_z \partial(\alpha_{O_2} p_{O_2} + 1.34 C_{Hb} s)/\partial z \quad (16)$$

where 1.34 means the cc(STP) of O_2 that saturate 100 g of hemoglobin. In the case of carbon dioxide, in turn, the convective term is given by

$$V_z \partial \{(C_{CO_2})_c H/100 + (1 - H/100)(C_{CO_2})_p\}/\partial z \quad (17)$$

There is a relationship between $(C_{CO_2})_c$ and $(C_{CO_2})_p$ given by[10]

$$D = D_{ox} + (D_{red} - D_{ox})(1 - s) \quad (18)$$

where
$$D = \frac{(C_{CO_2})_c}{(C_{CO_2})_p}$$

$$D = D_{ox} \quad \text{when} \quad s = 1$$

$$D = D_{red} \quad \text{when} \quad s = 0$$

Both D_{ox} and D_{red} depend upon pH

$$D_{ox} = 0.590 + 0.2913(7.4 - \text{pH}) - 0.0844(7.4 - \text{pH})^2 \quad (20)$$

$$D_{red} = 0.664 + 0.2275(7.4 - \text{pH}) - 0.0938(7.4 - \text{pH})^2 \quad (21)$$

The total concentration of CO_2 in plasma is given by

$$(CO_2)_p = \alpha_{CO_2} \cdot p_{CO_2} \cdot \{1 + 10 \exp(\text{pH} - \text{pK})\} \quad (22)$$

where

$$\text{pK} = 6.086 + 0.042(7.4 - \text{pH}) + (38 - t)\{0.0047 + 0.0014(7.4 - \text{pH})\} \quad (23)$$

and α_{CO_2} = solubility of CO_2 in plasma.

The extent of hemoglobin saturation is a function of the partial pressures of O_2 and CO_2, temperature and pH. This term, s in Eqs.(16) and (18), is given by

$$s = \frac{(a_1 \cdot w + a_2 \cdot w^2 + a_3 \cdot w^3 + w^4)}{(a_4 + a_5 \cdot w + a_6 \cdot w^2 + a_7 \cdot w^3 + w^4)} \quad (24)$$

where $a_1 \ldots a_7$ are constants given in ref.(11), and w is a corrected p_{O_2} given by

$$w = p_{O_2} \cdot 10 \exp\{0.024(37 - t) + 0.040(\text{pH} - 7.4) + 0.06(\log 40 - \log p_{CO_2})\} \quad (25)$$

The pH of blood plasma may be written as[13],

$$\text{pH}_{\text{plasma}} = 8.059 + 0.012(1 - s) + 0.0045(1 - s)(C_{Hb}) - \left[\text{HCO}_3^-\right]_p \left[0.005\left(\frac{1}{C_{Hb}}\right)\{0.273 - 0.01(1 - s)\}\right] \quad (26)$$

where $[\text{HCO}_3^-]_p$ is the concentration of bicarbonate in plasma given by

$$[\text{HCO}_3^-]_p = \alpha_{CO_2} \cdot p_{CO_2} \cdot 10 \exp(\text{pH} - \text{pK}) \quad (27)$$

The two coupled partial differential equations can now be rewritten

$$V_z \partial(\alpha_{O_2} p_{O_2} + 1.34 C_{Hb} s)/\partial z = D_{O_2} \partial^2(\alpha_{O_2} p_{O_2})/\partial x^2 \quad (28)$$

$$V_z \partial[\alpha_{CO_2} p_{CO_2}\{H/100(D - 1) + 1\} \times \{1 + 10 \exp(\text{pH} - \text{pK})\}]/\partial z = D_{CO_2} \partial^2(\alpha_{CO_2} p_{CO_2})/\partial x^2 \quad (29)$$

where V_z is given by Eqs.(7) to (13).

The two PDE (28) and (29) are coupled by the above-shown relationships. As an analytical solution is impossible, these equations were numerically solved, using an implicit Krank-Nicholson Method, by an IBM 360/50.

Standard criteria for convergence and stability[12] were met by proper selection of space coordinates.

The inlet conditions are fed to the computer as initial values of saturation and pH. Typical values for $H = 42\%$ are pH=7.3 and $s = 58\%$.

The boundary conditions are taken as follows. A mass balance of the gas is used at the blood membrane interface

$$\{(p_{ex_i} - p_i)/\phi\} D_{m_i} \alpha_{m_i} = D_i \partial(p_i \alpha_i)/\partial x \quad (30)$$

where p_i is the gas pressure in the blood side of the membrane, p_{ex_i} is the gas pressure outside the membrane, D_{m_i} the diffusivity of the gas in the membrane and α_{m_i} the solubility of the gas in the membrane material. The suffix i indicates either CO_2 and O_2.

At the impermeable wall

$$\partial p_i/\partial x = 0 \quad \text{at } x = 0 \quad (31)$$

The simultaneous solution of Eqs.(28) and (29) shall be referred to as case 1; Eq.(28), which was individually solved taking a constant value of p_{CO_2}, shall be named case 2.

Results of the Analytical Investigation

The computer program is written so that all the experimental conditions may be inserted directly. Due to the complexity of the system, a large number of parameters must be specified. The results of the calculations are presented as:
(a) local saturation s, when profiles along x are shown, and (b) mean saturation $\bar{s}$, when they are functions of

either the length of the flow path z or of the blood flow rate. A temperature of 37 °C and a total pressure of –60 mmHg in the surrounding gas were chosen.

Solutions were obtained for different blood flow rates, various compositions of the surrounding gas and two values of hematocrit. The already mentioned cases 1 and 2 were studied.

Figure 3 shows the profile of local saturation s in terms of x^x, the blood film width, for cases 1 and 2. The width x^x is dimensionless $x/(2 \cdot b)$; $x^x = 1$ at the membrane and $x^x = 0$ at the impermeable wall. The hematocrit was $H = 42\%$, the flow rate $q = 0.709$ cc/min, and $z = 15$ cm.

The sharp gradient in the saturation profile reflects an inward movement of the oxygen after it saturates almost all the hemoglobin at the external pressure; a clear diffusion front becomes visible.

Case 1 shows a deeper penetration than case 2 because changes in p_{CO_2} are considered. The release of CO_2 is favorable to the equilibrium of the system oxygen-hemoglobin.

Figure 4 presents the results for three different flow rates. As was expected, the larger the flow rate, the smaller the oxygen penetration. The shape of the profiles, however, does not change. Although the results correspond to case 1, case 2 gives almost the same portrait. The values of H, z and q appear in the caption.

Figure 5 presents the results of mean saturation as a function of z, for $H = 42\%$, $q = 0.709$ cc/min and cases 1 and 2.

The saturation increases with z, but the rate of the increment, say the derivative of the curve, decreases as z increases.

The figure mentioned may be very useful for calculations of an optimum membrane length. Even if in general the economic considerations that motivate an analysis of chemical plant equipment are not present in oxygenator design, the price of the membranes used is still very high, and such analysis may be worthwhile.

Case 1 shows a smaller decrease in the slope of the $\bar{s}$ vs. z curve. From 10 to 15 cm, $\bar{s}$ increases by 19%, while an increase of only 8% corresponds to case 2.

Figure 6 presents more $\bar{s}$ vs z curves, this time with the flow rate q as a parameter. The curves correspond to case 1 and $H = 42\%$. It is clearly understood that a compromise solution must be found between flow rate and membrane length. A small flow rate needs a very short membrane length, and if we increase the flow rate too much, too long a membrane may be necessary.

In **Fig. 7**, results of $\bar{s}$ for cases 1 and 2 are plotted against flow rate q, with $H = 42\%$ and $z = 15$ cm. The two curves are almost parallel, case 1 being represented by the higher one.

Figure 8 presents the dependence of oxygen partial pressure on the surrounding gas composition for cases 1 and 2 and three concentrations of CO_2 in the gas. The dimensionless partial pressures are defined as p_i/p_{ref}, where p_{ref} is 125 mmHg for O_2 and 40 mmHg for CO_2.

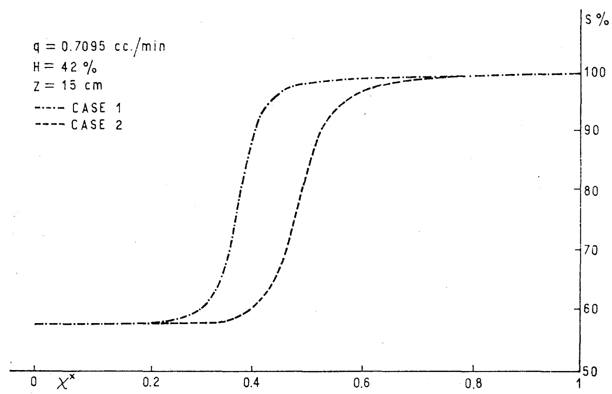

Fig. 3 Profile of local saturation in terms of blood film width

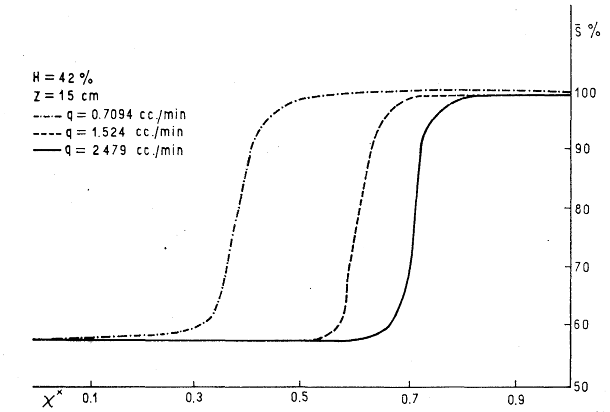

Fig. 4 Effect of flow rate on oxygen penetration

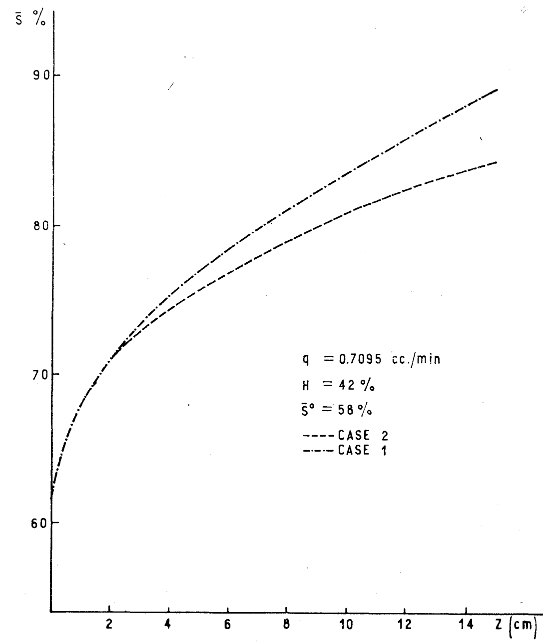

Fig. 5 Mean saturation vs. length

It is clearly seen that the performance of the oxygenator will not be seriously affected by the presence of discrete amounts of carbon dioxide, although p_{O_2} is somewhat decreased. A similar effect is observed in both cases.

Figure 9 presents the results of $\bar{s}$ vs. z for a flow rate of 2.475 cc/min for two values of H; $H = 42\%$, which is

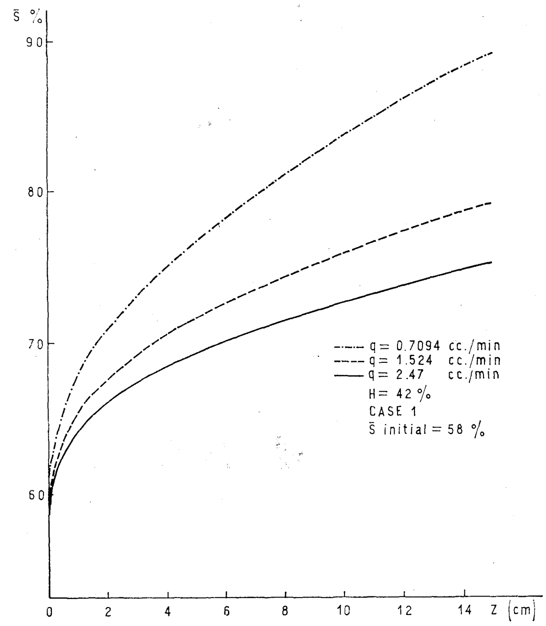

Fig. 6 Effect of flow rate on mean saturation

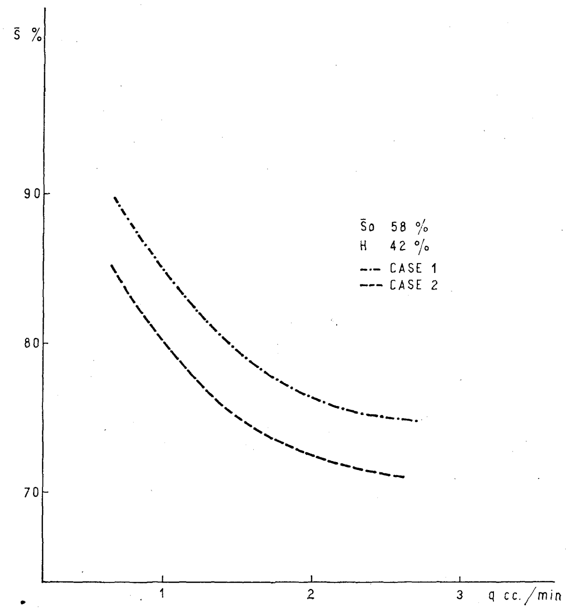

Fig. 7 Effect of flow rate on final mean saturation

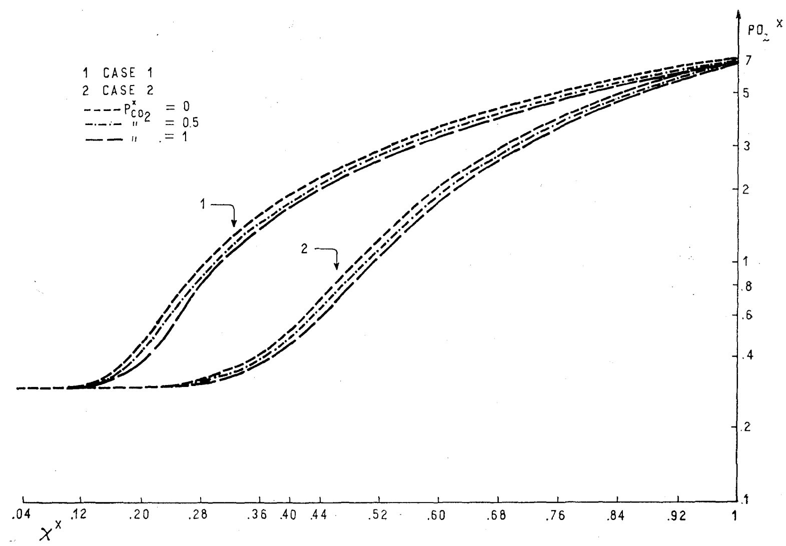

Fig. 8 Dependence on oxygen partial pressure on surrounding gas composition

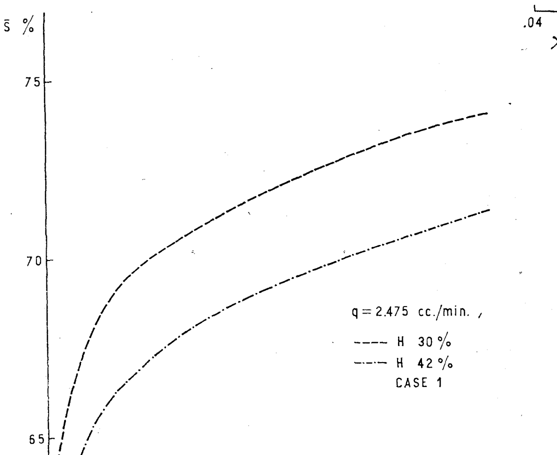

Fig. 9 Mean saturation vs. flow rate of H

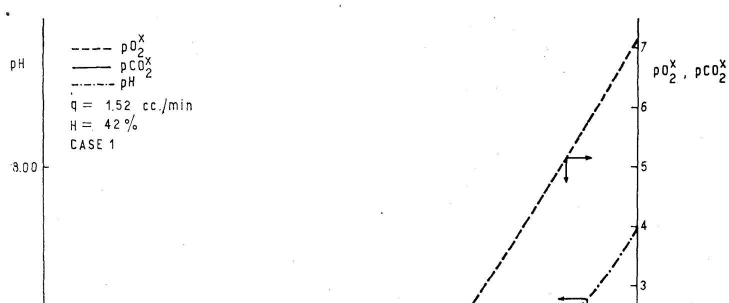

Fig. 10 Profiles of p_{CO_2}, p_{O_2} and pH

the normal hematocrit value of human or cattle blood, and $H=30\%$, which corresponds to actual conditions during intracardiac surgery, where fair amounts of serum are added. The corresponding values of hemoglobin concentration are approximately 15 and 10 g/100 cc.

The $H=30\%$ blood shows a much higher s. That does not mean better oxygen transport properties. The diluted blood, which corresponds to the clinical case of anemia, is easier to bring to a given saturation level, because its total transport capacity is smaller. After any length z, the $H=42\%$ blood carries the largest amount of oxygen.

Figure 10 presents the profiles of p_{O_2}, p_{CO_2} and pH for case 1, with $q=1.52$ cc/min and $H=42\%$. The variation of the pH is small, because of the buffer properties of blood; entering with pH=7.28 the maximum value, at the membrane, is pH=7.6, where blood is completely saturated.

The partial pressure of the gases and the pH at $x^x=0$ correspond to the typical initial conditions of the blood.

Conclusions

The foregoing represents an investigation of oxygenation of a film of blood through a gas-permeable membrane with a simultaneous release of CO_2 from blood to the surrounding gas. Both mass transfer PDE were integrated.

Results were confronted with the integration of oxygen transfer alone, making p_{CO_2}=ct.

Influence of the flow rate, hematocrit and gas composition on blood saturation were observed. There is a possibility of optimizing the length of the membrane for a given value of blood flow rate.

Gas composition does not strongly affect the results of the oxygenation process if the CO_2 concentration remains low, say 50 mmHg.

The solution of the partial differential equation that describes oxygen transfer to blood, assuming a constant value of CO_2 concentration, gives conservative values for the design of an artificial lung.

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Nomenclature

b	= half the width of the blood film	[cm]
B	= Casson's constant	[dynes$^{0.5}$/cm]
C_{O_2}	= total oxygen conc.	[cc(STP)/cc]
C_{CO_2}	= total carbon dioxide conc.	[cc(STP)/cc]
C_{Hb}	= hemoglobin conc.	[g/100cc]
D_{O_2}	= oxygen diffusivity	[sq.cm/sec]
D_{CO_2}	= carbon dioxide diffusivity	[sq.cm/sec]
H	= hematocrit, the volume per cent of erythrocytes	
M	= Casson's constant	[(dynes sec)$^{0.5}$/cm]
p_{O_2}	= partial pressure of oxygen	[mmHg]
p_{CO_2}	= partial pressure of carbon dioxide	[mmHg]
q	= blood flow rate	[cc/min]
r	= radial coordinate	[cm]
R_0	= point of transition of flow regime	[cm]
R_1	= point of transition of flow regime	[cm]
R_2	= point of transition of flow regime	[cm]
R_{O_2}	= rate of chemical reaction of oxygen in blood	
R_{CO_2}	= rate of chemical reaction of carbon dioxide in blood	
s	= percent saturation of hemoglobin with oxygen	
t	= temperature	[°C]
V_z	= velocity in z direction	[cm/sec]
V_{max}	= maximum velocity in z direction	[cm/sec]
V_0	= velocity given by Eq.(10)	[cm/sec]
x	= transversal coordinate, perpendicular to the permeable membrane	[cm]
y	= transversal coordinate, parallel to the permeable membrane	[cm]
z	= longitudinal coordinate	[cm]
T_w	= shear stress at the wall	[dynes/cm]
w	= given by Eq.(25)	
α_{O_2}	= solubility of O_2 in serum	
α_{CO_2}	= solubility of CO_2 in serum	
ϕ	= thickness of the membrane	

<Subscripts>

c	= cell
p	= plasma
m	= membrane
w	= wall

<Superscript>

x	= dimensionless

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