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Effect of Heterogeneous Oxygen Delivery on the Oxygen Distribution in Skeletal Muscle

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Abstract

Calculations of the oxygen distribution in resting and contracting skeletal muscle are presented, based on a mathematical model and experimental data obtained on the hamster cremaster muscle [Klitzman et al., *Microvasc. Res.* 25:108–131 (1983)]. The model considers a slab of tissue penetrated by a regular square array of capillaries with concurrent flow. The intracapillary resistance to oxygen transport is neglected. The capillary red blood cell flux and capillary inlet oxygen tension are assumed random variables following certain probability distributions. The sensitivity of the tissue and intracapillary PO_2 to variations of these probability distributions are investigated. The mean tissue PO_2 decreases as the dispersion of the random variables increases, provided that their mean values remain constant. Hypoxic regions appear gradually, especially in the case of contracting muscle, as the dispersion increases. The effect of the number of capillaries in the sample on the resultant distribution of oxygen is studied systematically. The calculated tissue PO_2 histograms are compared with previously reported PO_2 distributions obtained experimentally for resting and contracting skeletal muscle.

1. Introduction

In recent years, several factors of potential importance for oxygen transport to tissue have been identified through experimental and theoretical studies. The heterogeneity of capillary diameters [10] and the geometrical and functional capillary lengths [22, 13] have been studied; the heterogeneity of capillary red blood cell (RBC) flux and hematocrit have been investigated [33, 17, 30, 3]; precapillary oxygen losses have been reported [4, 21] that may result in nonuniform distribution of inlet capillary hemoglobin saturation; and the distributions of intercapillary distances and diffusion distances in several tissues have been quantified [15, 32, 16]. In mixed skeletal muscles composed of fibers of different types, there exists fiber-to-fiber heterogeneity of the O_2 diffusion coefficient, consumption rate, and local capillary geometry [7, 31, 1]. For the intracapillary domain, the importance of the particulate nature of blood has been evaluated using theoretical analysis [12, 2, 8]. It has been shown that to neglect the effect of discrete red blood cells on oxygen transport and to

assume that hemoglobin is uniformly distributed inside the capillary may cause a significant overestimation of the capillary-tissue O_2 flux.

To fully assess the physiological significance of the above factors, a model more general than the classical Krogh model is needed. The effect of capillary geometry was explored in [11], where several types of geometrically regular microcirculatory tissue units were considered (see review [19]). A model of parallel but otherwise arbitrarily distributed capillaries was formulated in [23], and an analytic solution for the PO_2 distribution in the tissue was derived under the assumption of a constant rate of O_2 consumption. Numerical results based on this model were obtained for two types of geometry of the microcirculatory tissue unit [24, 26], and the effect of unequal velocities and inlet PO_2 's in the adjacent capillaries was investigated. It was shown that the mean tissue PO_2 decreased when the difference between the blood velocities in the adjacent capillaries was increased with the arithmetic average of the velocities remaining constant. A similar effect was demonstrated for the inlet PO_2 , i.e., the mean tissue PO_2 decreased when the difference between the inlet PO_2 's in the adjacent capillaries was increased, provided that the arithmetic average of the inlet PO_2 's remained constant. In addition, the importance of oxygen diffusive shunting between adjacent tissue units was demonstrated. Thus, the assumption of no interaction between the units—the no-flux condition at the unit boundary (e.g., [11])—needed to be reassessed. An extension of the model included the diffusive interaction of the tissue with the environment through the tissue surface [25]. The model was applied to the analysis of O_2 distribution in superfused resting and contracting hamster cremaster muscle [18] based on an extensive set of experimental data.

In the present work, the effect of heterogeneity of capillary RBC flux and inlet PO_2 on the characteristics of O_2 distribution in the tissue and the capillaries is studied systematically. Tissue units with a variable number of capillaries are considered, and the effect of no-flux versus periodic boundary conditions at the boundary of the tissue unit is examined. The capillary RBC flux and inlet PO_2 are assigned random values from a lognormal and a truncated gaussian (normal) distribution, respectively, with preassigned mean and standard deviation (a Monte Carlo simulation). An ensemble of tissue units is generated, and the numerical results on O_2 distribution are ensemble-averaged. The numerical scheme used in the present work is capable of solving strongly nonlinear equations, particularly when the tissue PO_2 becomes close to zero (hypoxic and anoxic regions). This feature is especially important when the scheme is combined with Monte Carlo simulation, because regions of low tissue PO_2 might appear even in the case when the mean tissue PO_2 is sufficiently high.

Although the numerical scheme allows the consideration of an arbitrary distribution of parallel capillaries within the tissue unit, the present work considers only a regular square capillary arrangement. Also, the effect of intracapillary resistance to O_2 transport has not been incorporated into the model. The effects of stochastic capillary geometry and of the intracapillary resistance to O_2 transport on the distribution of oxygen in the tissue will be described elsewhere.

2. The Model

The model of capillary-tissue O_2 transport considered here is an extension of the model formulated in [23, 18]. The geometry and the governing equations are summarized as follows. Consider a tissue slab penetrated by parallel cylindrical capillaries arranged in a square array (Figure 1). The governing equations for time-independent transport of oxygen in the tissue and the capillaries, respectively, are given by [18]

$$D_t \alpha_t \left(\frac{\partial^2 P}{\partial x^2} + \frac{\partial^2 P}{\partial y^2} \right) - M = 0, \quad (1)$$

$$\frac{\partial}{\partial z} [Q_i \alpha_b P_i + V_c f_i C_{Hb} \Psi(P_i)] = -J_i, \quad i=1, 2, \dots, k. \quad (2)$$

Here $P(x, y, z)$ is the tissue PO_2 , which is a function of all three coordinates, $P_i(z)$ is PO_2 in the i th capillary, D_t is the diffusion coefficient of O_2 in the tissue, α_t is the solubility coefficient of O_2 in the tissue, M is the O_2 consumption rate, Q_i is the volumetric blood flow rate, α_b is the solubility coefficient of O_2 in the blood, V_c is the mean volume of RBC, f_i is the RBC flux (number of cells per second crossing any cross section in the capillary), C_{Hb} is the oxygen-binding capacity of hemoglobin solution inside the cells, Ψ is the oxygen-saturated fraction of hemoglobin, and J_i is the O_2 flux from the capillary to the tissue per unit length of the capillary per unit time. The axial diffusion in the tissue has been neglected, which can be justified when the ratio of capillary length to intercapillary distances is sufficiently large [11, 29]. For the cases considered in the present paper this ratio is ~ 10 . Hence, only the x and y derivatives of P are present in Equation (1). The first term in the left side of Equation (2) represents the flux of free oxygen, dissolved in both the plasma and the hemoglobin solution inside red blood cells. The second term represents the flux of oxygen bound to hemoglobin. It is recognized that the PO_2 distribution inside the capillary might be nonuniform in the red blood cells and plasma. The capillary oxygen tension P_i is introduced here in such a way that the expression under the derivative in left side of (2) is the volumetric flux of O_2 through the capillary at a position z .

At the capillary-tissue interface Γ_i , the following boundary conditions are imposed:

$$J_i = -D_t \alpha_t \int_{\Gamma_i} \frac{\partial P}{\partial n} d\Gamma_i, \quad (3)$$

$$P = P_i, \quad (4)$$

where n is an outward unit vector normal to the boundary. At the capillary inlets the PO_2 is specified:

$$P_i = p_{i0} \text{ at } z=0. \quad (5)$$

We considered two kinds of boundary conditions at the lateral surfaces of the slab:

periodic,

$$P(0, y, z) = p(L_x, y, z), P(x, 0, z) = P(x, L_y, Z), \quad (6)$$

and no-flux,

$$\frac{\partial P}{\partial n} = 0. \quad (7)$$

As discussed below, the no-flux boundary conditions are not suitable in the case of heterogeneous distribution of variables among capillaries, because they imply a strong symmetry present in the capillary arrangement. The periodic boundary conditions are much less restrictive. We examined the effect of these boundary conditions on the distribution of O_2 in the tissue.

It is known that under physiologic conditions the amount of free oxygen is much smaller than the amount of oxygen bound to hemoglobin [34]. Thus the flux of free oxygen in Equation (2) can be neglected in comparison with the flux of bound oxygen. When the first term in Equation (2) is neglected, the remaining term contains only the flux of red blood cells, f_{RBC} , and not the capillary hematocrit or the blood flow rate. The red blood cell flux can be measured directly in experiments [17, 30, 3], and its experimental values have not been questioned. On the other hand, the values of capillary hematocrit and volumetric blood flow rate are not measured directly, but calculated using measurements of the capillary diameter, and have been the subject of a recent controversy [5]. Thus, neglecting the flux of free oxygen makes the calculations independent of the assumptions regarding the capillary hematocrit and blood flow.

3. Parameters of the Model

The goal of this study was to investigate the effect of heterogeneity in the spatial, capillary-to-capillary distribution of RBC flux and inlet PO_2 on the distribution of oxygen in the tissue and inside the capillaries. The obtained results are compared with the case of uniform distribution of RBC flux and inlet PO_2 reported in [18] for the hamster cremaster muscle. It has been shown [18] that in the case of low PO_2 in the solution superfusing the cremaster muscle, the PO_2 values 75–100 μm below the tissue surface should not be strongly affected

by the surface. Therefore, in this study we utilize the PO_2 values measured at these depths and consider them as representing “deep” tissue values. This approach is consistent with present calculations that do not take into account the effect of tissue surface.

In order to close the set of equations (1)–(2), the functional forms of M and Ψ have to be specified. The Michaelis-Menten kinetics is assumed for the oxygen consumption rate,

$$M = M_0 \frac{P}{P + P_{cr}}, \quad (8)$$

and the Hill equation for the oxygen-saturated fraction of hemoglobin (oxygen dissociation curve),

$$\Psi = \frac{(P/P_{50})^n}{1 + (P/P_{50})^n}. \quad (9)$$

It is recognized that Equation (9) is not accurate for small values of PO_2 and more accurate expressions are available for this range. However, Equation (9) was used in [18], and preserving it in the present work makes it possible to compare the results of the two studies. It should be noted that the value of P_{cr} in (8) is a subject of considerable disagreement [14].

The distribution of capillary RBC flux has recently been measured by several investigators (the data are reviewed in [27]). The mean values of the flux, $\langle f_{RBC} \rangle$, vary significantly from the resting to the contracting state of the muscle, but the relative dispersion characterized by the coefficient of variation of flux appears to remain fairly constant [3]. The data on RBC flux have not been fitted by a probability density function, so that the statistical distribution needed for the simulation has to be assumed. A lognormal two parameter distribution agrees, at least qualitatively, with the data. The corresponding probability density function is

$$g_1(f_{RBC}) = \frac{1}{\sqrt{2\pi}\sigma' f_{RBC}} \exp \left[- \left(\frac{\ln f_{RBC} - \sigma'}{\sqrt{2}\sigma'} \right)^2 \right] \quad (10)$$

where a' and σ' are related to the mean RBC flux, $\langle f_{RBC} \rangle$, and the coefficient of variation of flux, $CV(f_{RBC})$, by

$$\langle f_{RBC} \rangle = \exp \left(a' + \frac{\sigma'^2}{2} \right), \quad CV(f_{RBC}) = \sqrt{\exp(\sigma'^2) - 1} \quad (11)$$

Thus, the flux distribution is specified by two parameters, $\langle f_{\text{RBC}} \rangle$ and $\text{CV}(f_{\text{RBC}})$. The values of f_{RBC} were drawn randomly from this distribution using a computer-generated sequence of pseudorandom numbers [28] as described in the following section. For a sufficiently large sample, the sample mean and coefficient of variation approach, in the statistical sense, the corresponding preassigned values.

There is evidence that the capillary inlet PO_2 level in resting muscle is well below the systemic level [4, 21]. This is a result of precapillary oxygen exchange between the blood and the surrounding tissue. Very little is known at present about the level of capillary inlet PO_2 in the contracting muscle, although some recent studies suggest that in this case it is approximately the same as in the resting muscle [6, 20]. The heterogeneity of precapillary blood flow pathways intrinsic in the structure of microvascular networks should lead to a nonuniform distribution of capillary inlet PO_2 . However, experimental information on this distribution reported in the literature is scarce and not definitive. Thus, for the purpose of this study, the distribution is assumed gaussian with a specified mean $\langle P_0 \rangle$ and coefficient of variation $\text{CV}(P_0)$. To avoid the occurrence of very low or negative values of P_0 , the left tail of the distribution is truncated at two standard deviations away from the mean. Thus, the corresponding probability density function is

$$g_2(P_0) = \begin{cases} \frac{1}{\sqrt{2\pi}\sigma} \exp \left[-\left(\frac{P_0 - \langle P_0 \rangle}{\sqrt{2}\sigma} \right)^2 \right] & \text{if } P_0 > P^* \\ 0 & \text{if } P_0 < P^* \end{cases} \quad (12)$$

where σ is the standard deviation, and $P^* = \langle P_0 \rangle - 2\sigma$ is the cutoff tension for the truncation. The coefficient of variation is $\text{CV}(P_0) = \sigma/\langle P_0 \rangle$. Although the function g_2 is not normalized, i.e., its integral is not equal to unity, the error introduced by the truncation is small and no correction for it is introduced.

In principle, a correlation might exist between RBC flux and inlet capillary PO_2 . For example, if a given capillary is part of a low flow pathway, then precapillary losses on this pathway may exceed the average level, which would lead to a lower value of P_0 . On the other hand, there may be other factors affecting both variables that would lead to statistical independence of these variables. This problem has not been addressed experimentally; in this study we assume that f_{RBC} and P_0 are independent random variables.

The values of parameters used in this study are listed in Table 1 (the geometric parameters are defined in Figure 1). All these values are taken from [18]. Thus, some of them were measured directly, and some were computed using a model with uniform distribution of capillary blood flow and capillary inlet PO_2 .

In accordance with the main goal of this study—to investigate the effect of heterogeneity of O_2 delivery on PO_2 distribution—we considered a wide range of indices of heterogeneity, $\text{CV}(f_{\text{RBC}})$, and $\text{CV}(P_0)$. $\text{CV}(f_{\text{RBC}})$ is varied between 0 and 1.0 in accordance with a large volume of experimental data [27]; $\text{CV}(P_0)$ is varied between 0 and 0.2.

Modeling the heterogeneity of microvascular oxygen delivery using Monte Carlo simulation is not a standard technique, and a number of aspects of the computational scheme need to be examined. In the following sections several technical aspects of this method are investigated, e.g., the effect of sample size on the computed PO_2 distribution.

4. Numerical Scheme

Equation (1) is discretized using a central finite difference scheme, and the solution for each layer $z = \text{const}$ is obtained using the SOR method [9]. Once the tissue PO_2 distribution for a given z is obtained, the capillary-tissue fluxes J_i are calculated according to Equation (3) using the trapezoidal integration scheme [9]. These values are then substituted into Equation (2), and the set is integrated numerically using the fourth order Adams-Bashforth method [9] to yield the values of P_i at $z + \Delta z$. A grid size of 22×22 per capillary in the x - y plane has been found sufficient, resulting in an 88×88 grid for the standard geometry shown in Figure 1. The length in the z direction is divided in 52 equal intervals. To generate the PO_2 distribution in a slab, pseudorandom sequences of f_{RBC} and P_0 are drawn from lognormal and truncated gaussian distributions, respectively, using random number generators based on the multiplicative congruential algorithm [28]. Briefly, a sequence of numbers from the interval $(0, 1)$ is generated first. This sequence is completely deterministic, but it passes the set of statistical tests which permits us to treat it as one of random numbers; hence the term pseudorandom. Using this sequence, sequences following arbitrary probability distributions can be constructed using the procedures described in [28].

Each computation of the PO_2 distribution in a single tissue unit takes about one hour of CPU time on Data General MV/8000 computer. This has imposed certain limitations on the sample size and the number of cases we have been able to investigate.

5. Results

Sensitivity Study

We systematically examined the sensitivity of the calculated PO_2 distributions to the choice of geometrical and hemodynamic parameters of the model. Whenever possible, the calculations pertain to resting and contracting hamster cremaster muscle. The tissue unit considered in the calculations, illustrated in Figure 1, has the shape of a parallelepiped penetrated by a square array of parallel capillaries. Generally, m_1 columns and m_2 rows of capillaries are considered, hence $m = m_1 m_2$ capillaries per unit. Figure 1 shows the case of 4×4 capillaries.

As a standard type of boundary conditions on the lateral surface of the slab, the periodic boundary conditions (6) are employed. If the tissue unit is regarded as a representative microvolume of a macroscopic volume of tissue, then the periodic boundary conditions correspond to side-by-side arrangement of identical microscopic volumes which compose the macroscopic volume.

The computational procedure for solving the set of partial differential equations (1) and (2) combined with Monte Carlo simulation requires a large amount of computer time, imposing

a restriction on the number of capillaries in the tissue unit. On the one hand, this number should be sufficiently large to avoid distortion of the diffusive interaction between capillaries by artificial boundary conditions; on the other hand it should be reasonably small to make the computations tractable. In order to choose the size of tissue unit for subsequent computations, we generated a sequence of 96 random numbers representing values of the capillary RBC flux drawn from a lognormal distribution, and a different sequence of 96 numbers representing values of the capillary inlet PO_2 drawn from a truncated normal distribution.

The set of parameters in Table 1 chosen for the calculations corresponds to resting muscle. The values of the coefficients of variation are specified: $CV(f_{RBC}) = 0.4$, $CV(P_0) = 0.2$.

The results are presented for four cases: an ensemble of $N = 96$ tissue units and $m = 1$ capillary per unit, with the RBC flux and inlet PO_2 in each capillary assigned from the two sequences described above; an ensemble of $N = 24$ tissue units and $m = 4$ ($m_1 = 2$, $m_2 = 2$) capillaries per unit; an ensemble of $N = 8$ tissue units and $m = 12$ ($m_1 = 4$, $m_2 = 3$) capillaries per unit; and an ensemble of $N = 6$ tissue units and $m = 16$ ($m_1 = 4$, $m_2 = 4$) capillaries per unit. The periodic boundary conditions (6) are imposed. Clearly, in the first case, due to symmetry of the problem, no diffusional exchange takes place between adjacent capillaries, whereas in the other cases diffusional exchange is permitted. In the case $m = 4$ the periodic boundary conditions impose a rather artificial constraint on capillary interactions: each capillary has two pairs of identical capillaries as its immediate neighbors. The last case, $m = 16$, imposes the weakest constraint on capillary interactions: each capillary is separated by three different capillary layers from another capillary with identical characteristics resulting from the periodic boundary conditions.

The distributions of tissue PO_2 in these four cases are presented in Figure 2 in the form of frequency histograms. The tissue PO_2 is calculated at every grid point in the slab; for the standard case there are $89 \times 89 \times 53 \approx 420,000$ points minus the ones that fall inside the capillaries. These points are divided into classes depending on the corresponding PO_2 values, and the frequency histograms are computed. Throughout this work, unless specified otherwise, PO_2 histograms are presented in the following form: the width of each class is equal to 2.5 mmHg starting from $PO_2 = 0$; the number below a histogram bar denotes the right end of the interval, e.g., the bar above $PO_2 = 5$ mmHg represents the class $2.5 < PO_2 \leq 5$. Figure 2 demonstrates the effect of capillary interaction on the distribution of tissue PO_2 : the spatial variation of PO_2 becomes smaller as more capillaries are included in the unit. In particular, the areas of low tissue PO_2 , smaller than 2.5 mmHg, present in the cases $m = 1$ and $m = 4$, disappear for larger values of m .

For the concurrent capillary arrangement considered in the present study, the supply of O_2 from the venous ends of the capillaries is most unfavorable. Thus it is interesting to examine the distribution of capillary and tissue PO_2 at $z = L_z$. Two variables that characterize this distribution are considered here: the end capillary PO_2 , P_{ec} , and the intercapillary “minimum” tissue PO_2 , P_{min} , defined as PO_2 at the points equally distant from the nearest capillaries. For the square capillary arrangement these points are located at the intersections of lines connecting centers of closest capillaries. Both P_{ec} and P_{min} are random variables due

to stochasticity of the inlet capillary parameters. Therefore, ensemble-averaged values, $\langle P_{ec} \rangle$ and $\langle P_{min} \rangle$, as well as their statistical moments can be calculated. The coefficients of variation, $CV(P_{ec})$ and $CV(P_{min})$, can be regarded as indices of heterogeneity of PO_2 distribution, because in the case of no dispersion in the values of inlet parameters, both coefficients of variation vanish. Table 2 presents the characteristics of the PO_2 distribution for tissue units of different size. The variation of the mean values, $\langle P_l \rangle$, $\langle P_{min} \rangle$, and $\langle P_{ec} \rangle$, is not as significant as the variation of the dispersion around the means, characterized by the corresponding coefficients of variation. For example, $CV(P_{ec})$ changes from 0.89 for $m = 1$ to 0.26 for $m = 16$, whereas $\langle P_{ec} \rangle$ changes only slightly from 9.0 to 10.4 mmHg.

The above results indicate that the use of tissue units containing less than 16 capillaries may lead to a significant overestimation of PO_2 heterogeneity. Although for computational reasons we have not attempted to do the calculations for larger tissue units, it is clear from physical considerations that the units with $m = 16$ do not introduce a strong bias by placing capillaries with identical characteristics close to one another. Thus, the following calculations were performed for tissue units with 16 capillaries.

The next two issues to be addressed are the effect of the type of boundary condition at the lateral surface of a tissue unit, and the effect of the size of the sample (ensemble), i.e. of the number of units with different inlet parameters. As discussed above, the periodic boundary conditions (6) are less restrictive than the no-flux conditions (7). The latter introduce a strong bias of the capillaries situated next to the boundary of the unit because these capillaries are adjacent, through the boundary, to the capillaries with identical characteristics. Nevertheless, most previous simulation studies on tissue units utilized the no-flux boundary conditions [11]. Thus, for the sake of assessment of the validity of previously reported results, we present distributions of the end capillary oxygen tension, P_{ec} , for these two types of boundary conditions. Also, four pairs of random sequences of length 96 each are drawn for f_{RBC} and P_0 (denoted 1–4 in order) from lognormal and gaussian distributions, respectively. With $m = 16$ capillaries in a unit, each sequence corresponds to $N = 6$ units with different values of the capillary inlet parameters.

It is interesting to compare the distributions of capillary input parameters for the four sequences generated. Figure 3 (upper panel) shows four frequency histograms of RBC flux values f_{RBC} drawn from a lognormal distribution with preassigned mean and coefficient of variation $CV(f_{RBC}) = 0.4$; each histogram is calculated for sample of 96. The lower panel shows histograms for the four sequences combined, as well as a theoretical frequency distribution (corresponding to an infinitely large sample) with the same mean and coefficient of variation. Clearly, for sample size of $96 \times 4 = 384$ the calculated and theoretical flux distributions are very close. It should be noted that sample means for the four sequences are close to each other and to the preassigned mean, $f_{RBC} = 7.0 \text{ sec}^{-1}$ (Table 3). A similar analysis can be performed for the capillary inlet PO_2 distribution. Table 3 shows that the mean values of PO_2 are also close to each other for different sequences. However, there are significant differences in the distributions of PO_2 characterized by the corresponding coefficients of variation: $CV(P_{ec})$ ranges between 0.16 and 0.33, and hence changes by a factor of 2, whereas the variation of $\langle P_{ec} \rangle$ from sequence to sequence does not exceed 1.4 mmHg, i.e., approximately 15% of the mean value. Frequency histograms of P_{ec} are

depicted in Figure 4 separately for each sequence 1–4 and combined together, thus representing a sample of 24 tissue units with 16 capillaries in each. The results below were obtained using this sample size.

Comparison of the PO_2 distributions corresponding to the periodic and no-flux boundary conditions shows that the differences may be significant for small sample size but average out for the large sample (Figure 4). As has been discussed above, the periodic boundary conditions are preferable in representing a large volume of tissue. Therefore, they are used in the following computations.

Using $CV(f_{RBC})$ and $CV(P_0)$ as indices of heterogeneity of oxygen delivery to the capillaries, we will now systematically study the effect of these parameters on PO_2 distributions for resting and contracting muscle. Frequency histograms of P_t and P_{ec} for the cases $\{CV(f_{RBC}), CV(P_0)\} = \{0, 0\}$, $\{0.4, 0.2\}$ and $\{0.8, 0.2\}$ are presented in Figure 5. In the first case all capillaries have identical PO_2 's, represented by a single bar in the upper right panel. In particular, for the end capillary $P_{ec} = 13$ mmHg. The case of no dispersion of f_{RBC} and P_0 is an analog of the Krogh cylinder model with the exception that the capillaries form a square array. Thus the tissue unit is a parallelepiped and not a circular cylinder. It has been shown that these geometrical differences have very little effect on the characteristics of the O_2 distribution [24]. The distribution of oxygen tension undergoes significant qualitative changes as the dispersion of inlet values increase. Most importantly, the fraction of tissue with low values of PO_2 increases.

Table 4 lists the values of the mean and coefficient of variation of P_t , P_{min} , and P_{ec} for resting and contracting muscles. In both cases the mean PO_2 values decrease as the dispersion increases. In contrast, the corresponding CVs increase with increasing $CV(f_{RBC})$. When $CV(P_0)$ is changed from 0 to 0.2, $CV(P_t)$ decreases, owing apparently to the asymmetry of the O_2 dissociation curve, whereas $CV(P_{min})$ and $CV(P_{ec})$ increase from zero to small positive values. These results are in qualitative agreement with our earlier findings obtained with a model of diffusive interaction of two capillary layers [24]. Notice that with the increase of dispersion there appear PO_2 values below 2.5 mmHg, even though the mean PO_2 values remain relatively high. This may be of importance for the regulation of blood flow.

To better understand the details of diffusive interaction between neighboring capillaries, we examined the variation of intracapillary PO_2 along the capillaries for a particular random realization of input parameters. Table 5 lists the values of f_{RBC} and P_0 for four capillaries situated in the middle of a tissue unit (Figure 1) for three different cases: dispersion of P_0 only, dispersion of f_{RBC} only, and both dispersions present. Figure 6 shows the distribution of normalized capillary PO_2 in these cases. If the capillary RBC fluxes are equal but the inlet PO_2 's are different, PO_2 equilibration among the capillaries occurs within about 20% of their length; for the remaining 80% of the length the PO_2 distribution in different capillaries is the same. This is true not only for the four capillaries shown but for all 16 capillaries in the unit. If the inlet PO_2 's are identical but the fluxes are different, then no equilibration occurs along the length. As can be seen in Table 5, capillaries 6, 7, and 11 happen to have similar RBC fluxes, whereas the flux in capillary 10 is significantly higher. As a result, the PO_2 profiles along the length are similar in the first three capillaries, and the values of PO_2 are higher in

the last. The lower panel in Figure 6 illustrates the case when both dispersions are present; qualitatively, it is a superposition of the two preceding cases. These results suggest that the dispersion of RBC flux has a larger effect on the PO_2 distribution than the dispersion of capillary inlet PO_2 because of quick equilibration of capillary PO_2 's in the case of unequal P_0 values.

Comparison of Calculated and Experimental PO_2 Distributions

The calculations presented above were done with the set of parameters listed in Table 1. These parameters either came from direct experimental observations ($\langle f_{RBC} \rangle$, r , L_z , d) or were derived from experimental data indirectly (M , $\langle P_0 \rangle$) using a mathematical model that did not take into account flow heterogeneity but did take into account the effect of diffusive interaction with the muscle surface [18]. In the latter case, the parameters were calculated from measurements of the mean tissue PO_2 between capillaries, which approximately corresponds to $\langle P_{min} \rangle$ introduced in the present work. Experimental frequency histograms of this variable were also reported in [18] for resting and contracting muscles. The following is a comparison between the calculated and the experimental PO_2 histograms.

First, the sample size in the experiments reported in [18] is rather small. Indeed, the RBC velocity data for either resting or contracting muscle consist of $n = 15$ values; based on these values, $CV(v_{RBC}) \approx 1.0$. Analysis of available experimental data suggests that the coefficient of variation of RBC flux in the hamster cremaster muscle and in other muscles is at least as large as the coefficient of variation of RBC velocity [27]. In our calculations we assumed $CV(f_{RBC}) = 1.0$. Since at present very little is known about the dispersion of capillary inlet PO_2 , we assumed $CV(P_0) = 0$. This assumption is probably not realistic, but the comparison is presented for illustrative purposes only, not as a quantitative fit to the data. The values of parameters from Table 1 are used for resting and contracting muscles, with the exception that $\langle P_0 \rangle$ was increased to 29 mm Hg in order to match the calculated and experimental values of the mean intercapillary PO_2 , $\langle P_{min} \rangle$, in resting muscle.

Frequency histograms of calculated values of P_{min} , and the corresponding experimental values of the intercapillary “minimum” tissue PO_2 , are shown in Figure 7. The histograms are presented in the same form as the experimental data in [18]: each interval on the horizontal axis equals 5 mmHg, and the number under a bar identifies the right end of the 5 mmHg interval. Although significant quantitative discrepancies of calculated and experimental results are obvious, a qualitative agreement exists, especially in the case of contracting muscle. It should be noted that in the case of zero dispersion of RBC flux examined in [18], the values of P_{min} are identical in all capillaries. Thus they can be represented by a single bar. In the case of resting muscle, the calculated PO_2 distribution is sharper than the experimental, with about 50% of the values concentrated between 10 and 15 mmHg. It appears that there are additional sources of heterogeneity not taken into account in the calculations, e.g., a significant dispersion of P_0 , which might be different in the resting and contracting states.

A discussion is in order concerning the comparison between experimental and theoretical histograms when the sample size is small. Indeed, the results presented in Figure 4 for the end capillary O_2 tension P_{ec} , corresponding to four samples of 96 capillaries each, for

$CV(f_{\text{RBC}}) = 0.4$, $CV(P_0) = 0.2$, demonstrate the dependence of the PO_2 distribution on a particular realization. If these results were to be extended to the experimental situation, it would mean that if the measurements were divided randomly into groups corresponding to about 100 capillaries each, significant differences could be found between histograms corresponding to different groups. In reality, the differences between groups are expected to be even larger because the dispersion of the RBC flux is typically higher than that assumed in Figure 4: probably $CV(f_{\text{RBC}}) \approx 0.6\text{--}1.0$ [27]. Notice now that the experimental histograms are based on only $n = 63$ and 25 measurements for resting and contracting muscles, respectively. Even though the sample is too small for reliable evaluation of frequency histograms, it may be sufficient for an accurate determination of the mean and, to a lesser degree, the coefficient of variation (Table 3). To calculate higher statistical moments with any degree of accuracy, a much larger sample is necessary.

For the comparison shown in Figure 7 additional work could have been done to determine a set of parameters leading to a better fit between the theoretical and experimental distributions; within the framework of the present model, the variation of $\langle P_0 \rangle$, M , and $CV(P_0)$ can have an effect on the PO_2 distributions. However, no further investigation has been done, because, on the one hand, calculations where three parameters are varied require an unreasonably large amount of computer time, and on the other hand the experimental sample size does not appear large enough to justify an extensive fitting effort.

6. Discussion

This study is a first step towards establishing quantitative relationships between heterogeneity of capillary flow and the distribution of O_2 in tissue. The spatial distribution of RBC flux was specified by a lognormal probability density function, and the flow dispersion was characterized by the coefficient of variation, which was varied systematically within a wide range. An important question, not addressed in the present study, is how the tissue PO_2 distribution would change during simultaneous variation of both mean flow and flow dispersion provided that the capillary geometry and O_2 consumption remained constant. For example, if the mean flow increases, with a simultaneous increase in variance, will the O_2 supply become more adequate or less adequate? This problem can be investigated with the help of the model.

It has been shown that for a realistic level of flow heterogeneity the sample size is an important factor affecting the shape of PO_2 frequency distributions. A significant variability between groups of 96 capillaries has been found even for a moderate dispersion of the RBC flux, $CV(f_{\text{RBC}}) = 0.4$. However, when the sample size was quadrupled, the RBC flux distribution was in close agreement with theoretical sample-independent distributions. It is not known whether similar relationships are valid in vivo or additional factors lead to a more uniform distribution of PO_2 . The effect of sample size on the representation of experimental PO_2 histograms has not been discussed exhaustively in the experimental literature, and, in view of the present results, care should be taken to ensure that the obtained experimental PO_2 distributions are “sample-independent.”

In the present study, we purposely simplified certain geometric and transport characteristics of the capillary bed in order to make the computations tractable and to separate the effects of flow heterogeneity on PO_2 distribution from other factors. In recent years, the spatial capillary patterns in different tissues have been studied extensively using statistical approaches (e.g., [15, 32, 16]), and it has been found that intercapillary distances are not evenly distributed. Thus, yet another kind of heterogeneity exists in the capillary circulation that might have an effect on O_2 distribution. Another factor is the presence of capillary anastomoses [22, 13]. Knowledge of the O_2 delivery function of capillary anastomoses is not sufficient at present, but with minor modifications of the present model, these aspects of O_2 delivery can be investigated.

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Fig. 1.
Geometry of tissue unit.

Fig. 2. Frequency histograms of tissue PO_2 in units with 1, 4, 12, and 16 capillaries. Each sample contains 96 capillaries. Resting muscle parameters: $CV(f_{RBC}) = 0.4$, $CV(P_0) = 0.2$.

Fig. 3. Frequency histograms of f_{RBC} distributions. Upper panel: four sequences with 96 values each drawn from a lognormal distribution; $CV(f_{RBC}) = 0.4$. Lower panel: combined distribution for the four sequences and a theoretical distribution corresponding to infinitely large sample size.

Fig. 4. Frequency histograms of capillary end PO_2 in units with 16 capillaries for different random sequences of f_{RBC} and P_0 . Results are shown for periodic and no-flux boundary conditions at the lateral boundary of the unit. Resting muscle parameters: $CV(f_{RBC}) = 0.4$, $CV(P_0) = 0.2$.

Fig. 5. Frequency histograms of P_t and P_{ec} for resting muscle parameters: $CV(f_{RBC}) = 0, CV(P_0) = 0$ (upper panel); 0.4, 0.2 (middle panel); 0.8, 0.2 (lower panel).

Fig. 6. Profiles of capillary P_{O_2} for four capillaries identified in Fig. 1 with input parameters listed in Table 5.

Fig. 7. Comparison of frequency histograms of calculated intercapillary tissue oxygen tension $P_{\min}$, and the corresponding experimental values reported in [18] for resting and contracting muscle: $\langle P_0 \rangle = 29$ mmHg, $CV(f_{RBC}) = 1.0$, $CV(P_0) = 0$.

Table 1**Parameters of the Model**

Parameter	Value
D_p , $\text{cm}^2 \text{sec}^{-1}$	1.6×10^{-5}
α_p , $(\text{cm}^3 \text{O}_2)/(\text{cm}^3 \text{tissue})(\text{mmHg})$	3.1×10^{-5}
V_{cs} , cm^3	63.5×10^{-12}
r , cm	2.53×10^{-4}
L_z , cm	5×10^{-2}
P_{50} , mm Hg	26
n	2.55
C_{Hb} , $(\text{cm}^3 \text{O}_2)/(\text{cm}^3 \text{Hb solution})$	0.5
P_{cr} , mmHg	0.5
$\langle P_0 \rangle$, mmHg	27
Resting muscle	
$d_x = d_y$, cm	5.10×10^{-3}
$\langle f_{\text{RBC}} \rangle$, sec^{-1}	7.0^a
M , $(\text{cm}^3 \text{O}_2)/(100 \text{ cm}^3 \text{tissue})(\text{min})$	0.4
Contracting muscle	
$d_x = d_y$, cm	4.18×10^{-3}
$\langle f_{\text{RBC}} \rangle$, sec^{-1}	27.2
M , $(\text{cm}^3 \text{O}_2)/(100 \text{ cm}^3 \text{tissue})(\text{min})$	2.4

^aThe values of the mean RBC flux were calculated using the data in [18].

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Table 2
Characteristics of PO_2 Distribution for Tissue Units of Different Size

Ensemble ^a	P_t		P_{min}		P_{ec}	
	Mean	CV	Mean	CV	Mean	CV
1×96	17.0	0.48	8.3	0.90	9.0	0.89
4×24	18.0	0.25	9.1	0.48	10.0	0.46
12×28	17.8	0.24	9.0	0.41	10.0	0.38
16×6	17.9	0.21	9.4	0.27	10.4	0.26

^a $m \times N$, where m is the number of capillaries in the tissue unit, and N is the number of units in the ensemble.

Table 3
Characteristics of PO_2 Distribution for Four Different Random Sequences of Input
Parameters for Periodic Boundary Conditions

Sequence	f_{RBC}		P_{ec}	
	Mean	CV	Mean	CV
1	7.00	0.36	11.2	0.33
2	6.61	0.45	10.4	0.26
3	6.89	0.42	11.5	0.17
4	6.93	0.40	10.1	0.16
Combined	6.86	0.41	10.8	0.25

Table 4
Characteristics of PO_2 Distribution for Different Dispersions of Input Parameters

Input parameters		P_t		p_{min}		P_{ec}	
CV(f_{KBC})	CV(P_0)	Mean	CV	Mean	CV	Mean	CV
Resting muscle							
0	0	19.0	0.21	11.9	0.00	13.0	0.00
0	0.2	18.4	0.18	11.2	0.07	12.3	0.06
0.4	0.2	18.0	0.20	9.8	0.26	10.8	0.25
0.6	0.2	17.6	0.24	8.6	0.47	9.6	0.45
0.8	0.2	16.9	0.29	7.8	0.54	8.8	0.52
Contracting muscle							
0	0	16.4	0.25	8.7	0.00	12.6	0.00
0.4	0.2	15.0	0.30	5.7	0.47	9.4	0.44
0.6	0.2	11.4	0.58	1.5	1.37	3.5	1.45

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Table 5
Variation of PO_2 along Four Capillaries under Different Conditions

$CV(f_{RBC})$	$CV(P_0)$	Cap. 6		Cap. 7		Cap. 10		Cap. 11	
		f_{RBC}	P_0	f_{RBC}	P_0	f_{RBC}	P_0	f_{RBC}	P_0
0	0.2	7.0	32.5	7.0	29.4	7.0	35.2	7.0	23.2
0.4	0	3.9	27.0	3.1	27.0	10.5	27.0	2.7	27.0
0.4	0.2	3.9	32.5	3.1	29.4	10.5	35.2	2.7	23.2