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Mathematical Modeling of Oxygen Transport Near a Tissue Surface: Effect of the Surface PO_2

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Abstract

The effect of the surface oxygen tension on the oxygen-tension distribution in the tissue is considered. A mathematical formulation of the problem is presented, and the solutions are obtained numerically using a finite-element method. It is shown that the oxygen tension at the surface of the tissue may significantly affect the oxygen-tension distribution in layers of tissue situated within several intercapillary distances below the surface.

1. Introduction

Measurements of tissue oxygen tension (PO_2) with oxygen microelectrodes are most valuable when combined with intravital microscopy, but are limited to the vicinity of the tissue surface superfused with a solution containing a certain percentage of oxygen [1–6]. Variation of the solution PO_2 may cause variation of PO_2 in the surface layers of the tissue accompanied by variation of the capillary velocities [2, 3, 5–7], the capillary hematocrit [7], the density of flowing capillaries [3, 8], and the inlet capillary PO_2 [2]. Therefore, oxygen transport in surface layers of tissue is a complex process that may involve many factors. A careful analysis of these factors is needed in order to separate regulatory adjustments of the microcirculation from “passive” effects of diffusion and convection. Obviously, the Krogh cylinder model [9], widely used for estimates of oxygen delivery in deep layers of tissue, generally cannot be applied to the surface layers. In the present paper a mathematical model of oxygen transport in the surface layers of tissue is formulated, and the effect of the surface PO_2 on the tissue PO_2 is analyzed while such variables as capillary velocities, capillary hematocrit, intercapillary distances, and oxygen consumption rate remain constant. In subsequent papers the effect of variation of these parameters on the oxygen transport in surface layers of tissue will be examined.

2. Mathematical Model

Consider a slab of tissue bounded by plane surfaces $-\infty < x < \infty$, $0 \leq y \leq H$, $0 \leq z \leq L$, as shown in Figure 1. The capillaries are parallel to the surface of the tissue and form a square lattice. The intercapillary distances equal $2d$, and the distance between the tissue surface and the row of capillaries closest to the surface is d_1 .

Steady-state oxygen transport in the tissue is governed by the diffusion equation

$$D\alpha\nabla^2 P - M=0, \quad (1)$$

where D is the oxygen diffusion coefficient, α is the solubility coefficient, P is the tissue oxygen tension, and M is the oxygen consumption rate per unit volume of tissue.

It has been shown that the oxygen transport equation for the capillary lumen can be written in the form [10, 11]

$$\pi r^2 v_i \frac{\partial}{\partial z} [\alpha_b P_i + C_i \psi(P_i)] = -J_i, \quad i=1, 2, \dots, \quad (2)$$

where the left-hand side is a derivative of the flux of oxygen through a cross-section of the capillary (see Appendix). In Equation (2) r is the capillary radius, v_i is the velocity of blood in the i th capillary, α_b is the solubility coefficient of oxygen in blood, P_i is the mixing-cup oxygen tension in the i th capillary, C_i is the oxygen-binding capacity of blood, ψ is the oxygen saturation fraction of hemoglobin, and J_i is the oxygen flux from the capillary to the tissue per unit length of the capillary.

The oxygen tensions $P(x, y, z)$ and $P_i(z)$ satisfy the following boundary conditions. At the tissue surface the tissue PO_2 is given

$$P=P_s \quad \text{at} \quad y=0. \quad (3)$$

At the lower tissue surface the no-flux boundary condition is imposed:

$$\frac{\partial P}{\partial y}=0 \quad \text{at} \quad y=H. \quad (4)$$

At the capillary-tissue interface the oxygen tension is continuous, and the oxygen flux from the capillary, J , is equal to the total oxygen flux into the tissue:

$$P=P_i, \quad J_i = -D\alpha \int_{\Gamma_i} \frac{\partial P}{\partial n} d\Gamma_i \quad \text{on} \Gamma_i \quad (5)$$

where Γ_i is the intersection of the i th capillary cylinder with a plane $z = \text{const}$, and $\partial/\partial n$ denotes the derivative in the direction of the outward normal to Γ_i in the plane $z = \text{const}$. At the arterial end of the capillary the intracapillary PO_2 is given by

$$P_i=P_{ai} \quad \text{at} \quad z=0. \quad (6)$$

It is realized that Equation (2) might be an oversimplification in view of recent analyses by Hellums [12], who pointed to a potential intracapillary radial resistance to diffusion of oxygen, and by Fletcher [13], who took into account nonlinear kinetics of oxygen binding by hemoglobin. Both factors could be incorporated into the theory; however, it is felt at this point that excessive details might cloud the main issue under consideration, i.e. the effect of the tissue surface PO_2 .

Replacement of the boundary condition (3) above with

$$\frac{\partial P}{\partial y}=0 \quad \text{at} \quad y=0$$

corresponds to a sealed tissue surface. This boundary condition will be used to compare oxygen distributions in the case of a sealed boundary and in the case of specified PO_2 at the surface.

Assuming that capillary oxygen distributions in horizontal rows are identical, the spatial domain can be reduced to $0 \leq x \leq d, 0 \leq y \leq H, 0 \leq z \leq L$ (Figure 1, darkened area), with the no-flux boundary condition, $\partial P / \partial x = 0$, on the tissue portion of the planes $x = 0$ and $x = d$.

If all second derivatives in the Laplace operator in (1) are of importance, the described mathematical formulation is incomplete without some kind of boundary conditions on the tissue portion of the planes $z = 0$ and $z = L$. In the present work the so-called axial diffusion and, associated with it, the second derivative in (1) in the direction parallel to the capillary axes are neglected (the effect of axial diffusion is discussed in [14, 15]); thus Equation (1) reduces to the form

$$D\alpha \left(\frac{\partial^2 P}{\partial x^2} + \frac{\partial^2 P}{\partial y^2} \right) - M = 0. \quad (7)$$

In this case the mathematical formulation of the problem is complete and no additional boundary conditions are required.

3. Parameters of The Model

This study is not aimed at a quantitative description of the PO_2 distribution in any particular tissue under realistic experimental conditions, but rather at an investigation of the effect of surface PO_2 variation under the condition that other parameters remain constant. Such a consideration is hardly applicable to physiological situations, since it is well known that in reality a change of the surface PO_2 induces changes in such parameters as capillary velocity, capillary hematocrit, intercapillary distances, etc. However, this idealized case is a necessary step toward more detailed modeling.

The following parameters were chosen for simulation: $D = 1.6 \times 10^{-5} \text{ cm}^2/\text{sec}$; $\alpha = 3 \times 10^{-5} (\text{cm}^3 \text{ O}_2)/(\text{cm}^3 \text{ tissue})(\text{mmHg})$; $\alpha_b = 2.9 \times 10^{-5} (\text{cm}^3 \text{ O}_2)/(\text{cm}^3 \text{ blood})(\text{mmHg})$; $M = M_0 =$

$10^{-4} \text{ (cm}^3 \text{ O}_2\text{)/(cm}^3 \text{ tissue)(sec)}$ if $P > 0$, and $M = 0$ if $P = 0$; $C = 0.145 \text{ (cm}^3 \text{ O}_2\text{)/(cm}^3 \text{ blood)}$; $r = 2.5 \times 10^{-4} \text{ cm}$; $d = d_I = 4 \times 10^{-3} \text{ cm}$; $H = 3.2 \times 10^{-2} \text{ cm}$; $L = 8 \times 10^{-2} \text{ cm}$; $v = 5 \times 10^{-2} \text{ cm/sec}$, $P_a = 60 \text{ mmHg}$. Most of these parameters are the same as in a recent paper [16]. Four horizontal capillary layers are considered. The surface oxygen tension P_s was varied within a wide range: 10–80 mmHg. The Margaria equation was chosen for description of the oxygen dissociation curve:

$$\psi(p) = hp \frac{(1+hp)^3 + m(hp)^3}{(1+hp)^4 + m(hp)^4} \quad (8)$$

with $h = 0.01278$, $m = 124$ [17].

4. Method of Solution

Equations (7) and (2) were rewritten in the form of a single parabolic nonlinear partial differential equation

$$U(S) \frac{\partial S}{\partial z} = \lambda \left(\frac{\partial^2 S}{\partial x^2} + \frac{\partial^2 S}{\partial y^2} \right) - Q(S), \quad (9)$$

where

$$S = \begin{cases} P_i & \text{in the } i\text{th capillary,} \\ P & \text{in the tissue,} \end{cases}$$

$$U = \begin{cases} \pi r^2 v_i \alpha_b (1 + C_i \alpha_b^{-1} d\psi/dP_i) & \text{in the } i\text{th capillary,} \\ 0 & \text{in the tissue,} \end{cases}$$

$$\lambda = \begin{cases} \alpha_b D_b & \text{in the capillaries,} \\ \alpha D & \text{in the tissue,} \end{cases}$$

$$Q = \begin{cases} 0 & \text{in the capillaries,} \\ M & \text{in the tissue.} \end{cases}$$

Here D_b is the oxygen diffusion coefficient in blood. It has been shown that the results are practically independent of D_b if $D_b \gtrsim 10^{-5} \text{ cm}^2/\text{sec}$, which suggests the equivalence of Equation (9) with (2) and (7); a value $D_b = 2 \times 10^{-5} \text{ cm}^2/\text{sec}$ was used in calculations.

The previously formulated boundary conditions can be rewritten in the form

$$S=P_s \quad \text{at} \quad y=0, \quad (10)$$

$$\frac{\partial S}{\partial x}=0 \quad \text{at} \quad x=0 \quad \text{and} \quad x=d, \quad (11)$$

$$\frac{\partial S}{\partial y}=0 \quad \text{at} \quad y=H. \quad (12)$$

The distribution of S at $z=0$ (“initial” condition) was determined by solving Equation (7) at $z=0$.

Equation (9) was solved numerically using a computer program IMSL TWODEPEP implementing a finite-element scheme with triangular elements. The numerical scheme was tested on a number of geometries, including the simplest case of identical capillaries forming a square lattice as well as more complex geometries studied by the author [19, 16]. Figure 2 shows a comparison of intracapillary PO_2 obtained by application of the finite element scheme to equation (9) with boundary conditions (11), (12) and $S|_{y=0}=0$ at $y=0$ corresponding to a sealed tissue surface, with the “exact” solution governed by the conservation-of-mass relationship (Fick’s principle):

$$\pi r^2 v \frac{d}{dz} [\alpha_b P + C \psi(P)] = -\pi (R^2 - r^2) M_0, \quad (13)$$

$$P(0)=P_a, \quad (14)$$

where $R=2d/\pi$ is the effective “Krogh cylinder” radius. In all cases considered to test the numerical scheme, the discrepancy between the solutions obtained with the finite-element technique and the solutions of (13) (or, for more complex geometries, solutions obtained by the author [16, 18]) did not exceed 1 mmHg.

5. Results And Discussion

It will be seen now how the diffusive interaction between the surface and the tissue affects the oxygen distribution in the surface layers of tissue. For convenience the results are presented in terms of dimensionless coordinates

$$x^* = x/d, \quad y^* = y/d, \quad z^* = z/L. \quad (15)$$

Figure 3 demonstrates variation of intracapillary oxygen tensions along the capillary length for $P_s = 40$ mmHg. The dashed line depicts the intracapillary PO_2 in the case of a sealed tissue surface (due to geometrical symmetry, PO_2 distributions in all capillaries are identical). The notation P_K is used to point out the similarity between this case and that of the Krogh tissue cylinder [9, 16]. It can be seen that for $0 \leq z^* \leq 0.4$ the intracapillary oxygen tensions are below P_K , namely $P_1 \leq P_2 \leq P_3 \leq P_4 \leq P_K$, while these inequalities reverse for $0.4 \leq z^* \leq 1$. It should also be noted that the oxygen tension in the deepest capillary, P_4 , is very close to P_K ; thus the influence of the tissue surface at this depth is small. The tissue PO_2 distributions in the planes $x^* = 0$ and $x^* = 1$ for $P_s = 40$ mmHg are shown in Figures 4 and 5. In the plane $x^* = 0$ located half way between the capillaries, PO_2 is nearly a monotonic function of y^* with only small spatial “oscillations” due to the presence of capillaries. Conversely, significant spatial “oscillations” are seen in the plane $x^* = 1$ that contains the capillary axes. The slope of the PO_2 distribution near the tissue surface indicates that part of the tissue surface adjacent to the arterial end of the capillaries is a sink of oxygen, whereas the part adjacent to the venous end of the capillaries is a source of oxygen, i.e., it supplies oxygen to the tissue. The complex PO_2 distribution in this case is further illustrated in Figure 6. The first three panels show PO_2 distributions in the planes $z^* = 0, 0.5$, and 1, respectively; numbers on the isobars designate the tissue PO_2 in mmHg. The right panel illustrates the PO_2 distribution in the tissue in the absence of blood flow, in which case it is described by the relationships

$$P = \begin{cases} P_s(1 - \frac{y}{l})^2 & \text{for } 0 \leq y \leq l, \\ 0 & \text{for } l \leq y \leq H, \end{cases} \quad (16)$$

where $l = (2D\alpha P_s M_0^{-1})^{1/2}$ is the penetration depth. Comparison of the last two panels shows that even though the gradients between the capillary closest to the surface and the surrounding tissue are very small, the PO_2 distribution near the surface is significantly different from the distribution at zero blood flow.

Figures 7–9 show intracapillary and tissue PO_2 distributions in the case of a lower surface PO_2 (20 mmHg). In this case intracapillary oxygen tensions in all four capillary layers, P_1 – P_4 , are below the values of P_K . Both Figures 8 and 9 demonstrate that the tissue PO_2 increases with y^* near the surface of the tissue for almost all z^* except a small region close to $z^* = 1$; thus the surface acts as a sink of oxygen.

PO_2 distributions in the tissue were studied within a wide range of variation of the surface PO_2 : 10 to 80 mmHg. In Figure 10 the intracapillary oxygen tensions at the venous end of the capillaries are plotted for different values of P_s , together with the value of P_K (the end-capillary PO_2 in the case of sealed tissue surface). Clearly, the effect of the surface PO_2 is more pronounced for the capillary layer closest to the surface; however, this layer does not

“shield” the rest of the tissue from the surface. In fact, even the PO_2 in the deepest capillary layer is not entirely independent of the surface PO_2 . Figure 10 also indicates that the “perturbation” of the near-surface PO_2 distribution is minimal when the oxygen tension at the surface “matches” the end-capillary oxygen tension P_K ; it follows from the fact that all curves in Figure 10 intersect near a point where $P_K \simeq P_S$. However, the perturbation introduced by the surface near the arterial end of the capillaries can be significant even in this case. Figure 11 illustrates the variation of the tissue PO_2 at different depths along the line $x^* = 0$, $z^* = 1$ with variation of P_S . Also shown are oxygen tensions in the case of zero capillary flow. The slope of the curves, which characterizes the sensitivity of tissue PO_2 to variation of the surface PO_2 , diminishes as the depth y^* increases.

The results obtained in the present work generally indicate that variation of oxygen tension at the surface of the tissue can significantly alter the oxygen distribution in the surface layers of tissue. Therefore, the use of an appropriate mathematical model, applicable to this geometry, is required for correct interpretation of experimental data on oxygen distributions obtained in the surface layers of exposed tissue.

6. Nomenclature

C	oxygen-binding capacity of blood
D	oxygen diffusion coefficient
H	thickness of the tissue
H_t	tube hematocrit
J	capillary-tissue diffusive flux
L	length of the capillary
l	penetration depth
M	oxygen consumption rate per unit volume of tissue
P	oxygen tension
r	capillary radius
R	Krogh cylinder radius
v	velocity of blood
v_{pl}	mean velocity of plasma
v_c	mean velocity of red blood cells
x, y, z	dimensional coordinates
x^*, y^*, z^*	dimensionless coordinates

GREEK SYMBOLS

α	oxygen solubility coefficient
ψ	oxygen saturation fraction of hemoglobin

SUBSCRIPTS

a	pertaining to arterial end of the capillaries
b	pertaining to blood
Hb	pertaining to hemoglobin solution
$i = 1, 2, 3, 4$	pertaining to capillaries
K	pertaining to “Krogh-like” geometry
pl	pertaining to plasma
s	pertaining to the surface of the tissue

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Appendix. Calculation of Oxygen Flux in The Capillary

If the hemoglobin solution inside red blood cells and the surrounding plasma are in local thermodynamic equilibrium, and therefore a mixing-cup intracapillary oxygen tension P can be introduced, then the oxygen flux through any cross-section of the capillary can be determined from the expression

$$F = \pi r^2 [v_{pl}(1 - H)\alpha_{pl}P + v_c H_t \alpha_{Hb} P + v_c H_t C_0 \psi(P)] \quad (A1)$$

where P is the mixing-cup oxygen tension in the capillary, v_{pl} is the mean velocity of plasma, such that $\pi r^2 v_{pl}(1 - H)$ is the volume flux of plasma, v_c is the mean velocity of red blood cells, H_t is the “tube hematocrit” [20], α_{pl} is the oxygen solubility coefficient in plasma, α_{Hb} is the oxygen solubility coefficient in hemoglobin solution inside red blood cells, C_0 is the oxygen-binding capacity of hemoglobin solution inside the cells, and $\psi(P)$ is the oxygen saturation fraction of hemoglobin. The first term in (A1) represents the volume flux of free oxygen dissolved in the plasma, the second term represents the flux of free oxygen dissolved in the hemoglobin solution inside red blood cells, and the last term represents the flux of oxygen bound to hemoglobin.

Using the relationships between the mean velocity of blood, v , the discharge hematocrit H_D [20], and the variables in (A1), we have

$$v = v_{pl}(1 - H_t) + v_c H_t, \quad (A2)$$

$$v H_D = v_c H_t, \quad (A3)$$

from which follows

$$v(1 - H_D) = v_{pl}(1 - H_t). \quad (A5)$$

The relationship (A1) can be rewritten in the form

$$F = \pi r^2 v [\alpha_b P + C \psi(P)], \quad (A5)$$

where $C = C_0 H_D$, and α_b is an effective oxygen solubility coefficient in blood, defined by

$$\alpha_b = \alpha_{pl}(1 - H_D) + \alpha_{hb} H_D. \quad (A6)$$

This implies

$$\min(\alpha_{pl}, \alpha_{hb}) \leq \alpha_b \leq \max(\alpha_{pl}, \alpha_{hb}). \quad (A7)$$

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Fig. 1.
Assumed geometry of the model.

Fig. 2. Comparison between intracapillary oxygen tensions obtained by the finite-element method and the exact solution of (13), (14).

Fig. 3.
Distribution of intracapillary oxygen tensions P_{1-4} when $P_s = 40 \text{ mmHg}$; P_K is the intracapillary oxygen tension when the tissue surface is sealed.

Fig. 4.
Distribution of tissue oxygen tension in the plane $x^* = 0$ for $P_s = 40$ mmHg.

Fig. 5.
Distribution of oxygen tension in the plane $x^* = 1$ for $P_s = 40$ mmHg.

Fig. 6.
Panels 1–3: oxygen-tension distribution in the planes $z^* = 0, 0.5$, and 1 , respectively, for $P_s = 40$ mmHg. Panel 4: oxygen-tension distribution in the case of zero capillary flow. Numbers on the isobars designate oxygen tension in mmHg.

Fig. 7.
Intracapillary oxygen-tension distribution for $P_s = 20$ mmHg (P_{I-4}) and for a sealed tissue (P_K).

Fig. 8.
Distribution of tissue oxygen tension in the plane $x^* = 0$ for $P_s = 20$ mmHg.

Fig. 9.
Distribution of oxygen tension in the plane $x^* = 1$ for $P_s = 20$ mmHg.

Fig. 10.
End-capillary PO_2 versus P_s for all four capillary layers and for a sealed tissue.

Fig. 11. Oxygen tension at different depths ($y^* = 1-6$) for $x^* = 0$, $z^* = 1$ versus P_s (solid lines—with capillary flow; dashed lines—no capillary flow).