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Theoretical analysis of effects of blood substitute affinity and cooperativity on organ oxygen transport

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Kavdia, Mahendra, Roland N. Pittman, and Aleksander S. Popel. Theoretical analysis of effects of blood substitute affinity and cooperativity on organ oxygen transport. J Appl Physiol 93: 2122–2128, 2002.—Hemoglobin-based O2 carriers (HBOCs), which are developed as an alternative to blood transfusion, provide O2 delivery. At present, there is no model to predict the O2 transport for a red blood cell-HBOC mixture on a whole organ basis. On the basis of the first principles of mass balance, a model of O2 transport for an organ was derived to calculate venous PO2 (PvO2) for a given inlet arterial PO2 (PaO2), blood flow, and oxygen consumption. The model was validated by using several in vivo animal studies on HBOC administration for a wide range of HBOC oxygen-binding parameters and predicted PvO2 for various PaO2 in the same species. The model was also used to predict the effect of HBOC affinity and cooperativity on PvO2 for humans. The results indicate that PvO2 can be increased at a constant blood flow-to-oxygen consumption ratio by reducing the affinity of HBOC for normoxia and mild hypoxia; however, a high-affinity HBOC would be more efficient in maintaining higher PvO2 for severe hypoxia (PaO2 < 40 Torr).

HEMOGLOBIN-BASED OXYGEN CARRIERS (HBOCs) are under clinical investigation as an alternative to red blood cells (RBCs) in transfusions (28). The potential advantages of HBOC transfusion include unlimited supply, prolonged storage, chemical purity, and no blood-matching requirements. Over the last decade, advances in biotechnology have provided HBOCs of a wide variety, including cross-linked hemoglobin, recombinant hemoglobin, and encapsulated hemoglobin (19). In addition, the properties of HBOCs, such as oxygen-binding parameters, viscosity, and NO reaction parameters, can be controlled.

Although major advances in the design of HBOCs have been made, uncertainties regarding the fundamental characteristics of oxygen transport still exist. A quantitative understanding of oxygen transport parameters in the presence of HBOCs could guide the design of HBOCs to provide oxygen delivery to tissue for a desired clinical application. The oxygen transport parameters of HBOCs or RBCs are characterized by the oxygen-hemoglobin equilibrium dissociation curve (ODC) that describes the fractional hemoglobin saturation as a function of PO2.

Both experimental and theoretical studies have been used to evaluate oxygen delivery by HBOCs that depend on the convective transport of oxygen, the level of tissue metabolism, and the oxygen dissociation parameters of the blood (HBOC and RBC mixture). In vivo experimental studies on several species such as cat, hamster, and pig with a wide range of HBOC oxygen transport parameters have been performed (2, 7, 8, 22). Experimental studies have demonstrated that HBOCs can improve tissue oxygenation. Theoretical studies of oxygen transport in the presence of HBOCs are limited. Vadapalli et al. (24) formulated a model of flow of HBOC and discrete RBCs in capillaries and showed that the mass transfer coefficient increases with HBOC concentration. Sharan and Popel (18) developed a compartmental model of brain microcirculation that included arterioles, capillaries, and venules for oxygen transport in the presence of HBOCs. The model evaluated the HBOC oxygen transport parameters for the sheep brain microcirculation. Page et al. (11) modeled oxygen transport in arteriolar-size tubes for solution containing a mixture of RBCs and HBOC. The model predicted that the mixtures of RBCs and HBOC transport oxygen more efficiently than the RBC suspension alone. An increase in oxygenation efficiency for a RBC-HBOC mixture in arteriolar-size tubes was also reported by McCarthy et al. (9).

The knowledge of oxygen transport by an HBOC-RBC mixture would also be important at the whole organ level for optimizing oxygen delivery by HBOCs and interpreting results from animal and clinical studies. Presently, no theoretical studies are available to assess the whole organ oxygen delivery in the presence of HBOCs. A number of experimental and theoretical studies evaluated the changes in the RBC oxygen consumption; partial pressure of oxygen at 50% hemoglobin saturation; oxygen dissociation curve; cat; hamster

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Theoretical analysis of effects of blood substitute affinity and cooperativity on organ oxygen transport

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transport parameters, such as hemoglobin-oxygen affinity on the oxygen delivery to tissue. Turek et al. (21) developed a model of oxygen transport to analyze the effect of hemoglobin-oxygen affinity on the mixed venous oxygen level for hypoxia. Willford et al. (27) used a similar model of oxygen transport to conclude that, for normoxia or moderate hypoxia, a right-shifted ODC is advantageous, whereas for severe hypoxia or increased metabolic rates a left-shifted ODC is desirable. Another theoretical study by Ropars et al. (14) reported that a right-shifted ODC is advantageous for normoxic conditions.

HBOCs or RBC-HBOC mixtures deliver oxygen differently from an RBC suspension (12). The transport characteristics of the mixtures depend on the affinities of both RBCs and HBOCs for oxygen, among other parameters. Therefore, there is a need for the analysis of oxygen transport with an RBC-HBOC mixture on a whole tissue or organ basis. In this study, we analyze existing in vivo animal studies of oxygen transport in the presence of HBOCs by using Fick’s principle (mass conservation). The analysis is subsequently extended to provide a framework for oxygen transport with HBOCs in humans.

METHODS

We consider a macroscopic volume of tissue that may represent a whole organ or a part of it. The tissue is perfused by a mixture of RBCs and plasma; the plasma phase may contain HBOCs or volume-expanding solutions such as albumin and dextran. The oxygen balance for the tissue is as follows: total oxygen consumed by tissue (organ) = total oxygen in – total oxygen out. This conservation of mass equation can also be written as

$$V_{O_2} = Q[(\alpha_O P_{O_2} + \rho_{O_2} S_{O_2}(P_{O_2}) + \beta_{hbO_2} S_{hbO_2}(P_{O_2}))$$

$$- [\alpha_V P_{O_2} + \beta_{hb} S_{hb}(P_{O_2}) + \beta_{hbO_2} S_{hbO_2}(P_{O_2})]]$$ (1)

where $V_{O_2}$ is the oxygen consumption of tissue, $Q$ is the blood flow in the tissue, $\alpha_O$ is the blood oxygen solubility coefficient, $P_{O_2}$ and $P_{V_2}$ are the arterial (inlet) and venous (outlet) $P_{O_2}$, respectively, $\beta_{V_2}$ and $\beta_{hb}$ are the oxygen-carrying capacities of RBCs and HBOC, respectively (proportional to the corresponding hemoglobin concentrations), and $S_{hb}$ and $S_{hbO_2}$ are the fractional hemoglobin oxygen saturations for RBCs and HBOC, respectively. We assume here that $P_{O_2}$ is the same in the arterial blood, i.e., there are no $P_{O_2}$ gradients between the RBCs and the HBOC solution; the same holds for venous blood. This assumption is justified from the calculation of change in $P_{O_2}$ over a small distance $\delta$ from an RBC by using the equation

$$K \frac{\Delta P_{O_2}}{\delta} = O_2 \text{flux from single RBC} = \frac{\Delta \rho}{n} \frac{2 \pi R J_w}{n \lambda_{rbc}}$$ (2)

where the change in the $P_{O_2}$ is $\Delta P_{O_2}$, the Krogh diffusion coefficient is $K$, the oxygen flux at the arterial wall is $J_w$, the internal radius of the artery is $R$, the surface area of an RBC is $A_{rbc}$, and the number of RBCs per unit length of artery is $n$. The value of the Krogh coefficient is $6.15 \times 10^{-10}$ ml O$_2$ cm$^{-1}$ Torr$^{-1}$ s$^{-1}$, which is the product of an oxygen diffusivity of $2.18 \times 10^{-5}$ cm$^2$/s and an oxygen solubility of $2.82 \times 10^{-5}$ ml O$_2$ cm$^{-3}$ Torr$^{-1}$ in plasma (3). The typical range of $J_w$ is $1–10 \times 10^{-6}$ ml O$_2$ cm$^{-2}$ s$^{-1}$ (25). The human

RBC surface area and volume ($V_{rbc}$) are $135 \mu m^2$ and 95 $\mu m^3$, respectively (4). For an artery with a 1,000-$\mu m$ radius, hematocrit (Ht) of 0.45, and $V_{rbc}$ of 95 $\mu m^3$, $n/\Delta \rho$ (Ht$\pi R^2$/$V_{rbc}$) is $1.5 \times 10^6$ RBC/cm. These values provide a $\Delta P_{O_2}$ range of $0.01–0.05$ Torr. $\Delta P_{O_2}$ is small; therefore, the assumption of no $P_{O_2}$ gradients between the RBC and HBOC solution in the arterial and venous blood is justified. Another assumption implicit in Eq. 1 is that the free and bound oxygen are in chemical equilibrium; hence the ODCs are used. It has been shown in a number of theoretical studies that this assumption is valid under most conditions (13), even for the microvessels; it is certainly justified for the arteries and veins in which the fluxes of oxygen per RBC are small.

The fractional equilibrium hemoglobin-oxygen saturation is a function of $P_{O_2}$ described by the ODC. The ODC can be represented by several relationships (13, 17); however, only the parameters of the Hill equation have been reported for HBOCs (22). The Hill equation for RBCs and HBOCs is

$$S_{rbc} = \frac{P_{O_2}^{n_{rbc}}}{P_{O_2}^{n_{rbc}} + P_{O_2}^{n_{rbc}}}, S_{hbO_2} = \frac{P_{O_2}^{n_{hbO_2}}}{P_{O_2}^{n_{hbO_2}} + P_{O_2}^{n_{hbO_2}}}$$ (3)

where $P_{O_2}$ is $P_{O_2}$ at 50% hemoglobin saturation, and $n_{fl}$ is the Hill coefficient; these coefficients characterize oxygen affinity and cooperativity, respectively. $P_{O_2}$ plays an important role in the release of oxygen from hemoglobin. At high $P_{O_2}$ (low affinity, right-shifted ODC), hemoglobin would release oxygen readily at high values of $P_{O_2}$, whereas at low $P_{O_2}$ (high affinity, left-shifted ODC), oxygen release does not occur until low $P_{O_2}$ values are reached. Note that the ODC can be different for RBCs and HBOCs (i.e., different $P_{O_2}$ and $n_{fl}$).

The above equations can be used to investigate the dependence of physiological variables on the properties of HBOCs for given parameters of RBCs. The oxygen delivery to the tissue is assumed to be above the critical limit, where organ oxygen consumption is constant and independent of $P_{O_2}$. For a given $Q$, oxygen consumption rate or metabolic demand ($V_{O_2}$), and $P_{O_2}$, Eq. 1 can be solved to obtain $P_{V_2}$. Equation 1 was solved for $P_{V_2}$ by using the Solver feature of Microsoft Excel 2000.

RESULTS

Equation 1 involves several assumptions, including uniform $P_{O_2}$, uniform $P_{O_2}$, and constant $V_{O_2}$. The model is validated by using results from in vivo studies of oxygen transport in whole organs with administration of HBOCs. We used the data on oxygen transport with HBOC transfusion in cat brain (22, 23) and hamster dorsal skinfold (7). We briefly summarize the experimental parameters and results and present our model predictions.

Model validation: study 1. In a study of cerebral oxygen transport by Ulatowski et al. (23), cats were divided in the three groups of no transfusion, albumin exchange transfusion, and hemoglobin exchange transfusion. HBOC values of $P_{O_2}$ and $n_{fl}$ were 34 Torr and 2.2, respectively, for the cross-linked hemoglobin [prepared from outdated human blood by using the method described in Ulatowski et al. (23)] transfusion. The basal level of oxygen consumption was reported at 3.4 ml O$_2$ min$^{-1}$ 100 g$^{-1}$. The typical cat RBC values for $P_{O_2}$ and $n_{fl}$ are 36.4 Torr and 2.6, respectively.

Baseline (before transfusion) parameters were arterial Ht = 31, 30, and 29%, respectively, for the three
groups; \( \text{PaO}_2 = 120, 123, \) and 122 Torr; and cerebral \( Q = 53, 56, \) and 56 \( \text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1} \). On the basis of our model, the predictions for \( \text{PvO}_2 \) are 37.7, 38.7, and 37.9 Torr, respectively, for the three groups, which is in good agreement with the reported \( \text{PvO}_2 \) of 36.2, 39.0, and 40.0 Torr, respectively.

After exchange transfusion, the parameters were arterial \( \text{Ht} = 31, 21, \) and 21%, respectively, for the three groups; \( \text{PaO}_2 = 120, 119, \) and 126 Torr; and cerebral \( Q = 60, 79, \) and 67 \( \text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1} \). The predicted \( \text{PvO}_2 \) are 41.0, 39.7, and 40.3 Torr, respectively, for the three groups. The experimentally measured \( \text{PvO}_2 \) are 39.4, 38.7, and 38.1 Torr, respectively, for the three groups, is shown with the predicted \( \text{PvO}_2 \) in Fig. 1. In addition, the predictions of \( \text{PvO}_2 \) for changing \( \text{PaO}_2 \) in the range 0–120 Torr are also shown for all three groups. The predictions of \( \text{PvO}_2 \) are in good agreement with the measured \( \text{PvO}_2 \) for HBOC \( P_{50} \) and \( n_H \) that are similar to the native blood values.

Model validation: study 2. The second study was also on cat cerebral oxygen transport for isovolemic exchange transfusion (22). The cats were again divided into three groups: no transfusion, albumin exchange transfusion, and hemoglobin-exchange transfusion. In this study, HBOC \( P_{50} \) and \( n_H \) were 17 Torr and 1.7 for the bovine cross-linked hemoglobin (prepared according to the method described in Ulatowski et al. (22)); these values are significantly different from the native RBC values of \( P_{50} \) and \( n_H \) of 36.4 Torr and 2.6, respectively. \( \text{PaO}_2 \) (~160–180 Torr) is different in this study and was maintained at >100 Torr by administering supplemental oxygen compared with the \( \text{PaO}_2 \) of study 1 (~120 Torr), which was maintained between 80 and 120 Torr by administering supplemental oxygen.

After 180 min of exchange transfusion, the parameters were arterial \( \text{Ht} = 32, 18, \) and 19%, respectively, for the three groups; \( \text{PaO}_2 = 166, 180, \) and 162 Torr; and cerebral \( Q = 34, 65, \) and 41 \( \text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1} \). On the basis of a cerebral oxygen consumption of 3.4 ml \( \text{O}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1} \) (same as in study 1), the predicted \( \text{PvO}_2 \) of 33.9, 37.7, and 29.6 Torr are in good agreement with the experimental values of 34.0, 39.0, and 29.0 Torr, respectively, for the three groups. Figure 2 shows \( \text{PvO}_2 \) profiles for varying \( \text{PaO}_2 \) in addition to the close agreement between the experimentally measured \( \text{PvO}_2 \) and the predicted \( \text{PvO}_2 \) at 180 min of exchange transfusion.

Model validation: study 3. To validate the model in a different species and different conditions, we used a fluid resuscitation study of hemorrhagic shock in conscious male Syrian hamsters by Kerger et al. (7). The study compared the efficacy of cell-free hemoglobin (Hemolink, Hemosol, Etobicoke, ON, Canada; \( P_{50} = 17 \) Torr and \( n_H = 1.6 \)) with dextran 70 and other conventional resuscitation fluids for hemorrhagic shock. For the predictions, we use a \( \text{Vo}_2/Q \) of 0.065 ml \( \text{O}_2/\text{ml} \) of blood flow, which is calculated from the whole body values of male Syrian hamsters (26). The hamster RBC \( P_{50} \) and \( n_H \) are assumed to be 28 Torr and 2.8 (15). Control \( \text{PaO}_2 \) were 70.6 and 63.6 Torr, respectively, for Hemolink and dextran 70 groups. Hemoglobin concentration was 14.5 g/dl, and \( \text{Ht} \) was 48%. For control, the estimated \( \text{PvO}_2 \) values of 34.4 and 33.2 Torr, respectively, are in good agreement with the reported value of ~34 Torr for both groups (shown in Fig. 3 as a single point at \( \text{Pa}_O_2 = 67 \) Torr). Shock was induced by hemorraging to 50% of an animal’s total blood volume within 30 min. After 2 h, animals were resuscitated with Hemolink, dextran 70, and other fluids. After fluid resuscitation, \( \text{Pa}_O_2 \), hemoglobin, and \( \text{Ht} \) were 70.6 Torr, 8.9 g/dl, and 18.8%, and 110.3 Torr, 4.8 g/dl and 17.1%, respectively, for Hemolink and dextran 70. 

\( Q \) decreased to ~50% of the control flow; therefore, \( \text{Vo}_2/Q \) is changed to 0.125 ml \( \text{O}_2/\text{ml} \) of blood flow. With the use of Eq. 1, we estimate the mixed \( \text{PvO}_2 \) to be 14.6 and 3.9 Torr, respectively, for Hemolink and dextran 70, which agrees well with the reported values of 16 and 3.
Torr. Figure 3 shows the predictions of $P_{vO_2}$ for varying $P_{aO_2}$ within a wide range. Recently, Nagababu et al. (10) reported $P_{50}$ and $n_H$ values for Hemolink of 51 Torr and 0.97, respectively. With these values of $P_{50}$ and $n_H$ for the HBOC, the calculated value of $P_{vO_2}$ is 11.2 Torr, which is in the range of the experimentally measured $P_{vO_2}$ considering the uncertainties involved in parameters including the oxygen-transport parameters.

Predictions of the effect of HBOC $P_{50}$ on $P_{vO_2}$ for humans. We now apply Eq. 1 to simulate oxygen transport in the human circulation in the presence of an HBOC. Typical ODC parameters for human RBCs are assumed at $P_{50}/H_1 = 27$ Torr and $n_H/\Delta H = 2.7$. For different HBOCs, the reported values of $P_{50}$ vary within a wide range of 3.4 to 52.6 Torr (5). In these simulations, we assumed $n_H = 2.7$ for HBOC. To simulate oxygen transport in different organs and under different conditions, we vary the ratio of $V_{O_2}/Q$.

Figure 4 shows the mixed venous oxygen pressure for an HBOC-RBC mixture for varying HBOC $P_{50}$ for three different values of the $V_{O_2}/Q$ ratio. For the control case, $Ht$ is 45% and yields 15 g/dl of hemoglobin in the blood. For all other cases, $Ht$ is 15%, and the HBOC concentration in the blood is 5 g/dl. Thus the total hemoglobin concentration in the blood is 10 g/dl except for the control case. The typical value of the $V_{O_2}/Q$ ratio is 0.04 ml O$_2$/ml of blood flow for human heart (1); a similar value is estimated for heart. The mixed $P_{vO_2}$ as a function of $P_{aO_2}$ is shown in Fig. 4A. The calculations predict that a HBOC with $P_{50} = 40$ Torr would maintain $P_{vO_2}$ for normal $P_{aO_2}$ (normoxia). However, for severe hypoxic conditions, a $P_{50}$ of <20 Torr would be desirable to maintain $P_{vO_2}$ above zero. The mixed $P_{vO_2}$ variation for a low and a high $V_{O_2}/Q$ ratio value is also shown in Fig. 4, B and C, respectively. An HBOC with a $P_{50} = 40$ Torr would result in a higher $P_{vO_2}$ compared with the control case for low metabolism tissue (Fig. 4B). However, for tissue with high metabolism, even a HBOC with a $P_{50}$ of 40 Torr is inadequate to maintain $P_{vO_2}$ above anoxemia under conditions of arterial hypoxemia (Fig. 4C).

Fig. 3. In vivo hamster study. $P_{50}$ and $n_H$ for HBOC are 31 Torr and 1.6, and the native $P_{50}$ and $n_H$ are 28 Torr and 2.8. All symbols are same as in Fig. 1.

Fig. 4. Effect of HBOC affinity ($P_{50}$). The control-case represents hematocrit of 45% that yields 15 g/dl of hemoglobin in the blood. For all other cases, hematocrit is 15% and the HBOC concentration in the blood is 5 g/dl. $P_{50}$ and $n_H$ for red blood cells (RBC) are 27 Torr and 2.7, which are typical values for humans. The $n_H$ for HBOC is assumed to be 2.7. A: $P_{vO_2}$ profile for a typical value of oxygen consumption-to-blood flow ($V_{O_2}/Q$) ratio of 0.04 ml O$_2$ consumed/ml of blood flow for human heart and brain. B and C: $P_{vO_2}$ profiles for a lower and a higher $V_{O_2}/Q$ ratio of 0.02 and 0.06, respectively.
Figure 5, A–C, shows the PvO₂ profiles for constant PaO₂ of 100, 50, and 25 Torr, respectively. The PvO₂ profile is affected on the basis of the arterial condition of normoxia to severe hypoxia. The higher the P₅₀, the higher is the predicted PvO₂ for all Vo₂/Q ratio values for PaO₂ of 100 and 50 Torr. However, for PaO₂ = 25 Torr, the behavior of PvO₂ is nonmonotonic with respect to P₅₀, and an optimal P₅₀ of ~15 Torr results in the highest PvO₂ for most Vo₂/Q ratio values (Fig. 5C).

Predictions of the effect of HBOC cooperativity on PvO₂ for humans. Figure 6 shows the mixed PvO₂ for a mixture of RBCs and HBOC for varying HBOC cooperativity and for three different values of P₅₀. The control case is the same as in the previous section, with a Ht of 45%, which corresponds to 15 g/dl of hemoglobin in the blood, and the typical values of P₅₀ and nₜ for RBCs being 27 Torr and 2.7, respectively. For all other cases, Ht is reduced to 15% and HBOC concentration in the blood is 5 g/dl, thus yielding 10 g/dl hemoglobin concentration in the blood. The nₜ for HBOC is varied between 1 and 3.3. The value nₜ = 1 corresponds to noncooperative binding, and nₜ = 3.3 corresponds to very strong cooperativity. The mixed PvO₂ for a Vo₂/Q ratio of 0.04 ml O₂/ml blood flow are shown for HBOC P₅₀ of 5, 27, and 40 Torr in Fig. 6, A–C, respectively. The effect of cooperativity on PbO₂ is reversed for P₅₀ of 5 and 20–40 Torr; nₜ = 1 provides the highest PbO₂ for normal PaO₂, for a P₅₀ of 5 Torr compared with the lowest PbO₂ for a P₅₀ of 20 and 40 Torr.

DISCUSSION

This study of oxygen transport utilizing a mathematical model based on Fick's principle accomplished three objectives. First, we validated the model by using existing in vivo animal studies on HBOC administration for a wide range of HBOC oxygen-binding parameters; thus the model can be used to interpret experimental results. Second, we applied the model to predict mixed venous oxygen pressure for various PaO₂ values in the same animal species. Third, the model was used to predict the effect of HBOC oxygen affinity and cooperativity on the mixed PvO₂ for humans.

The developed model extends the analyses of the effect of RBC hemoglobin-oxygen affinity in hypoxia (21, 27). Turek et al. (21) and Willford et al. (27) used the arteriovenous oxygen saturation difference to analyze when a right- or left-shifted ODC is advantageous for oxygen delivery to tissue, as evidenced by higher P₅₀. These studies concluded that a low oxygen affinity results in favorable oxygen delivery only during normoxia and moderate hypoxia, whereas high affinity is advantageous in severe hypoxic conditions. For an RBC-HBOC mixture, the analysis becomes more complex because the oxygen-binding characteristics of the hemoglobin in RBCs and the HBOC may be different. The oxygen affinity and cooperativity of hemoglobin depend on several factors, including pH, temperature, and ion concentration, both for the HBOC and for the hemoglobin inside RBC. These factors vary with physiological conditions and may even vary from organ to organ.
organ. For HBOCs, we used the experimentally measured oxygen affinities at 37°C. The oxygen-carrying capacity of the whole blood is increased by exchange transfusion with an HBOC compared with albumin; but it can either increase or decrease on exchange transfusion with an HBOC compared with a RBC transfusion. Oxygen delivery for an RBC-HBOC mixture is affected by several factors, including the RBC and HBOC oxygen affinity and cooperativity, the composition of RBC-HBOC mixture, the metabolic state of the tissue, and PaO₂, as demonstrated in Figs. 4–6. Although the model (Eq. 1) represents the conservation of mass of oxygen (Fick’s principle), it is based on several assumptions: uniform PaO₂ (i.e., the inlet PO₂ in the RBCs and plasma is the same), uniform PvO₂, and chemical equilibrium between free and bound oxygen. We theoretically showed that these assumptions should be valid, and we also validated the model against several in vivo studies with RBC-HBOC mixtures. Figures 1–3 demonstrate that the model predictions are in good agreement with the experimental studies on cats and hamsters within a wide range of RBC and HBOC oxygen-binding parameters.

One of the limitations of the presented analysis is that only the mixed PvO₂ is predicted and not the tissue PO₂, which is important to estimate the metabolic state of the tissue. Sharan et al. (16) studied the relationship between tissue PO₂ and end-capillary PO₂ and demonstrated that the tissue PO₂ can be higher or lower than the end-capillary PO₂ depending on physiological conditions. Sharan and Popel (18) showed that the magnitude of the change in tissue PO₂ and PvO₂ is different depending on the cooperativity of HBOC. Therefore, prediction of tissue PO₂ in the presence of a HBOC requires a more detailed model, e.g., as developed by Sharan and Popel (18) or Vadapalli et al. (24). The model can be applied to predict the PO₂ exiting a small volume of tissue. For the small volume of tissue, the PaO₂ and PvO₂ in Eq. 1 are replaced by tissue inlet PO₂ and outlet PO₂, respectively. If more than one inlet or outlet of blood is present, then the flow-weighted PO₂ should be used. This approach can be used to assess oxygen transport in tissues such as tumors under hypoxic conditions (6), where inlet PO₂ is significantly lower than PaO₂.

The predictions of our model are in agreement with other theoretical models dealing with an RBC-HBOC mixture. Our model predictions of PvO₂ are similar to the PvO₂ values obtained from the detailed compartmental model of the brain microcirculation of Sharan and Popel (18); this is expected since Fick’s Principle represented by Eq. 1 should be part of any model, regardless of model details. As seen in Figs. 4 and 5, the mixed PvO₂ is affected significantly by the affinity of the HBOC at 50% extracellular hemoglobin, which is in agreement with the predictions by Page et al. (11). In addition, the prediction that high-affinity HBOC is less effective in maintaining PvO₂ than low-affinity HBOC in normoxia, under the assumption of constant VO₂, is in agreement with other theoretical models (11, 18). Our model predicts that the mixed PvO₂ can be
increased at a constant $Q$ by reducing the affinity of hemoglobin for oxygen. In addition, the model predicts that in severe hypoxia ($P_{O_2} < 40$ Torr) a high-affinity HBOC would be more efficient in maintaining a higher $P_{O_2}$. These predictions for an RBC-HBOC mixture are similar to the predictions for whole blood, which are reduced $P_{50}$ of RBCs for severe hypoxia and higher $P_{50}$ for normoxia or moderate hypoxia results in higher values of $P_{O_2}$ (21, 27). For severe hypoxia, our model predicts that an optimal $P_{50}$ of 15 Torr maximizes the mixed $P_{O_2}$.

The model also analyzed the role of cooperativity on the mixed $P_{O_2}$. High cooperativity of a low affinity HBOC is important to maintain the mixed $P_{O_2}$, as shown in Fig. 6. However, an HBOC with low cooperativity leads to a higher mixed $P_{O_2}$ for a high-affinity HBOC.

The appropriate HBOC oxygen-transport parameters have not yet been completely determined. The oxygen affinity of blood is an important factor in determining oxygen delivery to tissues. HBOCs with an oxygen affinity similar to or lower than that of RBCs should facilitate oxygen unloading by increasing the arteriovenous difference. However, it has been reported that faster release of oxygen (i.e., low-affinity HBOC) could be disadvantageous because it could lead to regulatory vasoconstriction and/or decreased functional capillary density in the peripheral circulation (20). The reported values of $P_{50}$ for HBOCs under development range from 3 to 53 Torr (5), which is the range we explored in our analysis. Our analysis suggests that optimum values of HBOC oxygen affinity and cooperativity may depend on the physiological or pathophysiologcal conditions under which HBOC is administered, e.g., these parameters may be specific to different tissues and conditions. Therefore, the presented analysis may serve as a guide for determination of optimal values of HBOC parameters.

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