A Compartmental Model for Oxygen Transport in Brain Microcirculation in the Presence of Blood Substitutes

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A compartmental model is developed for oxygen (O_2) transport in brain microcirculation in the presence of blood substitutes (hemoglobin-based oxygen carriers). The cerebrovascular bed is represented as a series of vascular compartments, on the basis of diameters, surrounded by a tissue compartment. A mixture of red blood cells (RBC) and plasma/extracellular hemoglobin solution flows through the vascular bed from the arterioles through the capillaries to the venules. Oxygen is transported by convection in the vascular compartments and by diffusion in the surrounding tissue where it is utilized. Intravascular resistance and the diffusive loss of oxygen from the arterioles to the tissue are incorporated in the model.

The model predicts that most of the O_2 transport occurs at the level of capillaries. Results computed from the present model in the presence of hemoglobin-based oxygen carriers are consistent with those obtained from the earlier validated model (Sharan *et al.,* 1989, 1998a) on oxygen transport in brain circulation in the absence of extracellular hemoglobin. We have found that: (a) precapillary PO_2 gradients increase as PO_2 in the arterial blood increases, P_{50p} (oxygen tension at 50% saturation of hemoglobin with O_2 in plasma) decreases, i.e. O_2 affinity of the extracellular hemoglobin is increased, the flow rate of the mixture decreases, hematocrit decreases at constant flow, metabolic rate increases, and intravascular transport resistance in the arterioles is neglected; (b) precapillary PO_2 gradients are not sensitive to (i) intracapillary transport resistance, (ii) cooperativity (n_p) of hemoglobin with oxygen in plasma, (iii) hemoglobin concentration in the plasma and (iv) hematocrit when accounting for viscosity variation in the flow; (c) tissue PO_2 is not sensitive to the variation of intravascular transport resistance in the arterioles. We also found that tissue PO_2 is a non-monotonic function of the Hill coefficient n_p for the extracellular hemoglobin with a maximum occurring when n_p equals the blood Hill coefficient. The results of the computations give estimates of the magnitudes of the increases in tissue PO_2 as arterial PO_2 increases, P_{50p} increases, flow rate increases, hematocrit increases, hemoglobin concentration in the plasma increases, metabolic rate decreases, the capillary mass transfer coefficient increases or the intracapillary transport resistance decreases.

Introduction

The primary function of the hemoglobin inside the red blood cells (RBC) present in the blood is

to transport oxygen to the tissue. An extensive research is being carried out to develop blood substitutes for clinical applications (Winslow, 2000). The advantages associated with the use of blood substitutes include easing shortages of blood for transfusions, avoiding viral disease transmission and mismatching the blood types of donors and patients receiving transfusions, and saving the patient's own blood during the surgical operation. In view of these, the majority of blood substitute products are being developed based on the hemoglobin (Hb)Fa natural oxygen carrier of red cells. Recent advances in biotechnology such as cross-linking, recombinant modification and encapsulation have resulted in the development of hemoglobin-based oxygen carriers (HBOC) that can temporarily replace RBCs. Hemoglobin-based oxygen carriers can be prepared using human and non-human hemoglobins, e.g. human or bovine polymerized and recombinant Hb.

Experimental studies have been carried out with the modified hemoglobin products in different animal species and tissues to measure arterial blood pressure and cardiac output (Sehgal et al., 1984; Rosen et al., 1990; Biro et al., 1991; Palaparthy et al., 2001), regional blood flow (Ulatowski et al., 1996a), pial arteriolar diameters (Asano et al., 1998) cerebral blood flow and oxygen transport (Ulatowski et al., 1996b, 1998), and the effect of O_2 affinity on microvascular flow and oxygen tension (Sakai et al., 1999). Experiments with hemoglobin-based oxygen carriers in the plasma have demonstrated an improvement in the delivery of oxygen to the tissues, espatially in the cases where the blood hematocrit is small (Habler & Messmer, 2000). The delivery of oxygen to the tissue from the hemoglobin in plasma in vivo will depend on a number of parameters including hemoglobin-oxygen binding characteristics and Hb concentration. Potential hemoglobin products presently in clinical trials have a wide range of oxygen affinities and cooperativities. Since it is not always feasible to perform the necessary experiments due to experimental difficulties and the cost involved, it is desirable to develop a mathematical model for oxygen transport in the presence of blood substitutes to analyse the delivery of oxygen to tissue under various physiological and pathological conditions.

Modeling studies on oxygen transport in the presence of blood substitutes are limited. Page et al. (1998) have described a mathematical model for oxygen transport by RBC/extracellular hemoglobin solution mixtures flowing in arteriolar-size tubes with diameters in the range of 20-100 mm. Their model predicts that RBC/hemoglobin solution mixtures transport oxygen more efficiently than RBC suspensions in plasma. Vadapalli et al. (2002) have developed a model for oxygen transport by RBCs and hemoglobin solution in the capillary-size vessels to investigate the influence of hemoglobin-based oxygen carriers on the delivery of oxygen to tissue. A discrete cell model is used with RBCs represented in their realistic parachute shape flowing in a single file through a capillary. They have shown that the intracapillary resistance reduces as much as 60% with a hemoglobin concentration of $7 g d P^x$ when hematocrit is 0.2. Experimental (Duling & Berne, 1970; Pittman & Duling, 1977; Duling et al., 1979; Ivanov et al., 1982; Swain & Pittman, 1989; Kuo & Pittman, 1990) and theoretical (Sharan et al., 1989, 1998a) studies suggest that significant longitudinal gradients in blood oxygen tension and Hb saturation exist in precapillary vessels. A model for oxygen transport in the microcirculatory network by red blood cells and hemoglobin solutions has not been developed.

Sharan et al. (1989) have developed a compartmental model for oxygen transport in the brain microcirculation. This model has been applied (Sharan et al., 1998a) to analyse the experimental data on cerebral flow and oxygen content collected in sheep in hypoxic (Koehler et al., 1983, 1984), anemic (Jones et al., 1981) and carbon monoxide hypoxia (Koehler et al., 1984). Prediction from the model (Sharan et al., 1998a) supported the proposition that the differences in the cerebral blood flow responses among various types of hypoxia are wholly or in large part correlated with differences in tissue PO_2. Ye et al. (1992) have described an averaging procedure to derive equations from the spatially distributed to a compartment model. Using this procedure, Ye and his co-workers have also proposed a compartmental

model in the microcirculation, similar to ours, for oxygen transport (Ye *et ah,* 1993) and combined oxygen and carbon dioxide transport (Ye *et al.,* 1994, 1998).

In the present study, we develop a compartmental model for oxygen transport in the presence of blood substitutes, which considers the arterioles, capillaries and venules, and apply it to the brain microcirculation. The intravascular transport resistance and the exchange between the arterioles and capillaries are incorporated.

Mathematical Description

A mixture of red blood cells and plasma/extracellular hemoglobin solution flows through the vascular bed from the arterioles through the capillaries to the venules. The vascular bed is represented as a series of vascular compartments surrounded by a tissue compartment (Fig. 1), which is similar to that of Sharan *et al.* (1998a) and Ye *et al.* (1994). The vascular bed consists of *m* arteriolar and *m* venular compartments, and a capillary compartment. Each vascular compartment contains vessel segments, arranged in parallel, with similar diameter and length. Each compartment exchanges oxygen with the tissue compartment.

The oxygen in the blood/mixture is present in the form: (i) the dissolved component in the plasma/extracellular fluid, (ii) in combination with hemoglobin inside the RBC and (iii) in combination with hemoglobin in the extracellular fluid. As the solution flows through the vascular bed, oxygen is transported by convection in the vascular compartments and by diffusion in the surrounding tissue where it is utilized. In steady state, the transport of oxygen in the vascular compartments is governed by the equations (Appendix A):

$$g(C_{fl(!\_i)}) - Cat) - E_{ai}\delta P_{ai} - P_t\dot{P} = 0;$$

$$i = 1; 2; y; m;$$

$$Q\delta C_{am} - C_{vm}) - E_c\delta P_c - Pt\dot{P} = 0; \qquad \eth l\dot{P}$$

$$Q\delta C_{vi} - C_{K(i\_D)} - E_{vi}\delta P_{vi} - P_t\dot{P} = 0;$$

$$i = m; m — 1; y;., 1;$$

where C_ai is the total oxygen conocentration at the outlet of i-th arteriolar compartment, P_{ai} is the oxygen partial pressure in the i-th arteriolar compartment, Q is the blood flow rate, E_{ai} is the diffusion conductance across the i-th arteriolar compartment, P_t is the oxygen partial pressure in the tissue, and $C_{ao} = C_a$ is the total oxygen concentration in the mixture entering the vascular network with the partial pressure P_a. The corresponding quantities in the venular and capillary compartments are referred to by the subscripts 'V and "c", respectively. C_{vi} represents the total oxygen concentration at the inlet of i-th venular compartment and $C_{vo} = C_v$ is the total oxygen concentration in the mixture
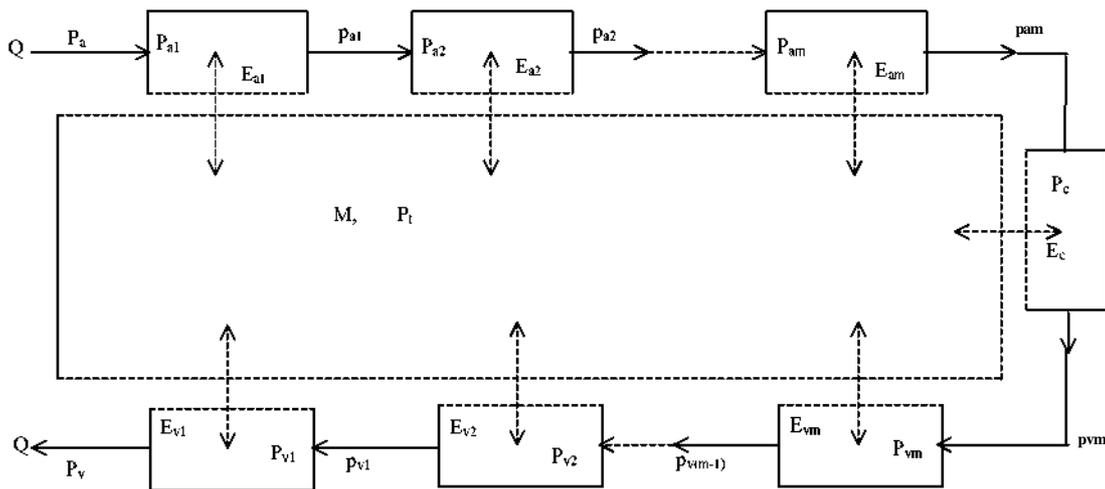

FIG. 1. Schematic diagram of the model.

leaving the vascular network with the partial pressure P_v:

The total concentration of oxygen in the blood/mixture can be expressed as

$$C = \alpha_m p + \beta_r S_r(p) + \beta_p S_p(p), \qquad (2)$$

where a_m is the solubility of O2 in the mixture, p is the PO2, S_r and S_p are, respectively, the fractional saturation of hemoglobin with O2 inside RBC and in extracellular fluid. Coefficients b_r and bp represent the oxygen carrying capacity of RBC and extracellular fluid.

Solubility of free O2 in the mixture is given by

$$\alpha_m = Hoc + (1 - H)oc', \qquad (3)$$

where H is the blood hematocrit representing volume fraction of RBC, a and a^0 are solubilities of O2 in the RBC and extracellular fluid.

The coefficients b_r and b_p in eqn (2) are defined as

$$\beta_r = 1.34[Hb]_r H$$
$$\beta_p = \backslash 34[Hb]_p(\backslash-H) \qquad (4)$$

where $[Hb]_r$ is the total hemoglobin in the RBC in gmP^1 and [Hb]p is the total hemoglobin content in the extracellular fluid in gml"[1].

In the non-capillary vascular compartments, oxygen partial pressure is taken as the arithmetic mean of inlet and outlet PO_2 (Ye *et al.*, 1994):

$$P_i = (pi-i \, \flat_{pi} \, P^=2; \qquad i = 1, 2, \ldots, m; \quad ð5Þ$$

whereas the average PO2 in the capillary compartment is obtained as described in Appendix B. In steady state, net transport of O2 from the vascular compartments is balanced by the utilization of O2 in the metabolic processes in the tissue and accordingly, we have

$$\sum_{i=\backslash}^{m} E_{ai}\delta P_{ai} - P_t \flat \, \flat \, E_c \delta P_c - P_t \flat$$

$$+ \sum_{i=1}^{m} E_{vi}(P_{vi} - P_t) - MV_t = 0; \qquad ð6Þ$$

where M is the metabolic rate and V_t is the volume of the tissue compartment.

BLOOD FLOW

Let q_a and q_v be the arterial and venous hydraulic pressures. Since the vascular compartments are arranged in series, the total blood flow, Q, is expressed as

$$Q=(q_a-q_v)R-\backslash \qquad (7)$$

where the total vascular hydraulic resistance is

$$R = \sum_{i=1}^{m} R_{ai} + R_c + \sum_{i=1}^{m} R_{vi}, \qquad (8)$$

in which R_i is the resistance of i-th compartment. Assuming the vessels are arranged parallel to each other in each of the vascular compartments, the total resistance in i-th compartment is given by

$$R_i = \frac{\backslash 2SLt}{\pi N_i D_i^4} \mu_s \mu_{rel}(D_i, H_D \flat; \qquad (9)$$

where N_i is the number of vessels in the i-th compartment, L_i is a characteristic length of each of the vessels, D_i is the vessel diameter, m_s is the viscosity of the suspending medium or plasma in presence of hemoglobin solution, $\backslash i_{app}$ is the apparent viscosity, and $m_{rel} = m_{app} = m_s$ is the relative viscosity that depends on the vessel diameter and hematocrit.

In the model, we would like to include the dependence of apparent viscosity of blood on tube diameter and hematocrit (Fahraeus-Lindqvist effect). We use an empirical equation developed by Pries *et al.* (1992) for the variation of relative apparent blood viscosity with H_D and $^D; \cdot m_{rel} = m_{app} = m_s = f \delta H_D; D \flat;$ This equation was developed on the basis of comprehensive analysis of data based on measurements at high shear rates in tubes with diameters ranging from 3.3 to 1978 mm at hematocrits up to 90%. The data were corrected for differences in suspending medium viscosity and temperature.

We assume that viscosity m_s in eqn (9) varies with extracellular hemoglobin concentration and can be determined using the fit of Mooney's relationship to experimental data (Monkos, 1994):

$$\mu_s = mpl^{ex} \, \flat \, I\left(\frac{A\backslash Hb]_t,}{l-B\backslash Hb],_{,^2}}\right) \qquad ð10Þ$$

where n_{px} is the viscosity of the plasma without hemoglobin and $[Hb]_p$, is the concentration of hemoglobin in gml^1 in the plasma. Constants A and B are adjustable parameters of the equation determined from an experimental fit of data, having values of 2.77 and 1.2 ml $g^{"1}$, respectively, for human tetrameric hemoglobin solution (Monkos, 1994).

HEMOGLOBIN SATURATION

The relationship between the fractional saturation of hemoglobin with oxygen, SO_2, and oxygen tension, PO_2 is known as the oxygen dissociation curve (ODC). A number of formulations (Sharan & Popel, 1989) are available to represent the ODC in the modeling of oxygen transport. However, for hemoglobin-based oxygen carriers, two-parameter Hill's is commonly used:

$$S(p) = \frac{(p/P_{50})^n}{1 + (p/P_{50})^n}, \qquad (11)$$

where $P50$ is the oxygen tension at 50% saturation and n is the dimensionless exponent. The saturation in RBC and extracellular hemoglobin can be computed using the corresponding values of P50 and n. The advantage of using Hill's equation is that the values of P50 and n are available for hemoglobin-based oxygen carriers (Ulatowski *et al.*, 1996a, 1998). Kinetic properties of O2 binding to either RBC or extracellular hemoglobin are not taken into account here.

DIFFUSION CONDUCTANCE FOR THE CAPILLARY COMPARTMENT

The diffusion conductance for the capillary compartment is computed from the Krogh-like tissue cylinder model by considering the intracapillary resistance (Sharan *et al.,* 1998b) and a diffusive influx term at the wall of the tissue cylinder (Appendix C):

where $w = r_c=r_t$, the ratio of radius of the capillary, r_c, to radius of tissue cylinder, r_t, N_c is the number of capillaries in the compartment and L_c is the characteristic length of the capillaries. D_t and a_t are the diffusion and solubility coefficients of O_2 inside the tissue and k_c is the mass transfer coefficient in the capillary. The diffusive influx g in eqn (12) is calculated as the diffusive loss from the arterioles/venules per unit volume occupied by the tissue surrounding the capillaries:

$$\gamma = \frac{Z_{tl}\ E_{ai}(P_{ai}-\ P_t) + Z_{tl}\ E_{vi}(P_{vi}-\ P_t)}{pMN_cL_cr_t^2\delta l - w^2 P}. \qquad (13)$$

DIFFUSION CONDUCTANCES FOR THE ARTERIOLAR/ VENULAR COMPARTMENTS

Transport of oxygen from the arteriolar vessel to the surrounding tissue depends on: (i) transport inside the vessel, (ii) transport through the vessel wall, and (iii) transport in the surrounding tissue. A part of oxygen that diffuses from the arteriolar vessel may be convected away by the blood capillaries, located in close proximity of the arteriole in the surrounding tissue region (Weerapulli & Popel, 1989). In the earlier compartmental models (Sharan *et al.,* 1989, 1998a; Ye *et al.,* 1994), the diffusion conductance through the arteriole was computed by considering a capillary-perfused tissue region with a characteristic penetration depth l_t. Ye *et al.* (1994) have used the Krogh tissue cylinder model applied to arterioles for computing the diffusion conductance. However, this approach is based on the assumption that arteriolar vessel is the only source of oxygen to the tissue in the vicinity of the arteriole. The intravascular transport resistance was taken into account by assuming parabolic radial profiles of PO_2 in the vessel.

Diffusion resistance to O_2 transport is the sum of the intravascular and extravascular

$$E_c = \frac{2\pi N_c L_c(1 - w^2)(\ - y)}{[(1 -w^2)(\ - g P=r_ck_c - (1/2D_t\alpha_t)\ ([2/(1 - w^2)]\ \ln(w) + (3 - w^2)/2) + (y/D_ta_t)(ln(w) + (1 - w^2)/2)]}$$

$$(12)$$

resistances:

$$\frac{1}{F} = \frac{1}{F} + \frac{1}{F},\qquad (14)$$

where E_{inv} and E_{exv} are the intravascular and extravascular conductances.

To overcome the limitations associated with the Krogh tissue cylinder model for arterioles and venules and the estimation of penetration depth, Weerapulli & Pope1 (1989) formulated a model to analyse the effect of capillary convection on oxygen transport around arterioles and venules. The model predicts the Sherwood number *(Sh)* representing the dimensionless flux of oxygen from the vessel. The results were corroborated by a more detailed model of Hsu & Secomb (1992) where discrete capillaries were considered. Here, we adopt this model for computing the extravascular conductance in ith arteriolar compartment:

$$E_{exv} = N_i L_i D_t a_t p Sh. \qquad (15)$$

Hellums *et al.* (1996) have expressed the mass transfer Nusselt number *(Nu)*, which is equivalent to Sherwood number, as a function of hemoglobin saturation with oxygen, vessel diameter and hematocrit on the basis of a two-phase model (Nair *et al.,* 1989) for the blood flowing in the arteriolar-size vessels. The intravascular conductance is expressed in terms of *Sh* as

$$E_{inv} = N_i L_i D_{pl} \alpha_{pl} \pi \, Sh. \qquad (16)$$

where $D_p l$ and $a_p l$ are the diffusion and solubility coefficients in the plasma.

In the present study, we use diffusion conductances corresponding to the blood according to eqns (15) and (16). Notice that the diffusive influx g in eqn (13) dependent on partial pressures in the vascular and tissue compartments which are, in turn, depended on g through E_c [eqn (12)]. Further, eqns (1) and (6) with the relations (2), (5), (7) and (11) form a nonlinear system of algebraic equations. The system is solved numerically using the Newton-Raphson method (Press *et al.,* 1986).

Parameters of the Model

To compute the distribution of PO_2 in the vascular and tissue compartments in any particular tissue, the values of the parameters such as geometrical parameters pertaining to the vascular bed, blood flow, metabolic rate, arterial PO_2, the solubility and diffusion coefficients, Hill's parameters P_{50} and n for hemoglobin in RBC and extracellular fluid, hematocrit, hemoglobin concentrations in the blood and extracellular fluid, blood viscosity, intracapillary resistance, etc. have to be specified. Here we have taken values of most of the parameters from our earlier study (Sharan *et al.,* 1998a) on the analysis of hypoxia in sheep brain; in that study the model was validated against experimental data.

A set of morphological parameters (Sharan *et al.,* 1998a) for the cerebral vascular bed of the

TABLE 1

Cerebrovascular system parameters of the lamb

	Arterioles					Capillaries
	a1	a2	a3	a4	a5	c
Diameter (mm)	0.12	0.06	0.03	0.02	0.01	0.0056
Length (mm)	5.39	2.69	1.35	0.90	0.45	0.6
No. of vessels in the group	1880	1.5×10^4	1.18×10^5	3.92×10^3	3.01×10^6	5.92×10^7
E	2.44×10^{-6}	8.33×10^{-6}	2.67×10^{-5}	4.88×10^{-5}	$1.2 \times CUT^4$	3.37×10^{-3}

	Venules				
	v5	v4	v3	v2	v1
Diameter (mm)	0.015	0.03	0.045	0.09	0.18
Length (mm)	0.45	0.90	1.35	2.69	5.39
No. of vessels in the group	3.01×10^6	3.92×10^5	1.18×10^5	1.5×10^4	1880
E	2.76×10^{-4}	1×10^{-4}	5.19×10^{-5}	1.45×10^{-5}	4.41×10^{-6}

Note: Weight = 75g, $Q = 70 ml(100g^{-1})mkT^{1}$.

sheep is given in Table 1. The total number of vascular compartments is 11 with $m = 5$ in eqns (1) and (6). For computing the flow, we have used the relations proposed by Pries *et al.* (1992) *in vitro* for relative apparent blood viscosity depending on discharge hematocrit and diameter of the tube. We have also chosen: arterial pressure (at the inlet of the arterioles with diameter 120 mm) $q_a = 60$mmHg, venous pressure $q_v = 10$ mmHg and plasma viscosity, in the absence of free hemoglobin, $mp_{pl} = 1.28$ CP.

The solubility coefficient for O_2 in the blood is assumed to be the same as in the tissue $a = a_t = 3x \ 1CT^5$ ml O_2ml^{-1} (mmHg)$^{-1}$. The value of a^0 in the hemoglobin solution is taken as $2.8x1CT^5$ml O_2ml^{-1} (mmHg)$^{-1}$ (Roy & Popel, 1996). The value of tissue diffusion coefficient is $D_t = 1.5 \times 10^{-5}$cm^{2}s^{-1}. For the sheep: hemoglobin in the blood $[Hb]_r = 0.11$gml^{-1} blood at normal blood hematocrit of 30%, metabolic rate $M = 4.8$ ml O_2(100g^{-1})min^{-1} (Koehler *et al.,* 1984), arterial blood oxygen tension $P_a = 95$ mmHg and Hill's parameters for whole blood P50 = 40 mmHg and $n = 3.23$ (Maginniss *et al.,* 1986) are taken under normal conditions.

The experiments with hemoglobin-based-oxygen carriers have not been carried out in sheep brain. However, experiments have been carried out with plasma-based hemoglobin in cat (Ulatowski *et al.,* 1996b, 1998). With the hemoglobin solution exchange transfusion, the hematocrit is reduced from 0.3 to 0.2. The transfusion is carried out with the hemoglobin solution with a concentration 7gdl^{-x} which under the experimental conditions leads to the same total hemoglobin available for transport of O_2 before and after the transfusion. To simulate these experimental conditions, we take $[Hb]_p = 4.58$ gdl^{-1} so that total hemoglobin concentration remains 11gdl^{-1}. For the hemoglobin solution, we take $P50 = 40$ mmHg and $n_p = 3.23$ in control case, matching the whole blood characteristics, and then change these parameters within a wide range to simulate hemoglobin-based oxygen carriers with different properties.

The values of diffusion conductances for non-capillary vascular compartments used in the computations are given in Table 1 based on the values reported by Hellums *et al.* (1996).

Recently, Vadapalli *et al.* (2002) have analysed the oxygen transport by red blood cells and hemoglobin solution in capillaries and computed the intracapillary mass transfer coefficients for a number of conditions; we take a typical value $k_c = 2x \ 10^{-6}$ml O_2cm^{-2}s^{-1}. We will show that these parameters do not play very important role under the present set of conditions.

Results and Discussion

Results obtained from the model on oxygen transport in the brain circulation with the whole blood have been discussed in our earlier paper (Sharan *et al.,* 1989) and this model has been used to analyse the experimental data (Jones *et al.,* 1981; Koehler *et al.,* 1984, 1986) on hypoxia in sheep. We will now simulate the effect of extracellular hemoglobin on the O_2 transport to tissue.

The total blood flow computed from the model without extracellular hemoglobin is 0.924 cm^3 s^{-1}, equivalent to 74ml(100g^{-1})min^{-1}, which is in good agreement (about 5%) with the measured flow of 70ml(100g^{-1})min^{-1} in the cerebral part of the brain weighing 75 g (Koehler *et al.,* 1984). The relative viscosity of the blood depends on discharge hematocrit. By reducing the hematocrit from 30 to 20% with the hemoglobin solution, the model predicts rise in blood flow from 74 to 84.5ml(100g^{-1})min^{-1}. By considering the dependence of plasma viscosity on hemoglobin concentration [eqn (10)], the blood flow predicted from the model in the presence of hemoglobin solution is 74ml(100g^{-1})min^{-1}, which is the same as obtained with the blood at normal hematocrit of 30% without the hemoglobin solution. Thus, the flow model that uses the relative apparent blood viscosity depending on tube diameter and discharge hematocrit (Pries *et al.,* 1992) and the plasma viscosity as a function of hemoglobin concentration (Monkos, 1994) predicts the blood flow in the presence of hemoglobin solution, the same as blood flow under the control conditions. Note that this model does not consider changes in vascular tone as a result of hemoglobin solution transfusion.

In the figures, "In" corresponds to the network inlet, "a1" to "a5" correspond to the
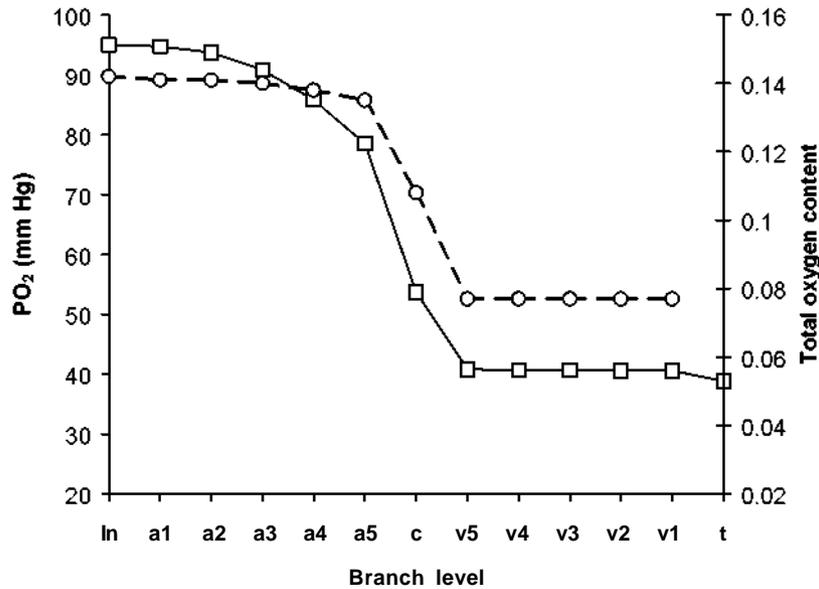
FIG. 2. Distribution of PO_2 and total oxygen content (CaO_2) in the vascular and PO_2 in tissue compartments: (—) PO_2; (—) CaO_2.

arteriolar compartments, "c" denotes the capillary compartment, "v5" to "v1" the venular compartments, and "t" designates the tissue compartment.

The PO_2 distribution in the vascular and the tissue compartments is found to be the same without/with hemoglobin solution if the total amount of hemoglobin remains constant and the characteristics of the hemoglobin in the plasma are the same as those in RBC. We refer to this case as the control case. The distribution of PO_2 and the total oxygen content (CaO_2) in the vascular compartments and the PO_2 in the tissue compartment are shown in Fig. 2. The PO_2 gradient increases in the successive arteriolar branch levels of the network. Total oxygen content falls marginally from 14.2 to 13.5% in the arterioles, it is constant (7.7%) in the venules and a significant fall occurs in the capillaries. The corresponding PO_2 decreases from 95 to 78.5 mmHg in the arterioles and it is almost constant in the venules. About 30% of the total drop of PO_2 between the inlet and outlet of the vascular network occurs in the precapillary vessels and the remaining 70% in the capillaries. The venous PO_2 is found to be 40.6 mmHg, close to the value 39 mmHg reported in the whole blood experiment in sheep (Koehler *et al.,* 1983). Ulatowski *et al.* (1998) have also reported

a value about 39 mmHg in their control and hemoglobin-transfusion experiments in cat. The calculated value of the tissue PO2 is 38.8 mmHg.

In the earlier models (Sharan *et al.,* 1989, 1998a; Ye *et al.,* 1994), the exchange of oxygen from the arterioles was considered, but it was not accounted for in the total O_2 mass balance for the organ in the sense that in the calculations of the capillary transport conductance the contribution of the arterioles was not taken into account. This feature is now incorporated into the model through a diffusive influx term in the capillary model, see Appendix C for detail. We found that out of the total oxygen exchange in the tissue, 18% occurs through the arterioles/venules. However, the effect of taking into account the diffusive influx term in the capillary model on the PO_2 in the vascular network is small; without the diffusive influx term, tissue PO_2 decreases from 38.8 to 38.5mmHg.

Recently, Vadapalli *et al.* (2002) have shown that the intracapillary resistance to oxygen transport is reduced by as much as 60% in the presence of hemoglobin solution with a concentration of 7 g dP[1] at 20% hematocrit. They have found that the intracapillary mass transfer coefficient k_c varies approximately in the range $1_x 10\~^6$-4x $10\~^6$ml O_2cm$\~^2$Torr$\~^1$s$\~^1$. For the sensitivity analysis in the present model, we

have taken $k_c = 1 \times 1CT^6$, $2 \times 1CT^6$, $4 \times 1CT^6$ and 2×10^6. The last value corresponds to the case when there is no intracapillary resistance to oxygen transport. Our calculations show that the effect of intracapillary resistance on vascular PO_2 in the network is negligibly small under the current conditions. However, the tissue PO_2 increases from 35.8 to 40.4mmHg as k_c increases from $1 \times 1CT^6$ to $4 \times 1(T^6 \text{ml O}_2 \text{ cm}^\wedge\text{Torr-}^1 \text{ s}"^1$. Without intracapillary resistance, tissue PO_2 is found to be 42.1 mmHg. The model predicts an additional precapillary loss of about 6.5 mmHg when the intravascular resistance in the arterioles is neglected. The change in venous and tissue PO2 is small.

During hypoxic hypoxia, arterial PO_2 is reduced. Figure 3 presents the distribution of PO2 in the network with the variation of PO2 in the arterial blood entering the network. Loss of oxygen from the precapillary vessels decreases as the PO2 in the arterial blood is reduced. The venous and tissue PO2 decrease as the arterial PO2 decreases. The tissue PO2 falls by 2 mmHg when arterial PO2 is reduced from 110 to 95 mmHg whereas it drops by 15 mmHg with the reduction in arterial PO_2 from 60 to 40 mmHg. Hence, for lower PO2 a small change in arterial PO_2 causes a significant variation in the tissue PO_2. The results found here are similar to those reported in our earlier study (Sharan et al., 1989). The sensitivity analysis with respect

to the parameters such as Q, M, $P50$ and hemoglobin concentration in the blood is carried out in the same way as was done in Sharan et al. (1989) and similar conclusions are drawn.

The oxygen-binding properties of plasma-based hemoglobin depend on the affinity to O_2 and cooperativity. Hence, the parametric study involved changing the values of $P50_p$, n_p, concentration of hemoglobin in the plasma and hematocrit that are likely to influence the PO_2 distribution in the network. The PO_2 losses through the precapillary vessels and PO_2 in the arteriolar and capillary compartments are not affected with the variation of cooperativity n_p [Fig. 4(a)]. However, the PO2 in the venules rises from 35.9 to 40.6 mmHg when n_p is increased from 1 to 3.23. The changes in venular PO2 could be attributed to the high degree of nonlinearity in the oxygen dissociation curve caused by the high value of n_p. The value $n_p = 1$ corresponds to non-cooperative binding that is encountered in some polymerized hemoglobins. The rate of increase of tissue PO2 decreases with increase in n_p [Fig. 4(b)]. Tissue PO2 increases rapidly with n_p initially and then levels off for $n_p > 2.5$. The tissue PO_2 reaches maximum at $n_p = 3.2$ and it decreases with a further increase in n_p. The difference between the venous and tissue PO_2 is increased from 0.5 to 2.4mmHg as np changes from 1 to 4.

$P50p$ describes the position of oxygen dissociation curve in the plasma. In the absence of 2,3-diphosphoglycerate (2,3-DPG) that cross-links the two b-chains of the hemoglobin molecule in the RBC, the value of $P50_p$ is known to be around 8 mmHg, an unfavorably high oxygen affinity that leads to an insufficient release of oxygen in the body (Alayash, 1999). In modified hemoglobin-based oxygen radicals scavengers and hemoglobin-based oxygen carriers, the value of $P50_p$ can be as low as 4mmHg (Doherty et al., 1998). Hence, to improve the oxygen releasing capacity of extracellular hemoglobin it is desirable to modify it (Alayash, 1999). In the modified hemoglobin, the value of $P50_p$ varies in a wide range (Bucci et al., 1996; Ulatowski et al., 1998; Sakai et al., 1999). Here, we study the PO2 distribution in the network by varying $P50_p$ in the range 4-50 mmHg while P50 in the red blood cells is held constant.
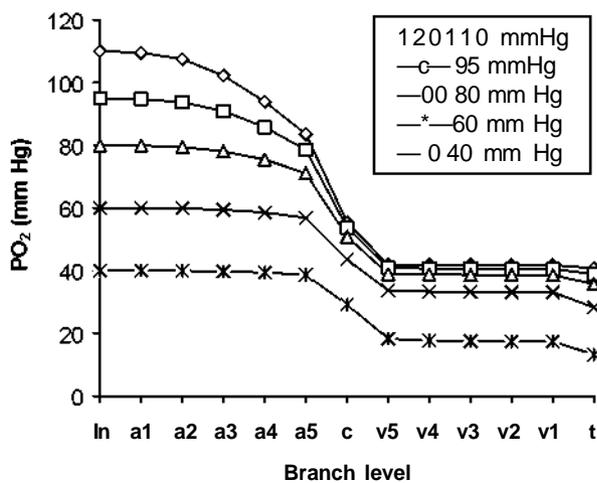

FIG. 3. Distribution of PO_2 in the vascular network for various values of inlet PO_2 for constant flow: (*) 40 mmHg; (x) 60mmHg; (D) 80mmHg; (&) 95mmHg; ({}) 110 mmHg.
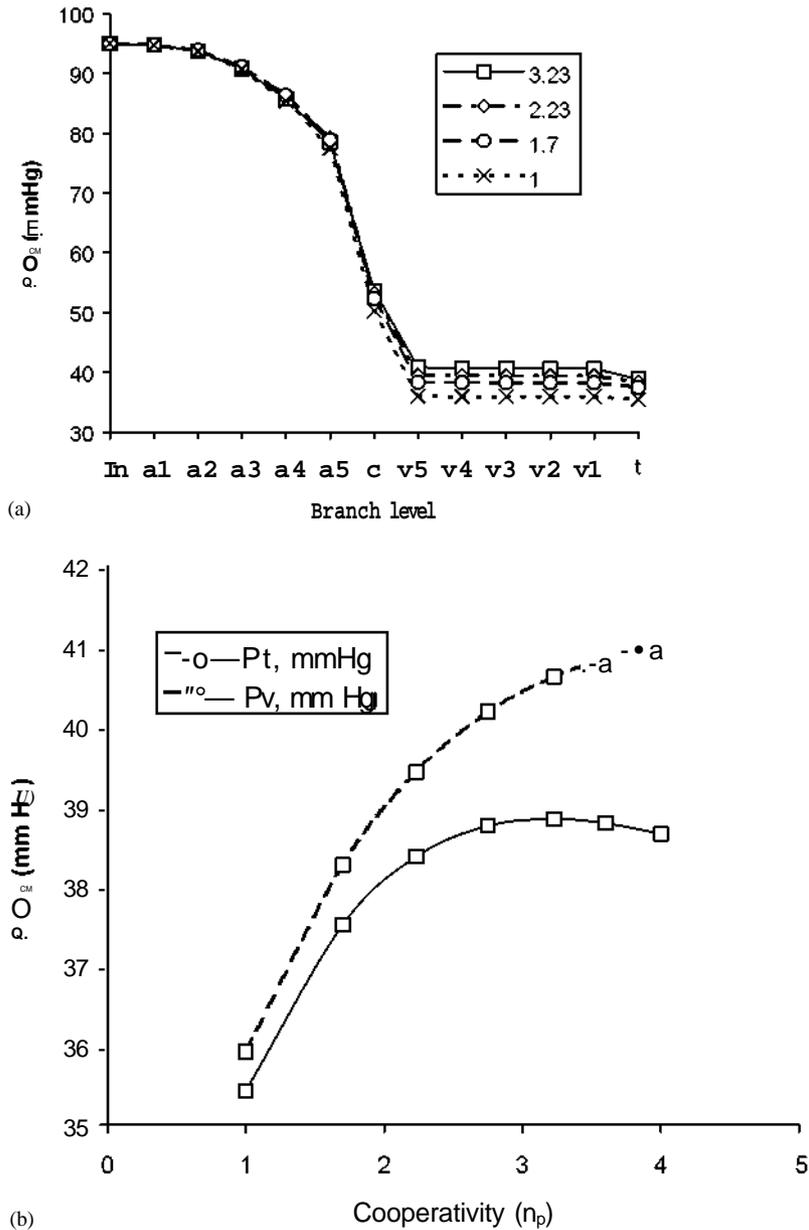
FIG. 4. (a) Distribution of PO_2 in the vascular network for various values of cooperativities n_p: (x) $n_p = 1$; (J) $n_p = 1.7$; (}) $n_p = 2.23$; (&) $n_p = 3.23$. (b) Variation of tissue PO_2 (F) and venous PO_2 (———) with the cooperativity n_p.

The distribution of PO_2 in the network for various values of $P50p$ is presented in Fig. 5(a). It shows that precapillary PO_2 gradients increase as P_{50p} is reduced. The total PO_2 drop in the arteriolar compartments rises from 14 to 22.3 mmHg when P_{50p} is reduced from 50 to 10 mmHg. The precapillary PO_2 gradients remain almost constant when $P50_p$ is reduced lower than 10 mmHg. A similar trend is observed for capillary and venular PO2. The reason for the increase in precapillary losses with decrease in

$P50_p$ is that the oxygen dissociation curve in the plasma becomes steeper with reduced P_{50p} and the reduction in fractional saturation of hemoglobin with O_2 in plasma causes smaller change in plasma PO_2 with reduced P_{50p}; as a result the gradient between the intravascular PO2 and the tissue PO_2 increases with decrease in P_{50p}. The precapillary PO_2 gradients increase further with the decrease in blood flow [Fig. 5(b)]. For $P50_p = 10$ mmHg, the drop in PO_2 in the precapillary vessels rises from 22.3 to 32.4 mmHg
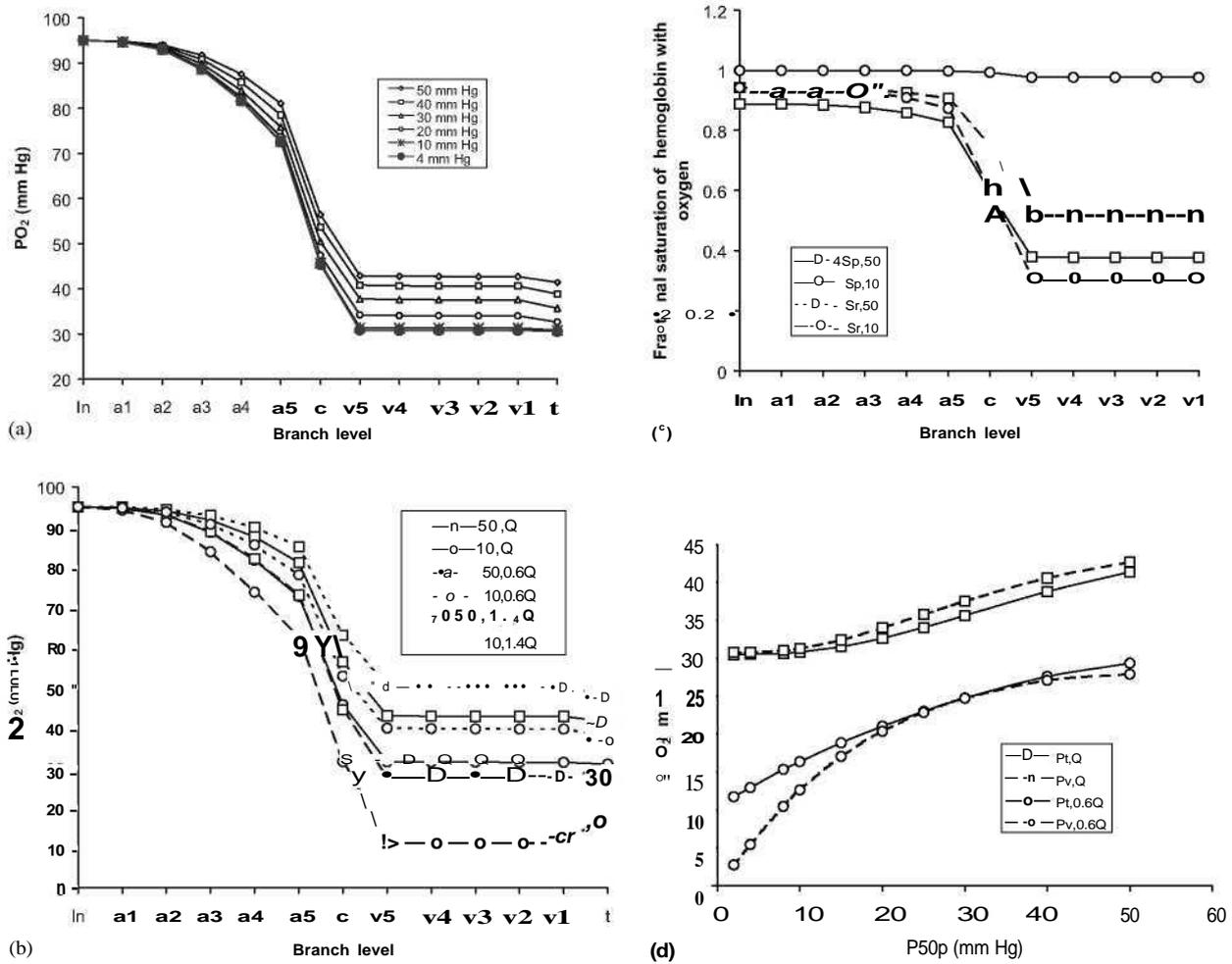
FIG. 5. (a) Distribution of PO_2 in the vascular network for various values of $P50_P$. (b) Distribution of PO_2 in the vascular network for two values of $P50_p$ when the flow (Q) is elevated/reduced by 40% from the control: (—) control flow; (——) 40% reduced flow; (？？) 40% elevated flow; (&) P_{50p} = 50 mmHg; (J) P_{50p} = 10 mmHg. (c) Distribution of fractional saturation of hemoglobin in RBC (S_r) and in plasma (S_p) with oxygen in the vascular network for two values of $P50_p$: (—) S_p; (——) S_r; (&) $P50p$ = 50 mmHg; (J) $P50_p$ = 10 mmHg. (d) Variation of tissue and venous PO_2 with $P50_p$ for control and 40% reduced flow: (—) tissue PO_2; (——) venous PO_2 (&) control flow; (J) 40% reduced flow.

when the blood flow is reduced by 40%. However, the drop reduces to 17 mmHg when the blood flow is increased by 40% from the control level.

Figure 5(c) represents the distribution of fractional saturation of hemoglobin with O_2 in RBC (S_r) and plasma (S_p) for two values of $P50_p$ (50 and 10 mmHg). For P_{50p} = 10 mmHg, the hemoglobin in plasma is almost fully saturated with O2 in the network and a little amount of oxygen is released due to high affinity. On the other hand with P_{50p} = 50 mmHg, S_p falls from 89 to 38% along the network and a significant drop in S_p occurs at the level of capillaries. The

drop in S_r in the network increases from 39 to 63% when the P_{50p} is reduced from 50 to 10 mmHg. The saturation S_r in arterioles is practically the same with the change in P_{50p} from 50 to 10 mmHg. The fully saturated hemoglobin in the plasma at low $P50_p$ helps in release of oxygen first from red blood cells [Fig. 5(c)].

The venous and tissue PO2 increase as $P50_p$ increases [Fig. 5(d)]. The increase in venous PO_2 with increased P_{50} in the cerebral blood has been observed experimentally (Koehler *et ah,* 1983, 1986). However, such measurements are not available with the hemoglobin-based oxygen

carriers. For the control flow, the difference between the tissue and venous PO_2 decreases as $P50p$ is reduced and the tissue PO_2 is lower than the venous PO_2. When the blood flow is reduced by 40%, the tissue PO_2 becomes higher than the venous PO_2 [Fig. 5(d)]. The difference between the tissue and venous PO_2 decreases as $P50_p$ is increased from 2 to 30mmHg and it increases when $P50_p$ rises from 30 to 50mmHg. The relationship between the tissue PO_2 and the venous PO_2 is consistent with our earlier study (Sharan *et ah*, 1998b) on the relationship between end-capillary and mean tissue PO2.

The amount of oxygen being carried by the plasma will depend on the amount of hemoglobin concentration [Hb]p present in it and the capillary hematocrit. An increase in hemoglobin concentration in the plasma at a constant hematocrit causes an increase in the total hemoglobin concentration in the mixture. Figure 6 shows the PO2 distribution in the vascular and tissue compartments for [Hb]p = 0, 2.29, 4.58, 6.87, 9.16gdP[1] by keeping the hematocrit constant at 20%. Figure 6 shows

that the precapillary PO_2 gradients remain nearly the same when $[Hb]_p$ is decreased by 50% or increased by 50 and 100%. The change in precapillary PO_2 gradients is small even in the absence of hemoglobin in the plasma. Thus, the effect of hemoglobin concentration in the plasma on the transport of O_2 from the precapillary vessels is marginal under the present conditions. However, the PO_2 in the venules and tissue change significantly. The venous PO_2 is decreased/increased by 2.4/1.67 from 38.2mmHg when the $[Hb]_p$ is decreased/increased by 50%. The corresponding tissue PO2 is decreased/increased by 2.1/1.5 from 38.8 mmHg. In the absence of hemoglobin in the plasma, the calculated values of venous and tissue PO_2 are 34.5 and 33.6mmHg, respectively.

Figure 7(a) and (b) represent the distribution of PO2 in the network by decreasing/increasing the blood hematocrit by 10% from the control value of 20% for a constant and variable flow; the concentration of extracellular hemoglobin remains constant. The hematocrit can change significantly in anemia and polycythemia (Jones
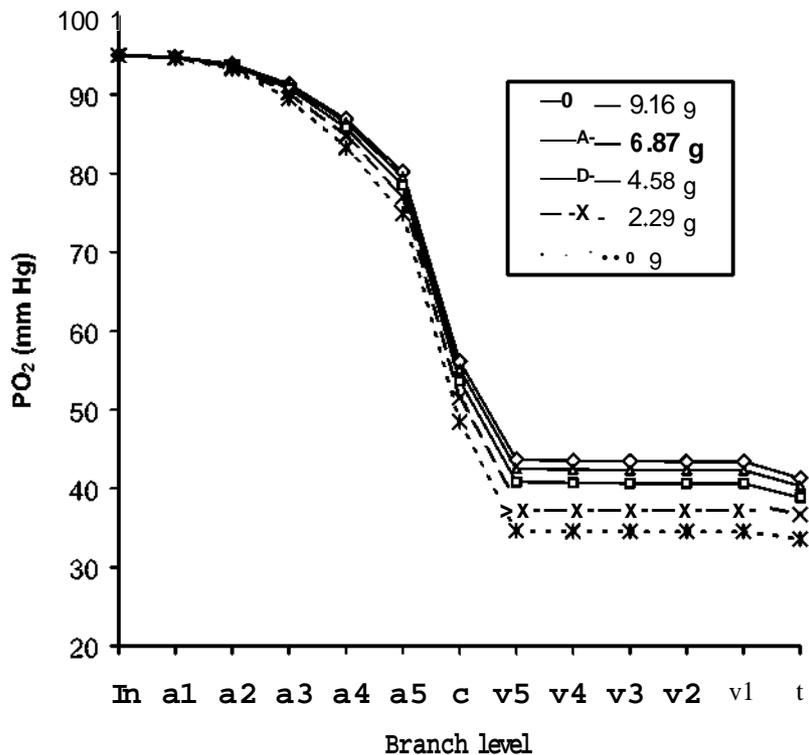

FIG. 6. Distribution of PO_2 in the vascular network for various values of hemoglobin concentration in plasma: (*) no hemoglobin; (x) 2.29gdT[1]; (•) -^g d l" [1]; (n) A 6.87gdl"[1]; *(0)* Q6 g dl^{-1}.
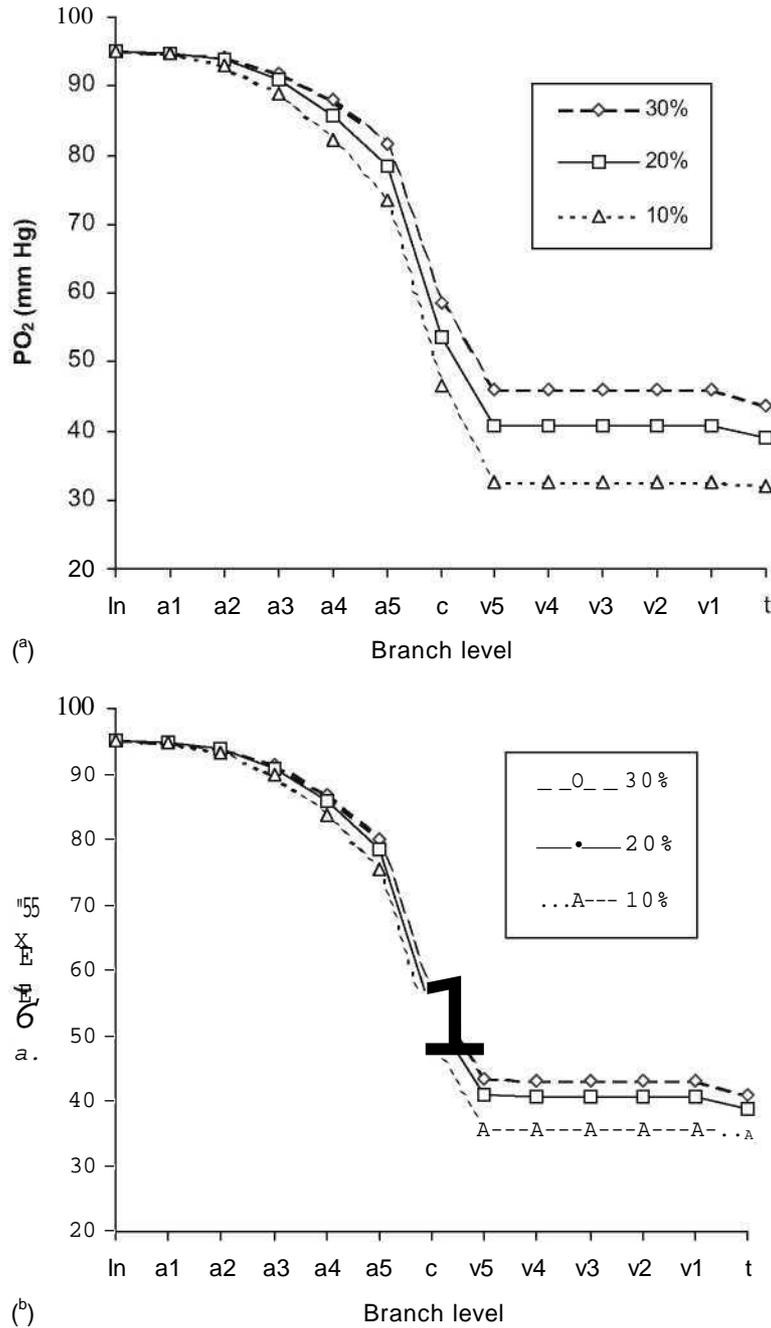
FIG. 7. (a) Distribution of PO_2 in the vascular network for various values of hematocrit *(H)* for constant flow: (——) H=30%; (F) H=20%; (.....) H=10%. (b) Distribution of PO_2 in the vascular network for various values of hematocrit *(H)* for variable flow: (——) H=30%; (F) H=20%; (......) H=10%.

et al., 1981; Massik *et al.,* 1987) and also as a result of hemodilution. The change in hematocrit is associated with a proportional change of hemoglobin concentration in the RBC. The change in hematocrit modifies the total oxygen content and the blood flow. For a constant flow, the precapillary PO_2 gradients increase as the hematocrit is reduced. The tissue PO_2 is decreased by 7mmHg as the hematocrit falls from 20 to 10%. The corresponding increase is 4.7mmHg with the rise in hematocrit from 20 to 30%.

Decrease in the blood hematocrit causes the viscosity of mixture to decrease and the flow rate

of the mixture to increase. When the flow rate is allowed to change with the hematocrit [eqn (10)], the difference between PO_2 at constant flow for increased or decreased hematocrit and control level at 20% hematocrit in a given compartment is decreased [Fig. 7(b)]. The tissue PO_2 is dropped by 4.3 mmHg when the hematocrit falls from 20 to 10%. When the hematocrit rises from 20 to 30%, tissue PO_2 increases by 2.2 mmHg.

For a constant flow, the increase in hematocrit increases the O_2 content in the mixture and causes an increase of tissue PO2. On the other hand, for constant O_2 content, the increase in hematocrit leads to a decrease of blood flow rate resulting in a decrease of tissue PO_2 [Fig. 5(b)]. In spite of these opposing tendencies, the model predicts that the tissue PO2 increases as the hematocrit increases [Fig. 7(b)].

Figure 8 presents the distribution of PO2 in the network with 50% elevation and 50% reduction of O2 consumption rate from control level for two values of $P50_p$ as 50 and 10 mmHg. The results show that the precapillary PO2 losses increase as the consumption rate is increased for

a given $P50_p$: Additional longitudinal PO_2 gradients occur as $P50_p$ is reduced. The venous and tissue PO_2 are reduced with an increase in consumption rate. The tissue PO_2 is lower than the venous PO_2 when the consumption rate is elevated by 50% from the control whereas it becomes higher than the venous PO_2 when the metabolic rate is reduced by 50% for both values of $P50p$. The prediction of tissue PO_2 lower/ higher than the venous PO_2 is consistent with the earlier studies (Ye et $al.,$ 1993, 1994; Sharan et $al.,$ 1998b).

In the discussion of the sensitivity of the results with respect to an individual parameter in Figs. 4-8, a fixed arterial PO2 is assumed. However, an alteration in the individual parameter might also affect oxygen transport processes in the lungs causing changes in the arterial PO_2.

Results computed from the present model in the presence of hemoglobin-based oxygen carriers are consistent with those obtained from the earlier validated model (Sharan et $al.,$ 1989, 1998a) on oxygen transport in brain circulation in the absence of blood substitutes. The
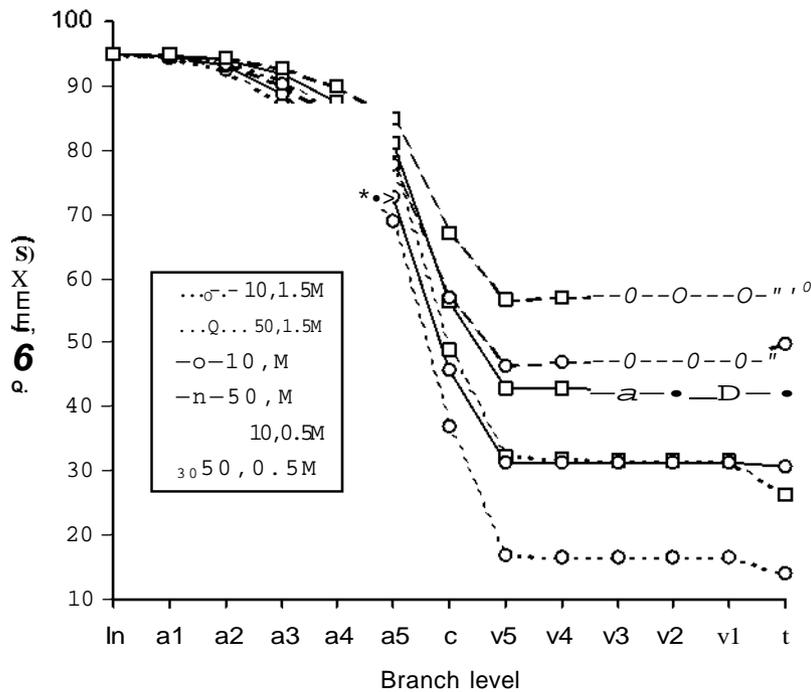

FIG. 8. Distribution of PO_2 in the vascular network for two values of $P50_p$ when oxygen consumption rate (M) is elevated/reduced by 50% from the control: (F) control; (——) 50% reduced; (......) 50% elevated; (&) P_{50p} = 50 mmHg; (J) P_{50P} = 10 mmHg.

variation of mean tissue PO_2 predicted from the model with various parameters pertaining to plasma hemoglobin is in qualitative agreement with the study on the transport of oxygen by RBC and hemoglobin solutions in the capillaries (Vadapalli *et al.*, 2002). However, the experimental measurements with hemoglobin-based oxygen carriers have not been carried out in sheep brain and, therefore, quantitative comparisons with experiments are not possible. Some experiments (Ulatowski *et ah,* 1996b, 1998) have been performed to analyse cerebral oxygen transport with plasma-based hemoglobin in cat during hypoxic hypoxia; the results of this study are in qualitative agreement with the experimental data. In the future, we will extend the model by constructing a suitable set of morphological parameters for the cerebral vascular bed of the cat and performing computer simulations for cat brain.

In the present model, the relationship between the relative viscosity of the blood and the tube diameter and hematocrit is used proposed by Pries *et al.* (1992) based on *in vitro* data. The flow computed from the model using *in vivo* viscosity relationship from Pries *et al.* (1994) is found to be 0.535 cm^3 s^1 equivalent to 42.8ml(100g~^{1})min~^{1} and this is lower than the measured flow 70ml(100g~^{1})min~^{1}. In order to predict the flow consistent with that measured, it is necessary to modify the length of the vessels at all the levels (Table 1). Further, relationship for relative viscosity *in vivo* has not been developed for sheep. Since the results computed using the set of morphological data constructed in our earlier study (Sharan *et al.,* 1989) are close to the measurements (Sharan *et ah,* 1998a) and the computed flow from the *in vitro* relationship is consistent with that measured, we have retained the same morphological data and accordingly we have used the *in vitro* relation for relative viscosity for comparing the results from the present model with those obtained for whole blood from the earlier model.

Conclusions

A compartmental model is formulated for oxygen transport in brain microcirculation in the presence of blood substitutes. The cerebrovascular bed is represented as a series of vascular compartments, on the basis of diameters, surrounded by a tissue compartment. A mixture of RBC and plasma/extracellular hemoglobin solution flows through the vascular bed from the arterioles through the capillaries to the venules. In the flow model, the relative viscosity of the blood dependency on the tube diameter and hematocrit proposed by Pries *et al.* (1992) *in vitro* is included. The dependence of the viscosity of the plasma on the hemoglobin concentration is also taken into account. The computed flow is found to be consistent with the measurements of whole blood. In the model, intravascular resistance and the diffusive loses of oxygen from the arterioles to the tissue are incorporated.

The model predicts that taking into account the amount of oxygen leaking from the arterioles in calculating the capillary transport conductance does not significantly affect the PO2 in the vascular and tissue compartments. The significant diffusion takes place at the level of capillaries. The computed venous blood PO2 is close to that measured in the experiments in the absence of extracellular hemoglobin. We have also found that:

(a) Precapillary PO_2 gradients increase as: PO_2 in the arterial blood increases; P_{50p} is reduced; the flow rate of the mixture decreases; hematocrit decreases at constant flow; metabolic rate increases; intravascular transport resistance in the arterioles is neglected;

(b) Precapillary PO_2 gradients are not sensitive to: (i) intracapillary transport resistance, (ii) cooperativity of oxygen with hemoglobin in plasma, (iii) hemoglobin concentration in the plasma and (iv) hematocrit when accounting for viscosity variation in the flow;

(c) For a given set of parameters, the PO_2 is almost the same in all the venular compartments;

(d) Tissue PO_2 increases as: arterial PO_2 increases; $P50_p$ rises; flow rate increases; hematocrit increases; hemoglobin concentration in the plasma rises; metabolic rate decreases; the capillary mass transfer coefficient increases or the intracapillary transport resistance decreases;

(e) Tissue PO_2 can be higher/lower than venous PO_2, depending on the choice of the parameters in the model;

(f) Tissue PO_2 increases as n_p increases from 1 to 3.23 and then it decreases with a further increase in n_p;

(g) Tissue PO_2 is not sensitive to the variation of intravascular transport resistance in the arterioles.

The predictions from the model are found to be consistent with those based on the whole blood. This model in brain will be validated either with the availability of experimental data with the hemoglobin-based oxygen carrier as blood substitute in sheep or in cat (Ulatowski *et ah,* 1996b, 1998) after constructing a set of morphological data for its cerebrovascular bed and performing computer simulations similar to those presented here.

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Appendix A

Derivation of Equations for O2 Transport in a Mixture of RBC, Plasma and Hemoglobin Solution in a Compartment

We consider a mixture of red blood cells, plasma and extracellular hemoglobin flowing through a tube of radius r_c. c and c^0 are, respectively, the concentration of O_2 dissolved in RBC and in the plasma/hemoglobin solution. y is the fractional saturation of hemoglobin with O_2 inside RBC and $/$ is the fractional saturation of extracellular hemoglobin with O_2. The RBCs are moving with velocity v_r and the solution of extracellular hemoglobin is moving with a velocity v_p: $h\partial r\text{Þ}$ is the volume fraction of RBCs and $1— h(r)$ is the volume fraction of plasma/

extracellular hemoglobin. According to the model proposed by Page *et al.* (1998), we briefly describe below the partial differential equations governing the oxygen transport by erythrocyte/hemoglobin solution mixtures.

Equations

THE RED BLOOD CELLS

Nair *et al.* (1989) have modeled the RBC phase as hemoglobin layer with the ratio of surface *(S)* to volume (V) of a RBC for estimating the intracellular resistance to oxygen transport. The interior of RBC is considered as a compartment with all intracellular and extracellular resistances lumped into mass transfer coefficients. Inside an RBC, the species are the oxygen, oxyhemoglobin and free hemoglobin. Since the hemoglobin molecule cannot penetrate through the cell membrane, the total hemoglobin concentration remains constant. The concentration of free hemoglobin can be expressed as a function of oxyhemoglobin concentration. Concentrations of oxygen and oxyhemoglobin inside an RBC are given by

$$v_r \frac{\partial}{\partial z} = -F\left[\frac{S}{V}\right]_{RBC} + C_H f(c,y), \quad \text{(A.I)}$$

$$v_r\frac{\partial}{\partial z}(C_H y) = -C_H f(c, \ y), \quad \text{(A.2)}$$

where C_H is the total hemoglobin concentration in RBC, F is the oxygen flux through the red cell membrane into the extracellular fluid and f represents the relationship between the fractional saturation of hemoglobin with oxygen and the concentration of oxygen. This relationship is described by the oxygen dissociation curve.

EXTRACELLULAR HEMOGLOBIN SOLUTION

In the extracellular fluid, oxygen is transported by molecular diffusion and convection in the free form and in combination with the hemoglobin. Also, an amount of oxygen is transported from the RBCs to the extracellular fluid. Concentrations of oxygen and oxyhemoglobin in the extracellular fluid are

governed by

$$(1-h(r))v_p \frac{dc'}{dz} = \frac{D_{O_2}'}{r}\frac{d}{dr}\left(r\frac{dc'}{dr}\right)$$

$$+ Fh(r)\left[\frac{S}{V}\right]_{RBC} + (1-h(r))C_{hb}f(c, \ y), \quad \text{(A.3)}$$

$$(1-h(r))\,v_p(r)\frac{\partial}{\partial z}(C_{hb}y') = \frac{D_{HbO_2}'}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}(C_{hb}y')\right)$$

$$-(1-h(r))C_{hb}f'(c',y') \quad \text{(A.4)}$$

where $D_O O_2$ and $D_{HbO}O_2$ are diffusion coefficients for O_2 and HbO_2 and C_{hb} is the total hemoglobin concentration in the extracellular fluid. In equations (A.3) and (A.4), the diffusion of O_2 and HbO_2 in the axial direction is ignored.

We assume chemical equilibrium of hemoglobin with oxygen inside the RBC as well as in extracellular fluid and neglect the transport resistance inside the RBC. From eqns (A.1-A.4), we have

$$v_r\frac{\partial}{\partial z}(c + C_H y) = -F\left[\frac{S}{V}\right]_{RBC}, \quad \text{(A5)}$$

$$(1-h(r))v_p(r)\cdot\left(c' + C_{hb}y'\right)$$

$$= \frac{D_{O_2}'}{r}\frac{\partial}{\partial r}\left(r\frac{dc'}{\partial r}\right) + Fh(r)\left[\frac{}{}\right]_{RBC}. \quad \text{(A.6)}$$

Adding eqns (A.5) and (A.6):

$$\frac{\partial}{\partial z}\left[(1-h(r))v_p(r)(c' + C_{hb}y')\right]$$

$$+ h(r)v_r(c + C_H y) = \frac{D_{O_2}'}{r}\frac{\partial}{\partial r}\left(r\frac{dc'}{\partial r}\right). \quad \text{(A.7)}$$

The resistance across the RBC membrane is small, implying the partial pressures of O_2 at the interface of RBC and extracellular fluid are continuous, i.e.

$$p = c/\alpha = c'/\alpha' = p', \quad \text{(A.8)}$$

where α and α^0 are solubilities of O_2 in RBC and extracellular fluid.

Taking the cross-sectional average in eqn (A.7), we get

$$2p \cdot \frac{d}{dz}\left[\int_0^{r_c} (\backslash\text{-}h(r))v_p(r)(c' + C_{hb}y')r\, \mathrm{d}r \right.$$

$$\left. + \int_0^{r_c} h\eth r\flat v_r \eth c \flat C_H y \flat r \, \mathrm{d}r \right]$$

$$= D'_{O_2} 2\pi \left[r \frac{\partial c'}{\partial r} \right]_{r_c}. \qquad (A.9)$$

Now we introduce the flow averages:

$$C_{pm} = \frac{2n\pounds v_p(r)(\backslash\text{-}h(r))c'r\,dr}{Q(1-H_D)}, \qquad (A.10)$$

$$S_{pm} = \frac{2n\pounds v_p(r)(\backslash\text{-}h(r))y'r\,dr}{Q(1-H_D)}, \qquad \eth A. 11\flat$$

$$C_{rm} = \frac{2\pi \ R\mathbf{f}^c\, v_r\eth r\flat\, h\eth r\flat cr\, dr}{QH_D}, \qquad (A.12)$$

$$S_{rm} = \frac{2n\pounds v_r(r)h(r)yr\,dr}{QH_D}, \qquad (A.13)$$

where,

$$Q_p l = Q(1 - H_D\flat = 2 \, \mathop{p}_{D0}^{\mathbf{f}^{r_c}} v_p\eth r\flat\, \eth 1 \text{ - } h\eth r\flat\flat r\, dr;$$

$$\eth A. 14\flat$$

$$Q_r = QH_D = 2 \, \mathop{p}_{D0}^{\mathbf{f}^{r_c}} v_r\eth r\flat\, h\eth r\flat r\, dr; \quad \eth A. 15\flat$$

and

$$Q = \mathop{\mathbf{f}^c}_{Jo} 2n v_h(r)r\,dr, \qquad \eth A. 16\flat$$

in which H_D is the discharge hematocrit and

$$v_b\eth r\flat = v_p(r)(l\text{- }h\eth r\flat\flat \flat v_r\eth r\flat\, h\eth r\flat; \ \eth A. 17\flat$$

Using the definitions from eqns (A.10)-(A.16) in eqn (A.9), we get

$$\frac{\partial}{\partial z}\, [Q(\backslash \text{ - } H_D\flat C_{pm} \flat QH_D \, C_{rm}\backslash$$

$$+ \frac{d}{@z}\, [Q(\backslash \text{ - } H_D\flat \, S_{pm}C_{hb} \flat QH_D C_H S_{rm}] = \ 2pr_c j_w;$$

$$\eth A. 18\flat$$

where j_w is the flux at the wall per unit area from the vessel wall.

Equation (A. 18) can be rewritten as

$$\frac{d}{\&} Q\eth C_m \flat S_m) = \ 2pr_c j_w; \qquad \eth A. 19\flat$$

where

$$C_m = \eth 1 \text{ - } H_D\flat C_{pm} \flat H_D C_{rm}; \qquad \eth A. 20\flat$$

$$S_m = \eth 1 \text{ — } H_D)C_{hb}S_{pm} + H_D C_H S_{rm}; \qquad (A.21)$$

in which S_m is the amount of oxygen carried by the hemoglobin in the mixture.

Integrating eqn (A. 19) with respect to z from 0 to z;

$$Q\eth C_m \flat S_m) = \ 2pr_c \mathop{I}_{c0}^{\mathbf{r}} j_w\, dz \flat \text{ constant}; \ \eth A. 22\flat$$

where the first term on the right-hand side represents the total flux J which can be expressed as

$$J = E\eth P_m \text{ - } P_t\flat \qquad \eth A. 23\flat$$

where E is the conductance, P_m is the mean partial pressure of O_2 in the vascular compartment and P_t is the corresponding partial pressure in the surrounding tissue compartment.

Equation for oxygen transport in a compartment becomes

$$Q(C_m^e - C_m^o) + Q(S_m^e - S_m^o) = E\eth P_m \text{ - } P_t\flat; \qquad \eth A. 24\flat$$

where the superscripts "e" and "o" denote the entry and outlet of the compartment. Notice that eqn (A.24) involves the unknowns $C_{pm;}$ $C_{rm;}$ S_{pm} and $S_{rm:}$ It is necessary to close eqn (A.24) by defining additional relationships. At the moment, it is not clear how to derive these in terms of flow-averaged variables. Ye *et al.* (1992, 1993) have derived the compartmental equation for the homogeneous blood by considering the cross-sectional averages which are in general valid for a uniform flow. Also, they have pointed out the discrepancy in evaluation of cross-sectional average of fractional saturation in terms of cross-sectional average of partial pressure.

In the present study, we assume that $p_{pm} = prm = pm$ i.^{e}. the averaged partial pressures in

the extracellular fluid, RBC and in the mixture are the same. This satisfies the relation (A.20) provided:

$$\alpha_m = (1 - H_D a^0) + H_D a; \qquad (A.25)$$

where a_m is the solubility of oxygen in the mixture.

Also, we assume that S can be expressed as a function of partial pressure of oxygen through oxygen dissociation curve in the RBC as well as extracellular fluid. Further, we take the flow average of S as the fractional saturation of hemoglobin with O2 evaluated using averaged partial pressure p_m. Accordingly, $S_{pm} = S_p(p_m)$ and $S_{rm} = S_r(p_m)$ where S_p and S_r will be described by a functional relationships for oxygen dissociation curves for extracellular fluid and RBC respectively. With these assumptions, eqn (A.24) will be well defined and involve only one unknown.

In terms of partial pressure, the transport of oxygen in a compartment is governed by

$$Q\alpha_m(p_m^e - p_m^o) + Q(S_m^e - S°) - E(P_m - P_t) = 0; \qquad (A.26)$$

where p is the partial pressure at the inlet/outlet of the compartment, P is the partial pressure inside the compartment and S_m is defined in terms of S_{pm} and S_{rm} through eqn (A.21). As a particular case when $a = a^0$ (solubilities in RBC and extracellular fluid are same) in eqn (A.25), the averaged dissolved concentrations of O2 in the extracellular fluid, RBC and mixture are the same.

Appendix B

Average PO2 in the Capillary Compartment

For computing the average PO_2 in the capillary compartment, we assume a linear drop of total concentration of O2 along the capillary in the form

$$C(z) = C_{am} - (C_{am} - C_{vm})\frac{z}{L}; \qquad (B.I)$$

where C_{am} and C_{vm} are the total oxygen concentrations corresponding to inlet and outlet

capillary PO_2, L is the capillary length and z is the coordinate along the capillary.

Equation (B.1) is a nonlinear algebraic equation in p_c (i.e. capillary PO_2), which is solved numerically using the method of bisection (Press et al., 1986).

Average partial pressure of O2 in the capillary is defined by

$$P_c = \frac{1}{L} \int_0^L p_c(z)\,dz; \qquad (B.2)$$

The integral in eqn (B.2) is evaluated numerically using Simpons's rule (Press et al., 1986).

Appendix C

Diffusion Conductance in the Capillary Compartment

The capillaries are modeled as a compartment with exchange properties equivalent to spatially averaged Krogh tissue cylinders with a modified boundary condition as described below. The steady-state transport of O2 in a tissue cylinder of radius r_t surrounding a capillary of radius r_c is governed by

$$D_t a_t \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial p_t}{\partial r}\right) - M = 0; \qquad (C.I)$$

where p_t is the partial pressure of O2 in the tissue, D_t is the diffusion coefficient of O2, a_t is the solubility coefficient of O2 and M is the metabolic rate assumed to be constant. It is assumed that the axial diffusion of O2 in the tissue is negligible as compared with the radial diffusion.

Equation (C.1) is subject to the following boundary conditions:

$$p_t(r_c, z) = p_w(r_c, z); \qquad (C.2)$$

$$\frac{\partial p_t}{\partial r} = j_c \qquad \text{at } r = r_t; \qquad (C.3)$$

where p_w is the PO_2 at the capillary-tissue interface, jc is the diffusive influx of O2 through the wall of the cylinder and z is the coordinate along the length of the capillary; jc will be determined from the mass balance in the compartmental model. The existing models

based on Krogh tissue cylinder assume that capillaries are the only source of O_2 to the tissue. However, there are experimental (Duling & Berne, 1970; Pittman & Duling, 1977; Duling *et al.,* 1979; Ivanov *et al.,* 1982; Swain & Pittman, 1989) and theoretical (Popel & Gross, 1979; Sharan & Popel, 1988; Sharan *et al.* 1989, 1998a; Weerapulli & Popel, 1989) studies demonstrating the losses of oxygen from the pre-capillary vessels. Thus, a part of oxygen diffuses in the tissue from the pre-capillary vessels and is exchanged with capillaries; this is taken into account by the diffusive influx term at the wall of the Krogh tissue cylinder.

Integrating eqn (C.1) and using the boundary conditions (C.2) and (C.3) to obtain

$$p_t \delta r; \; z \hspace{-0.1cm}P \; = \; p_w \delta r_c; \; z) + \frac{M}{2D_t\alpha_t}\left(\frac{r^2 - r_c^2}{2} - r_t^2 \, 2\ln\frac{r}{r_c}\right)$$

$$+ \; r_t j_\ell \ln\frac{r}{r_c}. \tag{C.4}$$

The average partial pressure of O_2, P_t; in the tissue cylinder of length L is defined as

$$P_t \; = \; \frac{1}{\%(yl_t \; - \; r_c^2)\pounds}\int_{(0)}^{L}\int_{r_c}^{r_t} 2prp_t \delta r; \; z\hspace{-0.1cm}P \; dr \; dz; \tag{ðC.5Þ}$$

Taking the average of eqn (C.4), we get

$$P_t = P_w \; + \frac{M}{8D_t\alpha_t}\left(3r_t^2 - r_{c\bar c}^{L-2} \; \frac{4r_t^7}{L\_\_L}I\ln\frac{r_c}{r}\right)$$

$$+ \; \frac{r_{tjc}}{r_t^2 - r_c^2}\left(r_t^2\ln\frac{r_t}{r_c} - r_t^2 \; - \frac{r_c^2}{2}\right), \tag{C.6}$$

in which

$$P^{TM} = 7\frac{1}{L}\int_{0}^{Z^L} P_w(r_c, z)dz. \tag{C.I}$$

Assuming the radial mixing of O_2 and neglecting the axial diffusion in comparison to convection, the transport of O_2 in the blood/mixture flowing through a capillary is governed by

$$\text{fif} \; = -2\pi r_c J, \tag{C.8}$$

where J is the flux of O_2 from the capillary to the tissue from per unit area per unit length, Q is the blood flow rate and C is the total oxygen content

defined as

$$C \; = \; a_{mpc} + PMPc) + \beta_p S_p(p_c), \tag{C.9}$$

in which a_m is the solubility coefficient in the mixture, S_r and S_p are the fractional saturations of hemoglobin with O_2 in the RBC and extracellular fluid, and b_r and bp_p are carrying capacities of hemoglobin inside the RBC and extracellular fluid respectively.

From the continuity of fluxes across the capillary-tissue interface:

$$J = -D_t\alpha_t\left[\frac{\partial p_t}{\partial r}\right]_{r=r_c}. \tag{ðC10Þ}$$

Using eqn (C.4), we get

$$J \; = \; -\frac{M}{(2r_c}\wedge \; -??) + D_t\alpha_t j_\ell\frac{r_t}{r_c}). \tag{C.11}$$

If the O_2 content in the blood entering the capillary at $z = 0$ with the partial pressure p_a; is C_a; the O_2 content along the capillary is obtained by integrating eqn (C.8) and using eqn (C. 11):

$$C(z) \; C \; C_a + \frac{2\pi}{Q}\left(\frac{M(r_c^2 - r_t^2)}{2} + r_c D_t\alpha_t j_\ell\right)z; \tag{ðC.12Þ}$$

This equation can be solved for the partial pressure $p_c \delta z \hspace{-0.1cm}P$ in the capillary. The average partial pressure of O_2 in the capillary is defined as

$$P_c = \frac{1}{L}\int_{0}^{L} p c\delta z\hspace{-0.1cm}P dz; \tag{C.I3}$$

The flux of O_2 from the capillary can be expressed as

$$J \; = \; h(P_c - P_w), \tag{ðC.14Þ}$$

where k_c is the mass transfer coefficient, the inverse of which, k_c^{-l}, characterizes the intracapillary resistance to oxygen transport (Roy & Popel, 1996; Vadapalli *et al.,* 2002).

Eliminating J from eqn (C.1 1) and (C.14) and taking the average in the capillary region, we get

$$P_w = P_c - \frac{1}{k_c}\left(\frac{M}{2r_c}if; \; - r_c^2\right) - D_t\alpha_t j_\ell \; r_t \; ; \tag{ðC.15Þ}$$

The diffusive flux for the compartment can be represented by the macroscopic transport equation:

$$J_c = N_c e (P_c - P_t), \qquad (C.16)$$

where N_c is the number of capillaries and e is the diffusion conductance. Total macroscopic flux of O_2 from capillary to tissue is

$$J_c = N_c M p \delta r_t^2 - r c^2 L - N_c D_t a_t j c 2 p r_t L. \qquad (C.17)$$

$$E_{exv} = \frac{2p N_c L D_t a_t \delta 1 - w^2 \delta 1 - g}{\left[-([1/(1 - w^2)] \ln (w) + (3 - w^2)/4) + y(\ln(w) + (1 - w^2)/2)] \right]'} \qquad (C.22)$$

Using the relations (C.6) and (C.15) - (C.17) we can express the diffusion conductance for the capillary compartment as

$$E_c = N_c e$$

$$= \frac{2p N_c L \delta 1 - w^2)(1 - y)}{[(1 - w^2)(1 - y)/r_c k_c - (l/2 D_t a_t) ([2/(1 - w^2)] \ln(w) + (3 - w^2)/2) + (y/D_t a_t) (\ln(w) + (1 - w^2)/2)]]} \qquad (C.18)$$

in which $w = r_c = r_t$ and g is the net dimensionless diffusive influx defined by

$$y = \frac{2 r_t D_t a_t j c}{M(r_t - r c^2_p)}. \qquad (C.19)$$

Equation (C.18) can be rewritten in terms of intravascular (E_{inv}) and extravascular (E_{exv})

conductances:

$$\frac{1}{E_c} = \frac{1}{\sim E_{tm}} + \frac{1}{E_{exv}}, \qquad (C.20)$$

which

$$F_{tm} = 2p N_c L r_c k_c \qquad (C.21)$$

and

If there is no diffusive influx from the wall of Krogh tissue cylinder $(g = 0)$, this reduces to the expression obtained in Sharan et al. (1998b). In the earlier model (Sharan et al., 1998a), the effect of intracapillary resistance on the diffusion conductance was not taken into account. If the intracapillary resistance is neglected, then $E_c = E_{exv}$.