Effects of anatomic variability on blood flow and pressure gradients in the pulmonary capillaries

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1Department of Mechanical Engineering and Center for Biomedical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139; 2Pulmonary Research Laboratory, University of British Columbia, Vancouver, British Columbia, Canada V6R 1Z3; and 3Physiology Program, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts 02115

Dhadwal, Amit, Barry Wiggs, Claire M. Doerschuk, and Roger D. Kamm. Effects of anatomic variability on blood flow and pressure gradients in the pulmonary capillaries. J. Appl. Physiol. 83(5): 1711–1720, 1997.—A theoretical model is developed to simulate the flow of blood through the capillary network in a single alveolar septum. The objective is to study the influence of random variability in capillary dimension and compliance on flow patterns and pressures within the network. The capillary bed is represented as an interconnected rectangular grid of capillary segments and junctions; blood flow is produced by applying a pressure gradient across the network. Preferred flow channels are shown to be a natural consequence of random anatomic variability, the effect of which is accentuated at low transcapillary pressures. The distribution of pressure drops across single capillary segments widens with increasing network variability and decreasing capillary transmural pressure. Blockage of one capillary segment causes the pressure drop across that segment to increase by 60%, but the increase falls to <10% at a distance of three segments. The factors that cause nonuniform capillary blood flow through the capillary network are discussed.

PULMONARY BLOOD FLOWS through a complex capillary network consisting of an interconnecting system of short capillary segments. The typical capillary pathway connecting an arteriole with a venule consists of 40–100 segments (24). Videomicroscopic studies in subpleural capillaries have revealed highly nonuniform flows, with some segments being constantly perfused and others in which the flow is intermittent (12, 13). It has been shown that recruitment within acini occurs at the level of the capillary bed rather than the arterioles or venules (1, 10, 12, 13) and that more segments are recruited as transcapillary pressure increases and as septal tension decreases (15). The physical basis for many of these observations has yet to be fully elucidated.

Previous investigations have taken one of two approaches to modeling capillary blood flow. Fung and Sobin (6, 7) developed the sheet-flow model for the pulmonary capillary network, recognizing the highly interconnected structure of capillaries in the alveolar septae. In this approach, blood is modeled as flowing in the space between two compliant sheets, with the effects of individual capillary geometry and the two-phase nature of blood represented by an increase in the effective resistance to flow. This model, combined with network representations for the arterial and venous networks, has been very helpful in understanding the pressure-flow behavior seen in the lung (6) but cannot address issues relating to the distribution of blood among the individual capillary segments. Flows and pressures predicted by this model are effectively averaged over a volume containing multiple capillary segments, and the flow through a single segment or the pressure drop across it cannot be directly inferred. Furthermore, the effects of segment-to-segment variability in dimension or compliance cannot be evaluated, since the averaging is performed before flow is calculated.

A different approach has been used in the systemic capillary bed, which is characterized by longer capillaries with fewer interconnections; in such models, discrete capillaries are arranged in a network with prescribed geometry and boundary conditions. Various models of this type have been developed (19–22), but in cases in which a direct comparison has been made between predictions and in vivo measurements, the predicted resistance has been lower than that measured by a factor of as much as 2 (20, 21). Despite these discrepancies, the discrete capillary model is the current standard used to represent systemic capillary blood flow.

Red blood cells (RBC) and neutrophils travel through the pulmonary capillary network, which is complex and vastly interconnected. Relative to RBC, which, on average, traverse the lung slightly more rapidly than plasma, a large percentage (50–80%) of neutrophils are delayed in their passage through the pulmonary capillary bed (8, 9). In their transit through 40–100 capillary segments, virtually all neutrophils encounter at least one capillary segment that is too narrow to pass through unimpeded (2), and the neutrophils must change shape before they can pass through. The transit time of neutrophils in the lung can be transiently lengthened by increasing intra-airway pressures (15, 16), which alters the dimension and configuration of the individual capillaries so as to make it more difficult for neutrophils to pass through. Because their transit times are longer than those of RBC, the concentration of neutrophils is greater in the lung than in the systemic circulation by a factor of 50 (9, 10, 12). This phenomenon, termed neutrophil margination, is thought to provide a means by which the body can maintain a reservoir of neutrophils in the lung for host defense.
The purpose of this study was to develop a computational model describing blood flow through the pulmonary capillary bed. Anatomical data describing the capillary segments were used as the basis for random variability in vessel size and network compliance. This model was utilized to examine the effect of physiologically relevant variability in capillary dimensions and compliance on blood flow through segments and on perfusion patterns within the capillary bed as a whole. In addition, the pressure gradient across a single capillary segment was calculated, as well as its variability between segments. This study tested the extent to which preferential pathways of perfusion are produced within the capillary bed as a direct consequence of random variability in capillary dimensions or compliance. Finally, the effect of blocking one segment (mimicking an obstructing neutrophil) on blood flow, resistance, and pressure gradients across neighboring segments was also evaluated.

METHODS

Description of the Computational Model

Governing equations. The model simulates blood flow in a single alveolar septum represented by a network of interconnected capillaries arranged into a $6 \times 6$ square matrix (Fig. 1). This network is divided into segments and junctions. A capillary segment is the vessel through which the blood flows; a junction is the connecting region between segments, defined as the hatched region in Fig. 1 (bottom left). The equations derived below governing flow through the network are written in terms of a unit cell, which we define as a junction, along with the four half-segments connected to it, i.e., the square region inside the dashed lines in Fig. 1, bottom left, with sides of length $W$. In this representation of septal geometry, the length of each segment is equal to the diameter of the tissue spaces that separate each capillary from its neighbors. These tissue spaces are taken to be all of the same diameter ($D_h$) at a given lung volume ($V_L$). The junction height ($h$) varies from one junction to the next. Each segment is divided in half, with each half sharing the height of its adjacent junction.

For the purpose of flow calculations, the segment is characterized by its hydraulic diameter ($D_h = 4A/S$, where $A$ is the local cross-sectional area and $S$ the inside perimeter of the cross section), which varies as a function of distance along the axis of the segment. The segment cross section is assumed to be elliptical, except in the comparison to the theoretical calculation of Tsay and Weinbaum (25), where it is assumed to be rectangular, consistent with their theoretical model.

The compliance of each unit cell is defined in terms of the ratio of the change in unit cell volume to the pressure change needed to produce it. Following Fung and Sobin (7), local segment or junction compliance ($\omega$) is assumed to be independent of transmural pressure and $V_L$, so the height of the capillary is locally given by

$$h = h_0 + \alpha(P - PA)$$

(1)

where $P$ is the local capillary pressure and $PA$ is alveolar gas pressure. The height at zero transmural pressure ($h_0$) is selected from a normal distribution with specified variance and assumed to vary in the same manner as the height of the intervening tissue space. For the purpose of calculating the local height, $P$ is assumed uniform over the junction and one-half the length of each of the four neighboring segments. Therefore, a volume compliance ($\beta$) is introduced, defined as that associated with a unit cell, analogous to Eq. 1

$$V_{uc} = V_{uc,0} + \beta(P - PA)$$

(2)

where $V_{uc}$ is the volume of a unit cell. The value of this unit cell compliance is allowed to exhibit random variability, being selected from a normal distribution. Volumes are calculated as the height multiplied by the area in the plane of the septum, with $V_{uc,0}$ being the unit cell volume at zero transmural pressure. In the simulations of breathing, $h_0$ and $V_{uc,0}$ are functions of $V_L$ and, therefore, of time.

The fluid dynamic calculations are complicated by the need to take into account the presence of RBC and the complex...
geometry of the network. The increase in flow resistance due to the deformation of RBC as they pass through small capillaries is represented by an apparent viscosity (μ_app) of the form (11)

\[
μ_{app} = \frac{μ_p}{1 - \left(1 - \frac{H_b}{μ_c}\right)\left(1 - \frac{2D_i}{D_h}\right)\left(1 - \frac{D_m}{D_h}\right)}
\]  

(3)

where \(μ_p\) is the viscosity of plasma (in Pa·s) and \(μ_c = \exp(0.48 + 2.35H_d)\), where \(H_d\) is the large vessel hematocrit, \(D_m = 2.7 \, \mu m\) is the diameter of the smallest vessel blood can flow through, and \(\Delta = 2.03 - 2.0H_d\). This expression is based on results for glass tubes with circular cross sections and is assumed to be approximately valid in the present application, when the capillary is assumed to be elliptical in cross section and the actual diameter is replaced by hydraulic diameter \((D_h = 4 \times \text{area/perimeter})\). Equation 3 also assumes that each capillary can be treated as having the same feed hematocrit at the capillary entrance.

An approximate form for the flow resistance of each capillary segment is used (4)

\[
\frac{ΔP}{Q} = \int_{-D/2}^{D/2} \frac{μ_{app}Re_{Dh}f_d}{2A_iD_h^2} \, ds
\]  

(4)

where \(\dot{Q}\) is flow rate, \(A_i\) is the local cross-sectional area of the segment at a location \(s\) along its axis, \(D_i\) is its hydraulic diameter, \(Re_{Dh}\) is the Reynolds number based on \(D_h\), and \(f_d\) is the Darcy friction factor defined by

\[
f_d = \frac{-\frac{dP}{dx}}{\frac{1}{2} \rho u^2} \quad (5)
\]

where \(u\) is the local mean velocity and \(ρ\) is fluid density. The integration is performed along the segment axis from one junctional boundary to the next. \(D_h\) is computed on the basis of the local height and width, assuming an elliptical cross section. Whereas the integral in Eq. 4 could be analytically determined, in practice, the integration is carried out numerically using the trapezoidal rule based on values of the integrand at five equally spaced locations; by use of this approach, other, less easily integrable, capillary geometries can also be considered.

The resistance of the junction is more difficult to calculate and subject to a greater degree of uncertainty, since it depends not only on junctional geometry, but also on the distribution of flow among the four adjacent segments. One limiting case is obtained by assuming the flow to be approximately unidirectional in passing from one segment to its opposite neighbor, with no flow entering or leaving from either side branch. In this case, the resistance \((R)\) of a square junction can be estimated from the equation for unidirectional viscous flow between parallel plates (4)

\[
R = \frac{ΔP}{\dot{Q}} = 12μ_{app}/h^3
\]  

(6)

When the flow is nonuniformly distributed among the four segments, the resistance of the junction will, in general, differ from that given by Eq. 6 but will likely be of similar form; i.e., the dependence of \(ΔP\) on \(h\) and \(μ_{app}\) would be the same as in Eq. 6, but the numerical coefficient would differ. The junctional resistance is therefore assumed to satisfy

\[
R_j = K_j \frac{12μ_{app}}{h^3}
\]  

(7)

where \(K_j\) is an undetermined numerical coefficient. The value used in the calculations was obtained by matching exact solutions for flow between parallel plates with periodic, identical cylindrical posts (25), as described below.

In the calculations, nodes were placed at the center of each junction. The resistance to flow between adjacent nodes was taken to be the sum of the resistance of the intervening segment (Eq. 4) plus one-half the resistance of each of the two junctions (Eq. 7). The compliance of each node is that given by Eq. 2. Thus the septal capillary bed can be thought of as a collection of resistors and capacitors arranged on a square grid and is solved accordingly.

In steady flow, mass conservation simply states that all flows entering and leaving a junction sum to zero. When the flow is unsteady due to breathing or pressure pulsations, the net rate at which blood flows into a unit cell is balanced by the accumulation of blood within it. The equation expressing mass conservation for the unit cell is

\[
\dot{Q}_1 + \dot{Q}_2 + \dot{Q}_3 + \dot{Q}_4 = \frac{dV_{uc}}{dt}
\]  

(8)

where the subscripts denote the four capillaries connected to a junction and \(\dot{Q}_1, \dot{Q}_2, \dot{Q}_3,\) and \(\dot{Q}_4\) represent volume flow rates in Fig. 1; flow into the junction is positive, and flow out of it is negative.

Solution procedures. This set of coupled equations (Eqs. 2–5, 7, and 8) completely describes the distributions of pressure and flow in the interior of the septal bed. It remains to specify the boundary conditions, which, in the present simulations, are stated in terms of the pressure distribution around the septal circumference. Pressure is assumed to be independent of time, varying linearly along the sides of the septum from a maximum at one corner to a minimum at the diagonally opposite corner.

Simulations are performed under static conditions and under conditions simulating breathing. The changes in \(V_L\) associated with breathing are modeled by specifying time-varying dimensions and compliance. Isotropy in the plane of the septum was assumed to occur during changes in \(V_L\), so that septal length (\(L\)), unit cell length (\(W\)), and \(D_h\) are each assumed to vary as \(V_L\). The tissue spaces are regions of essentially incompressible tissue separating the capillary segments; therefore, their volume, \(\pi D_h^2 h_i/4\), where \(h_i\) is the height of the tissue region, is assumed constant during changes in \(V_L\); \(h_i\) consequently varies as \(V_L^{-1}\). Because the capillaries are tethered to the surrounding tissue spaces, we also assume that the junction height at zero transcapillary pressure varies as \(V_L^{-1}\). For present purposes, breathing is simulated by a sinusoidal variation in \(V_L\) with a magnitude equal to 29% of the mean value (e.g., mean \(V_L\) of 3.5 liters and tidal volume of 1 liter).

In other simulations the effect of blockage of a single segment (as might occur as a neutrophil encounters a narrow segment) is investigated by setting the resistance of that segment to a high, effectively infinite value. These simulations are performed to investigate the sensitivity of segmental pressure drop and flow distribution to local blockage.

The set of governing equations and boundary conditions is solved numerically with a program written in the computational software Matlab (Mathworks, Natick, MA). The solu-
tion algorithm used is fourth-order Runge-Kutta. Pressures and flow rates depend on location and time when VL is varied with time to simulate breathing, but only on location when steady calculations are performed.

Selection of the Parameters

Variability in $h_0$ and $\beta$. Random variability in network dimensions and compliance is introduced by independently selecting $h_0$ and $\beta$ from normal distributions with means and standard deviations based on data available from the literature. The measurements of Doershuk and colleagues (2) provided an estimate of capillary segment width (in the plane of the septum), and variability in height was assumed to be of comparable magnitude. For the variability in compliance, the results of Sobin et al. (23) in cats were used as a rough guide to make our estimates. The standard deviation in height was estimated from the data to be $\sim 30\%$ and the standard deviation in compliance $\sim 50\%$; these values were used as maximum values in the simulations below.

Values of $K_j$. To determine $K_j$ for junctional resistance in Eq. 7, the results from the present model for a case with no variability (each junction and each segment identical to the rest) and zero compliance (so that capillary pressure has no effect on dimensions) are compared with the analytic predictions of Tsay and Weinbaum (25) (hereafter referred to as TW). For this comparison, boundary conditions of uniform pressure along one side of the septum, uniform but lower pressure along the opposite side, and a linear gradient in pressure along the two edges are imposed so that the mean flow direction is essentially parallel to the sides of the matrix. The TW results are expressed in terms of a friction factor ($C_f$), which, for the present comparison, is defined as follows

$$\frac{dP}{dx} = -12\mu C_f \frac{\bar{U}}{h^2}$$

where $\bar{U} = \dot{Q}/hW$. For flow between parallel plates without posts, $C_f$ would equal unity; the additional friction due to posts leads to values of $C_f$ considerably greater than unity, as shown in Fig. 2. To compare the exact analytic solution from the TW theory with the present approximate one, a value for $C_f$ can be determined from the present model by computing the resistances of the segment (Eq. 4) and junction (Eq. 7) and combining them to obtain the resistance of a unit cell. This results in the following relationship in terms of the friction factor

$$C_f = K_j + \int_{-D/2}^{D/2} \frac{h^4 R_e b f_d}{24 A_N D_i^2} ds$$

If we assume, just for this comparison, that the segments have a rectangular cross section (as in the TW analysis) and perform the integration indicated above, the result plotted in Fig. 2 is obtained and compared with the TW solution for a wide range of geometries that encompasses those anticipated for the capillary bed. Solutions for two values of $K_j$ are shown: 1.0 and 0. Interestingly, the value for $K_j$ that provides the best agreement with the exact theoretical result in the range of interest is $K_j = 0$, the case that neglects the resistance of the junction. This indicates that the present approximate calculation overestimates segmental resistance but that it is possible to compensate in part for these errors by neglecting the contribution to the resistance from flow through the junction. For this reason, it is assumed in all the following that $K_j = 0$.

The exact analytic solution could not be used in the present simulations, since that solution only pertains to the case of a noncompliant square matrix of identical posts with uniform sheet spacing and segments of rectangular cross section. No such solution exists in the more general case studied here.

Other parameters. The other parameters of the model are taken from the literature. The septal capillary network, assumed square in this study, has a length $L$ of 75 $\mu$m at a reference $V_L$ ($V_{L.ref}$) of 3.5 liters, approximating functional residual capacity. The mean height of the unit cell (segments and junctions) at zero transmural pressure and $V_{L.ref}$ is taken to be 3.5 $\mu$m; the estimates of variability range up to 30%, approximately consistent with morphometric measurements in dogs and rabbits (2). The pressures at the boundary are based on estimates of the fall in pressure between arterioles
and venules of 4–8 cmH₂O and on the assumption that blood passes through ∼40–100 capillary segments on its journey through the lung. This leads to an estimate for the total pressure drop across a complete septum of ∼0.5 cmH₂O. Inlet pressures are taken to be 9.5 or 0.5 cmH₂O to simulate two different elevations in the lung. The compliance of each unit cell (β) is given a value of 0.127 µm/cmH₂O, with a standard deviation of up to 50%, which is roughly consistent with studies on cat pulmonary capillaries (23).

In cases simulating breathing, the pressure variations in the alveolar gas due to airway resistance must also be taken into account. Here we assume alveolar pressure excursions of ±1 cmH₂O.

Data Analysis

Effects of random variability on segmental flow and pressure drop. The variability in flow parameters resulting from segment-to-segment differences in size and compliance is demonstrated using qualitative and quantitative representations. The variability is described qualitatively using a flow mapping for the entire septum, with shading used to denote the magnitude of the local flow rate: white regions correspond to highest flow rates and black to the lowest according to the scale provided in Fig. 4. Junctional flow values are obtained by averaging the magnitude of flow in each of the four adjacent segments. These plots are useful for evaluating the existence of preferential perfusion pathways and provide a visual representation of flow variability.

Whereas the flow maps provide qualitative information on preferential flow, a quantitative measure is also useful for comparison between simulations and, potentially, between simulation and in vivo observation. For this purpose, we define a preferential perfusion pathway as the largest number of contiguous capillary segments with a flow rate greater than the average flow rate through all the segments. A measure of preferential flow is defined as the maximum number of contiguous segments with flows greater than a particular threshold value averaged over many random realizations (typically N = 14) with a given degree of random variability in segment dimension and compliance. The number of such contiguous segments (Nₚ) is plotted as a function of threshold level and presented for moderate and large variability in capillary dimension and compliance within the range observed experimentally.

Effects of segment blockage. These effects are presented in three ways. First, visual flow maps of the type described above are presented to provide an overall view of the flow redistribution associated with blockage of a single segment. Second, the frequency distribution of pressure gradients across a capillary segment was calculated for "no variability" and "mild" and "maximum" degrees of variability in compliance and capillary height. Third, the effect on local pressure drop is plotted as a function of distance from the blocked segment, measured as the number of segments distant from the occluded segment along the shortest path. For this, a parameter

$$\Pi = \frac{\Delta P_{nb} - \Delta P_{b}}{\Delta P_{nb}}$$

(11)

is defined, where subscript b denotes the value when one segment is blocked and nb the value when no blockage is present. This parameter is plotted as a function of number of segments from the blocked segment.

RESULTS

Effects of Time-Varying Geometry

To justify the assumption that the flow can be treated as steady, despite the known time dependence associated with breathing, we first examined the effects of temporal variations in network dimensions and compliance, as described in METHODS. The results are illustrated in Fig. 3, which shows the time-varying flow rate and resistance across one segment in relation to the phase of the variations in septal length. The resistance curve is in phase with septal length, an indication that the resistance is determined by the dimensions of the segment, which, in turn, depend on septal length. Segmental flow rate is inversely related to resistance. The variations in pressure drop (not shown) are of small magnitude.

To examine the importance of unsteadiness during breathing, the unsteady results are compared at selected time points with corresponding steady calculations in which all parameters were identical. The results of these steady simulations are compared with results from the unsteady calculation in Fig. 3. The close agreement between the two substantiates our claim that the flows are essentially steady, despite the time-varying nature of septal geometry.

Effect of Variability in h₀ and β

The qualitative effects of random variability are shown in Fig. 4 for two levels of mean capillary pressure and three degrees of variability: no variability; mild variability, defined as 15% variability in h₀ and 25% variability in β; and maximal variability, defined as 30% variability in h₀ and 50% variability in β.
Blood flow generally proceeds along a path from the lower left toward the upper right (Fig. 4), initially uniformly for a network lacking any variability, but with increasing nonuniformity as the degree of variability is progressively increased. Even with the maximum variability modeled here, however, the direction of flow in each of the segments does not change from the completely uniform case.

The effect of geometrical and mechanical variability is quantitatively assessed by computing the coefficient of variation (standard deviation/mean) of all the segmental flows or pressure drops for ~12 realizations of a particular steady calculation (Table 1). As anticipated, the degree of nonuniformity in segmental flow increases with increasing variability in $h_0$ and $b$ but is somewhat smaller in magnitude; even with 50% variation in $b$ and 30% variation in $h_0$, the variability in flow rate is only 29% at high pressure but increases to 55% at low pressure. The results are more sensitive to changes in $h_0$, a fact that can be readily appreciated by noting in Eq. 1 that the capillary height is more sensitive to changes in $h_0$ than to changes in $b$.

One interesting feature of these results is the apparent existence of preferential perfusion pathways, which are characterized by several contiguous segments carrying a flow rate significantly greater than average. The extent of preferential flow increases at the lower inlet pressure. Although readily seen by eye in Fig. 4, preferential flow is expressed in more quantitative terms in Fig. 5. For example, at the high inlet pressure of 9.5 cmH$_2$O, the number of contiguous segments that carry a flow rate >125% of the mean (1.25 threshold fraction) is ~5 for the maximum amount of variability in $h_0$ and $b$ and drops to 3 when the variability is reduced twofold. These effects are accentuated as mean pressure is reduced. At the low inlet pressure of 0.5 cmH$_2$O and a threshold fraction of 1.3, the number of contiguous segments is >7 for maximum variability but decreases to <3 when variabilities are mild.

Of particular interest with regard to the transit of neutrophils through the capillary bed is the pressure drop across a single segment. The distribution of segmental pressure drops is shown in Fig. 6 for no, mild, and maximum variability at low and high inlet pressures. Note that the mean pressure drop is ~0.05 cmH$_2$O in each case, one-tenth of the septal pressure drop, and that the variability increases with increased variability and with reduced pressure. The coefficient of variation remains relatively small, however, increasing only to 0.28 for maximum variability.

### Effect of Segment Blockage

The effect of local blockage is characterized by first computing the segmental flow rates and pressure drops before blockage, then repeating the identical simulation but with a single segment blocked. These results are presented only for the higher capillary pressure. As one would expect, the flow distribution is markedly altered in the segments immediately adjacent to the blocked segment, but the effect lessens with increasing distance from the blockage site, as shown in Fig. 7 for a typical simulation. Figure 6 compares the frequency distributions for segmental pressure drop with no, mild, and maximum degrees of variability in compliance and height with and without one blocked segment. The distribution is no longer Gaussian in form when one segment is blocked because of the relatively large increases in pressure drop that occur across the blocked segment and those segments immediately adjacent to

**Table 1. Variability in flow rate among individual segments in a septum**

<table>
<thead>
<tr>
<th>Variability in</th>
<th>$h_0$</th>
<th>$h_0$</th>
<th>$h_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>0.004 (H)</td>
<td>0.15</td>
<td>0.23</td>
</tr>
<tr>
<td>25%</td>
<td>0.026 (L)</td>
<td>0.18 (H)</td>
<td>0.25</td>
</tr>
<tr>
<td>50%</td>
<td>0.17</td>
<td>0.26 (L)</td>
<td>0.29 (H)</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>0.23</td>
<td>0.55 (L)</td>
</tr>
</tbody>
</table>

Values are SD/mean for all 9 combinations of no variability, mild variability, and maximum variability in capillary compliance ($b$) and height ($h_0$). Values along diagonal are given high (H) and low (L) pressure cases; other values correspond to high pressure case only.
it. Interestingly, although the mean pressure drop increases, some segments experience a lower pressure drop than in the unblocked case; with the redistribution of flow, although most segments carry more flow, some also carry less. The difference in segmental pressure drop between the pre- and postblocked values, characterized by $p_{in}$ in Eq. 11, is plotted in Fig. 8 as a function of the shortest distance (in number of segments) separating the segment of interest from the blocked segment. For the greatest degree of variability, the pressure drop across a segment increases by an average of 60% when blocked, but that increase falls to just 14% two segments away from the point of blockage.

**DISCUSSION**

The model presented here departs from previous models of pulmonary blood flow, in that the individual capillary segments are treated as discrete vessels, rather than in an averaged sense, as in the sheet flow models of Fung and Sobin (6, 7). The advantage of this approach is that the flows and pressure drops across individual segments can be computed and the natural variability of the capillary network can be directly introduced. The disadvantages, of course, are greater computational complexity and the need for more detailed knowledge about the characteristics of individual capillary segments and junctions and the nature of their interconnectedness. Although we lack the detailed, quantitative anatomic information to fully utilize the capabilities of the present model, sufficient data exist to provide some approximate answers to questions concerning the factors that contribute to flow variability in the capillary network and the distribution of pressure drops across individual segments, with and without local obstruction.

**Preferred Flow Channels Resulting From Variability**

Preferred perfusion pathways were observed in our simulations with physiological levels of variability in $h_0$ and $\beta$. This was not altogether unexpected and is qualitatively consistent with in vivo observations. Preferred pathways might result from different factors related to variations in flow, anatomy, or compliance. In the presence of anatomic variability alone, certain junctions will necessarily have a greater than average rate of inflow while others have a lower than average rate. In those with greater inflow, outflow must, by conservation of mass, be greater than average as well. In addition, because the outflow segments have different resistances due to their own variability, one will carry a flow that is greater than the average inflow rate while the other will carry one that is less. The next junction encountered by the outflow segment with the greater flow rate is also more likely to have a higher than average total inflow rate, thus perpetuating the high-flow pathway. The greater the degree of variability in $h_0$ and $\beta$, the greater are these variations in local flows. That the degree of preferential flow observed is greater than would occur by chance can be demonstrated by the following calculation. For each of the 12 realizations in the case of maximum variability and low mean pressure, we take all the values for segmental flow, then reassign the individual flows to new segments by random selection. With this new distribution, the mean and standard deviation are unchanged, but the number of contiguous pathways at any given threshold is lower than in the original calculations, as shown by the solid curve in Fig. 5.

Anatomic features could accentuate the frequency or extent of preferential perfusion pathways that are present as a necessary consequence of variability and mass conservation. If, for example, an anatomic correlation existed, such that the presence of one large (low-resistance) inflow segment increased the likelihood that one of the outflow segments would also be large, then preferential flow would be greater than predicted in the present model, where each segment diameter is completely uncorrelated with that of adjacent seg-
ments. Another factor contributing to preferential flow is the presence of neutrophils. Should one segment become blocked, blood will be shunted to neighboring segments, producing regions of locally high flow. This tendency can be seen to some extent in Fig. 7, where one segment was blocked. In vivo, this effect may be even larger, and 1 of 11–16 capillary segments may contain a neutrophil at any moment in time (10).

The effect of differences in mean transcapillary pressure is readily demonstrated in Figs. 4–6. As one would expect, a reduction in mean pressure reduces the diameter of all segments, making it more difficult for RBC to pass through them. This can also be viewed in terms of the rapid increase in $\mu_{app}$ toward infinity (Eq. 3) as the capillary diameter approaches 2.7 µm. Because the viscosity and, consequently, resistance become more sensitive to vessel diameter as diameter is reduced, the variability in segmental flow rates and pressure drops increases as does the measure of preferential flow.

Our definition of preferential pathways should be distinguished from that used by Okada et al. (18). In their work, preferential pathways were those that were observed to convey blood flow consistently during multiple observations. The fact that the septal flow pattern was not consistent from one observation to the next suggests that some aspect of the network (e.g., the degree of local constriction) changed in the intervening time so as to redistribute the flow. Features such as these can obviously not be captured by the present model. Okada et al. (17) also observed that, at any instant, certain pathways were perfused while others had no discernible flow. Although there were segments in which the computed flow was considerably lower than average, flow approached zero only when the mean capillary pressure was reduced. Even then, the fraction of segments without flow was considerably smaller than observed by Okada and colleagues (17). A possible explanation for this discrepancy was found by West et al. (27), who demonstrated that much of the behavior associated with recruitment, including intermittent and reverse flow, could be captured with a network model in which there existed a critical segmental pressure drop (or “break-point pressure”) that had to be exceeded before any significant flow could occur. They suggested that nonzero break-point pressures could be caused by sticking of RBC, RBC aggregation, or occlusion of capillary segments by neutrophils. The critical pressure required for this behavior was found to be on the order of 0.02 cmH$_2$O, or roughly 40% of the mean segmental pressure drop in the present study. If the concept of a break-point pressure were introduced into the present model, more realistic flow patterns would likely be observed.
Pressure Drops

Pressure drops across a single capillary segment vary considerably (from 0.01 to 0.1 cmH2O) with a mean of ~0.05 cmH2O on the basis of the assumption that the total septal pressure drop is ~0.5 cmH2O. This estimate is based on limited information concerning the actual septal pressure gradients that may vary by as much as a factor of ~3 from this value. Despite this uncertainty, however, compared with the typical range of pressure drops across systemic capillaries, these segmental pressure drops are extremely small. Because of the different branching structure of the systemic vascular bed, the pressure drop across a single capillary can be estimated to be >3 cmH2O (14). These pressures are more than sufficient to deform a neutrophil to the point that it can rapidly pass through the capillary, consistent with the observation that neutrophils pass through the systemic capillary bed unimpeded. The behavior of neutrophils under the action of pressure drops as small as 0.05 cmH2O has not been studied. Measurements using micropipettes at higher pressures and for experiments of limited duration (3), however, show that at least 0.1 cmH2O is required to draw a neutrophil into a 5-µm-diameter pipette.

Effects of Local Blockage on Flow

Blockage of a single capillary segment produces significant effects locally, in flow rate and pressure drop. These effects fall off rapidly with distance from the site of obstruction due to the high degree of network interconnectedness. By a distance of three segments from the blockage, the perturbations in flow and pressure drop fall to <10% of the mean. Indeed, similar results were obtained by Wiggs (28) using a resistance network in which the values of resistance were randomly selected. The practical implication of this result is that blood flow is readily shunted to neighboring segments when one becomes blocked. These effects are also reflected in the overall network resistance. If we define septal resistance as the corner-to-corner pressure difference divided by the total flow entering through all the edge segments, septal resistance increases by an average of only 5% as a result of blockage of one segment.

A 60% increase in segmental pressure drop due to blockage will facilitate neutrophil transit through a segment in which it becomes lodged. Whether this increase alone is sufficient to passively push a neutrophil through a segment or whether active rearrangement of cytoskeletal protein is required remains to be determined.

These results should be contrasted with those obtained from models of the systemic microcirculation (5, 26). In those studies the effect of neutrophil plugging on overall resistance was found to be small, a result that was partly attributed to the roughly fivefold increase in segmental pressure drop associated with blockage. Although the present model also predicts a relatively small change in network resistance from blockage of one segment, the increase in segmental pressure drop due to blockage in the pulmonary circulation is considerably smaller (~60%). The magnitude of this increase is obviously a strong function of the degree of interconnectedness of the network. Because of this and because the initial segmental pressure drops in the lung are smaller as well, the pressure difference causing deformation of the neutrophil is greatly reduced in the lung compared with other parts of the circulation. This fact likely contributes to the formation of the large marginalized pool.

Critical Assumptions in the Current Model

Despite our attempts to incorporate into the model certain aspects of the discrete nature of the pulmonary capillary bed, this limitation is made necessary by the need to make certain assumptions and approximations. The alveolar septum is represented by a rectangular grid of capillaries in which each junction connects four capillary segments, whereas direct observation suggests a less regular structure. Corner vessels, which tend to behave differently from septal vessels, are not considered, except to assume that they lead to a linear variation in pressure around the septal boundary. Variability has been introduced, but in a somewhat limited fashion; dimensional variability is assumed only in the height of the capillaries, not in their width or in the dimensions of the intervening tissue spaces. Similarly, changes in transmural pressure are assumed only to affect the height of the capillary, the width being a function only of VL.

Various assumptions are also implicit in the fluid dynamic analysis, including our treatment of the effect on segmental resistance of RBC and our use of hydraulic diameter in calculating the resistance of the segments and junctions. Errors would arise due to the nonuniform hematocrit observed in the capillaries, leading to different viscosities according to Eq. 3. The dependence of viscosity on hematocrit, however, is not particularly strong and leads to a variation of only 10% in $\mu_{app}$ for hematocrits ranging from 0.2 to 0.45 in a 6-µm-diameter capillary. The errors introduced by the
use of hydraulic diameter to calculate segmental flow resistance are reflected by the differences of up to 30% shown in Fig. 2 between the present model and the TW theory (25). In this connection, we note the considerable errors (of up to 50%) that have been observed in the predictions of other capillary flow models (19, 20, 21) and argue that our errors are probably of comparable magnitude.

Finally, it should be noted that the calculated changes in flow patterns and pressure drops due to local blockage pertain only to the case in which the blockage is maintained sufficiently long enough so that the flow distribution has had time to readjust to the new flow condition and do not address issues associated with transient plugging. In view of the short time constant seen for flow adjustments during breathing, these results would be valid for blockages that persist even for times shorter than the breathing period. These results do not, however, provide any insight into the time-averaged flow characteristics of a network in which multiple segments are transiently blocked and unblocked.

Summary

This model uses the presently available anatomic and physiological data to begin to ask questions and frame testable hypotheses about the regulation of blood flow through the pulmonary capillary bed and the mechanisms important in neutrophil transit through this bed. The results show that the physiologically relevant degrees of variability in capillary diameter and compliance result in preferential perfusion patterns that become more accentuated at lower transcapillary pressures. The effects of a single obstruction serve to increase the pressure drop across the blocked segment by ~60%. These effects are felt only locally, dropping to <10% in a distance of three segments. The small pressure gradients across capillary segments likely lengthen the deformation times and the capillary transit times of neutrophils, contributing to the formation of the marginated pool.

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REFERENCES