Computational modeling of RBC and neutrophil transit through the pulmonary capillaries

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Huang, Yaqi, Claire M. Doerschuk, and Roger D. Kamm. Computational modeling of RBC and neutrophil transit through the pulmonary capillaries. J Appl Physiol 90: 545–564, 2001.—A computational model of the pulmonary microcirculation is developed and used to examine blood flow from arteriole to venule through a realistically complex alveolar capillary bed. Distributions of flow, hematocrit, and pressure are presented, showing the existence of preferential pathways through the system and of large segment-to-segment differences in all parameters, confirming and extending previous work. Red blood cell (RBC) and neutrophil transit times depend on how the effective capillary diameter is defined. Transient blockage by a neutrophil can increase the local pressure drop across a segment by 100–300%, leading to temporal variations in flow and pressure as seen by videomicroscopy. All of these effects are modulated by changes in transpulmonary pressure and arterial pressure, although RBCs, neutrophils, and rigid microspheres all behave differently.

The pulmonary capillary network is a geometrically complex, distensible, and vastly interconnected structure, containing a high concentration of neutrophils available on demand for host defense. In passing from arteriole to venule, a typical blood cell encounters 40–100 segments (3, 16, 17, 38). Because the average capillary diameter is similar to or smaller than the average size of a neutrophil (34, 39), a neutrophil often encounters a capillary segment that requires it to pause and change shape before passing through (2). Consequently, in contrast to red blood cells (RBCs), which generally traverse the lung in a few seconds with little or no observable delay (29), about one-half of the neutrophils stop at least once in their passage through the lung (14, 16) and take a few seconds to traverse the pulmonary capillary bed (24). Geometric changes in the capillary networks with changes in transpulmonary (Ptp) and transmural (transcapillary) pressure (Ptm) and the deformation of neutrophils during their transit are believed to play crucial roles in modulating neutrophil transit through, and capture within, the pulmonary microvasculature, although these effects have never been modeled. Because of their long transit times through the pulmonary capillaries, the concentration of neutrophils is 50-fold greater in the lung microvasculature than in the systemic circulation (23, 28, 31). This phenomenon, here termed neutrophil margination (not to be confused with the adhesion of neutrophils to venular walls), is thought to provide a means by which the body can maintain a reservoir of neutrophils in the lungs that can be recruited to combat infection.

Recently, our laboratory developed a discrete capillary model to describe blood flow through the pulmonary capillary bed (1). In that model, a single alveolar septum was represented by a network of interconnected capillaries arranged into a 6 x 6-square grid with a linear pressure distribution along the boundaries. While useful in many respects, this model is limited in the simulation of pulmonary blood flow by the idealized geometric arrangement in which the junction connects four perpendicular segments and by a fixed linear pressure distribution along the network boundaries. Also, although this model does account for capillary compliance to changing transcapillary pressure, it lacks the capability of simulating the effect of changes in lung volume with Ptp, which is crucial, more generally, in the evaluation of neutrophil transit time. Because of these limitations in the previous model, neutrophil transit was not considered.

In the present study, we develop new pulmonary flow and cellular transit models to address many of these complicating issues relating to RBC and neutrophil passage. The purpose of the model is both to provide further insight into existing experimental observations and to suggest new testable hypotheses concerning pulmonary microcirculatory transit. Geometrically re-
alistic pulmonary capillary networks are generated computationally, based on measurements of alveolar septal structure. A tissue-membrane model is developed to describe the geometric changes in capillary cross section with Ptm and Ptp. We develop models for blood flow through a single capillary, an alveolar septum, and multiple septa that lie between arteriole and venule and calculate the local blood flow, pressure distribution, and hematocrit distribution. Much of the paper is devoted to model development, but several issues of physiological significance are also investigated and discussed. We simulate RBC transit and compare our predicted RBC transit times with other investigators’ measurements. Capillary recruitment is also considered and compared with results from the literature. Neutrophil transit through the pulmonary microvasculature is simulated to study the effects of neutrophil-induced capillary blockage on the local resistance and pressure distribution, the delay of neutrophils during their transit, the venular aspect ratio of neutrophils, and neutrophil transit times. A sensitivity analysis is provided to show which of the various parameters exerts a strong influence on the results.

**BRIEF METHODS**

A detailed description of the model and the underlying equations is presented in the APPENDIX. Here we present a brief overview and discuss the fundamental assumptions of the model.

**Capillary networks.** The capillary segments are placed randomly in a plane representing a single septum. Their number, length, diameter, and level of interconnectedness (represented by the number of capillary segments that join at a junction) are based on the available anatomic data. A computer algorithm randomly generates the networks that match the mean statistics of the measurements. Examples of the networks generated in this way are shown in Fig. 1. The septum is considered to be a square sheet for the purpose of these calculations, bounded by corner vessels, each of which is shared by three intersecting septae. All flow is assumed to enter the septal network at one corner and exit from the opposite one.

**Capillary compliance.** A new theory was developed to describe the changes in capillary cross-sectional area and shape as a function of transcapillary pressure (capillary minus alveolar gas pressure) and Ptp (or lung volume). In the model, the circumference of each capillary is assumed to be composed of two parts: one that is tethered to the septal fiber matrix and expands and contracts with changes in septal dimension (length $a$), and another that is relatively thin and compliant, separating capillary blood from alveolar gas (length $C$) (see Fig. 2). Three parameters of the model, initial lengths $a_0$ and $C_0$, and wall stiffness $k_c$, are selected to best fit the available experimental data of Fung and Sobin (12, 13) (see Fig. 3).

**Capillary blood flow.** The model for flow through a single capillary segment and its associated junctions are loosely based on a previous model from our group (1) in which the flow speed is computed based on the segment dimensions, the pressure drop, and the apparent viscosity of the blood. The latter is calculated by first determining the hematocrit of the blood and then using an empirical expression based on measured pressure drops for flow through glass pipettes. Because the hematocrit in a given segment is a function of the rate of blood flow through the entire network, this calculation is performed by an iterative procedure that ultimately converges to the distribution of blood flow, hematocrit, and pressure that satisfies the complete set of governing equations. The resistance of the junction is also taken into account on the assumption that the junctional contribution is proportional to the portion of the junction’s surface area associated with a given segment.

**Corner vessels.** Corner vessels are treated differently because there are few data available on their dimensions or compliance. It is assumed that they remain circular and that each conveys a flow of blood equal to three times the average sepal capillary blood flow. This is admittedly arbitrary but, having tried several different assumptions, we found that it has relatively little effect on the overall flow characteristics. As new data on septal flow characteristics become available, these could be incorporated into the model.

**Hematocrit distribution.** It was mentioned above that the apparent viscosity, and hence the pressure drop across each segment, depends on the blood hematocrit. This is determined by computing, at each junction, the division of RBCs between the two or three tributaries. For this, we use the model of Levin et al. (23) to estimate the hematocrit in each branch, based on the flow rates down the branches. Note that, for highly nonuniform distributions, when the majority of the flow passes down one of the branches, the hematocrit in the opposite branch can become zero.
**PULMONARY CAPILLARY MODEL**

Fig. 2. Tissue-membrane structure of a capillary cross section. Ptm, transmural pressure; $a_1$, length of the tissue part of the circumference at Ptm $> 0$ for a given transpulmonary pressure (Ptp); C, length of the membrane segment of the circumference; $d$, distance between 2 capillaries; $R$ and $h$, radius and the height, respectively, of the cross section; $a_0$, angle.

**Network flow model.** Once the network has been constructed and the equations for compliance and flow resistance set, these can be cast into a set of equations that can be solved to yield the distributions of pressure, flow, and hematocrit throughout a given septum. The equations are those of mass conservation at each junction (the sum of the flows entering and leaving the junction equals zero) and the local relationship between blood flow rate through, and pressure drop across, each segment. The solution is based on pressures specified at the inlet and outlet to the network, alveolar gas pressure, and inlet hematocrit.

**Transit time calculations.** To estimate RBC transit time, we first calculate the time to pass through each individual segment and junction based on the computed flows and local geometry. It is assumed that the RBCs pass through at a speed equal to the mean speed of the blood multiplied by an empirically determined factor to account for the differences observed in transit time between the plasma and RBCs through the pulmonary capillary networks (29).

The time required for a neutrophil to stop and deform to a shape that would allow it to pass through a segment of a given dimension must also be considered. In addition, the pressure distribution in the entire network must be recomputed each time a neutrophil becomes lodged in a narrow segment to account for the subsequent redistribution of flow. The deformation and entry times were based on a combination of previous theoretical and experimental results. For small deformations (values of neutrophil radius to segment radius close to 1), we used the result from the linearized theory of Yeung and Evans (41) and for larger ratios, the experiments of Fenton et al. (8). The resulting expression for entrance time provided for a smooth transition between these two. It should be noted, however, that these results are all based on capillaries of circular cross section and need to be used with caution for capillaries that may have highly non-circular cross sections, such as those in the lung. This issue is discussed more at a later point. In addition to the entry times, the passing time through the segment and junction is also computed. For this purpose, we develop a model based on the prediction of Fenton et al. for the ratio of neutrophil velocity to bulk blood velocity in a capillary of circular cross section. The total time for entry and passage is summed for all segments traversed by a particular neutrophil and reported as the total transit time.

To simulate the transit times measured in vivo more realistically, it was necessary to link several septal networks together. We did this in serial fashion, letting all of the blood flow from one septum enter the next and so forth through to the venular end (Fig. 4). We chose to use a number of septae consistent with the number of segments encountered by a typical neutrophil on its passage through the lung as estimated by videomicroscopy (3, 16, 17).

**Parameter values.** To the extent possible, values for the model parameters were obtained from sources in the literature as indicated in Table 1. Values that could not be obtained directly were estimated. The effects of small variations in several of the more critical parameters are shown in the sensitivity analysis in Table 2.

**RESULTS**

**Changes in capillary height with pressures.** To evaluate this tissue-membrane model of the capillary cross section, our predicted relationship between capillary height ($h$) and Ptm was compared with Fung and Sobin’s (12, 13) measurements of cat septal thickness at Ptp = 10 cmH$_2$O over a range of Ptm. Figure 4 demonstrates that the curve predicted by the tissue-membrane model, with parameter values $a_0 = 6 \times 10^{-4}$ cm, $C_0 = 1.65 \times 10^{-3}$ cm, and $k_c = 16$ cmH$_2$O, agrees very well with Fung and Sobin’s experimental measurements. For the simulations presented in this

![Fig. 3. Comparison between our model-predicted capillary height ($a_0 = 6 \times 10^{-4}$ cm, $C_0 = 1.65 \times 10^{-3}$ cm, and $k_c = 16$ cmH$_2$O) with Fung and Sobin’s measurements of cat septal thickness at Ptp = 10 cmH$_2$O as Ptm is varied (12, 13). See Glossary for definition of terms.](image)

![Fig. 4. Serial connection of capillary networks (septa) simulating the pathway extending from arteriole to venule. A constant flow rate (Q) is maintained at each connecting exit-entrance site.](image)
Sensitivity analysis of parameters randomly chosen. The variation in these parameters around their mean values at the different locations of the network was ran-

capillary networks. Blood flows into the capillary networks from the lower left corner and out from the upper right corner. The arrows indicate the direction of flow and magnitude of the flow rate. These results are similar in character to those discussed at greater length by Dhadwal et al. (1) and are, consequently, not examined further here. Note, however, that, if any segment is blocked, the flow pattern will be changed. In contrast to the result of Dhadwal et al., who used a rectangular grid, blockage of one segment in this more realistic geometric model can, in some cases, even change the direction of flow.

**Hematocrit distribution.** The hematocrit distribution in the network with no segments blocked was examined by using a value at the entrance of 0.4. In the model, the nonuniform distribution arises due to the partitioning of RBCs at a bifurcation, with the segments receiving higher flows also having an increased hematocrit. Figure 6A shows that the hematocrits differ markedly in different capillaries, primarily as a result of variations in local flow rate caused by the combination of variations in segment diameter and network geometry. Some segments are almost void of RBCs, although plasma continues to flow, giving rise to hematocrits approaching zero. Figure 6B shows the hematocrit distribution in the same network but with one segment blocked. This blockage results in a significant change in the hematocrit distribution, especially in the vicinity of the blockage. Figure 7, A and B, gives the frequency distribution of hematocrits for the segments, which correspond to Fig. 6, A and B, respectively.

**Pressure distribution.** An estimate of the pressure drop across a capillary segment is critical for understanding neutrophil transit and calculating its transit

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**Table 1. Input parameters**

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source, Ref. No.</th>
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<td>$C_h$</td>
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<td>29</td>
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</tr>
<tr>
<td>$k_c$</td>
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<tr>
<td>$m$</td>
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<td>26</td>
</tr>
<tr>
<td>$N_r$</td>
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<td>24</td>
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<td>$P_{tp}$</td>
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<td>$\tau_0$</td>
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See Glossary for definition of terms.

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**Table 2. Sensitivity analysis of parameters**

<table>
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<th>Parameter</th>
<th>Variation, %</th>
<th>$\Delta Q/Q_0$</th>
<th>$\Delta_{RBC}/RBC_0$</th>
<th>$\Delta SD/SD_0$</th>
<th>$\Delta_{RBC}u/RBC_0u$</th>
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<td>3.8</td>
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<td>1.2</td>
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<td>$\Delta P_{av}$</td>
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<td>8.9</td>
<td>10.7</td>
<td>9.8</td>
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<td>$L$</td>
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<td>-23.9</td>
<td>0.4</td>
<td>31.4</td>
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<td>20.7</td>
<td>19.4</td>
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</tr>
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<td>$N_{seg}$</td>
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<td>$\mu$</td>
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<td>$\tau_0$</td>
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<td>50</td>
<td>2.9</td>
<td>6.1</td>
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See Glossary for definition of terms. A 10% decrease (or increase) in $k_c$ will result in a 7.6–10.0% increase (or 6.4–8.0% decrease) in capillary compliance when the Ptm is between 2 and 10 cmH$_2$O, $\Delta$ denotes change in each variable and the subscript 0 denotes reference conditions.
time. For a neutrophil to enter a narrow segment, the pressure difference across it must be greater than the “critical pressure,” which is here assumed to be that sufficient to draw a neutrophil into a micropipette of the same diameter (6). In many cases, the pressure drop across a patent capillary segment is insufficient to push a neutrophil through. The increase in segmental pressure drop due to blockage by a neutrophil, however, is often sufficient to raise the driving pressure above the critical level, thus allowing the neutrophil to pass. It is, therefore, crucial to evaluate the new pressure distribution in the network when a capillary is blocked.

Figure 8, A and B, shows the pressure distribution in the capillary network with and without a segment blocked, respectively. For these calculations, pressures are 10 cmH₂O at the network entrance and 9.1 cmH₂O at the network exit. Figure 9, A and B, corresponding to Fig. 8, A and B, gives the pressure drop across each segment. In this particular case, the pressure drop increases from 0.107 to 0.237 cmH₂O when the segment is blocked by a neutrophil. A single capillary obstruction typically results in a 100–300% increase in the pressure drop across the blocked segment. This estimate is considerably higher than previous estimates of ~60% (1). The increase is primarily due to a more accurate representation of network geometry; in
the present model, there are fewer capillary segments per septum, and, therefore, blockage of one induces a greater change in the blood flow distribution.

**Capillary recruitment.** Presson et al. (30) investigated the stability of capillary segmental opening in single alveolar septae by observing the reproducibility of the perfusion pattern when the same perfusion pressure was repeatedly applied to the networks. Their results show that, although there is variability in which pathways open, it is not a random process. The observation of nonrandom capillary recruitment suggests that the opening of a capillary is largely dependent on its initial diameter and the pressure distributions in the septum. Variability of the perfusion pattern in a septum is probably due to the changes in local pressure and flow pattern. For example, when a neutrophil blocks one segment, flow and pressure distributions in the network will be altered accordingly. In a separate study, Godbey et al. (15) evaluated the effect of capillary pressure and lung distension on capillary recruitment and found that capillaries in the excised lobes opened over a narrow capillary pressure range at low airway pressure, whereas, at higher airway pressures, recruitment occurred over a wider range of pressures.

Using our tissue-membrane structure model of capillary cross section, we simulated nonrandom capillary recruitment in alveolar septa. We assumed that the \( h \) distribution in a septum is in the range of a mean value \( \pm 1 \mu m \). We assumed that all values of height within this range were equally probable. When Ptp or capillary pressure is changed, the cross-sectional shape of the capillary will change. If the \( h \) calculated using our model is not \( <2.7 \mu m \), which is the minimum capillary diameter that a RBC can pass through, we consider it opened and capable of perfusion. Figure 10 shows the percentage of perfused capillaries at different Ptp and capillary pressures. The parameter values used here are \( a_0 = 6 \mu m, C_0 = 12 \mu m, \) and \( k_c = 30 \text{cmH}_2\text{O} \). Our results show that, for Ptp = 2 mmHg, ~50 and 97\% of capillaries are perfused at 3- and 8-mmHg capillary pressure, respectively, and for Ptp = 10 mmHg, ~10 and 100\% of capillaries are perfused at 14- and 22-mmHg capillary pressure, respectively. These results approximate those of Godbey et al. (15), who found that recruitment occurred over a range of capillary pressures from 2 to 10 mmHg when Ptp = 2 mmHg, and from 10 to 30 mmHg when Ptp = 10 mmHg.

**RBC transit.** Presson and colleagues (29) showed that RBCs travel from arteriole to venule in \( 4.1 \pm 0.4 \text{s} \), which includes \( \sim 0.56 \text{s} \) during which the RBC resides

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**Fig. 7.** Percentage of segments having different hematocrit values. \( A \) and \( B \) correspond to Fig. 6, \( A \) and \( B \), respectively.

**Fig. 8.** Pressure distribution in the capillary network without \((A)\) and with \((B)\) a single segment blocked \((X)\). The pressures are 10 cmH\(_2\)O at the network entrance and 9.1 cmH\(_2\)O at the network exit. Scale bar is pressure in cmH\(_2\)O.
in the arteriolar or venular networks. Capillary transit time is, therefore, estimated from these measurements to be ~3.5 s. Other results obtained with radiolabeled RBCs suggest mean transit times of 3.0 s (18) in resected lobes of human lungs. We calculated the RBC transit time using our multiple network model described above and in the Appendix and compared our predictions with the measurements of Presson et al. (29). For the network shown in Fig. 1, there are 27 major pathways (entrance to exit), which transport >99% of the RBCs. Of these, five pathways convey >50% of the flow; these are the “preferred pathways” described in Ref. 1 and observed in Ref. 27. Figure 11A, left and right, shows the RBC transit time distributions after passage through one and six networks, respectively. Network 1 connects to the arteriole, and network 6 connects to the venule. The Ptp used in this calculation is 5 cmH₂O. The Ptm values are set to 10 cmH₂O in the arteriole and 2 cmH₂O in the venule. The entrance-to-exit pressure drops are 0.9, 1.0, 1.1, 1.3, 1.6, and 2.1 cmH₂O, reflecting the progressive fall in internal pressure (and, therefore, capillary cross-sectional area) from arteriole to venule. This calculation yields a mean value of 2.6 s for the mean RBC transit time through this network.

For the purpose of this calculation, we assumed that all RBCs enter the first network from the arteriole at time 0, whereas in experimental measurements the injected bolus of labeled RBCs enters over a brief but finite period of time. If we simulate the experimental RBC distribution at the entrance (29), the distribution of RBC transit times through the series of six networks is shown in Fig. 12. Both this distribution and the mean RBC transit time of 3.1 s agree closely with the measurements of Presson et al. (29).

To evaluate the effects on RBC transit of changes in Ptp during breathing and the effects of different Ptm values, calculations were performed with an arteriolar Ptm of 10 cmH₂O, dropping to 2 cmH₂O in the venule, but keeping Ptp fixed at 3 cmH₂O (Fig. 11B). Ptp was then fixed at 5 cmH₂O with the arteriolar-to-venular pressure drop still set at 8 cmH₂O, but the Ptm in the arteriole was raised to 14 cmH₂O (Fig. 11C). In both cases, RBCs pass through the networks more quickly than at higher Ptp or lower arteriolar pressure (Fig. 11A). This is because decreasing the Ptp reduces the septal dimension (thereby shortening the RBC pathway length), and increasing the Ptm will increase capillary cross-sectional area and, therefore, decrease the resistance to RBC flow and increase flow velocities.

Neutrophil stops during transit. In an attempt to be consistent with the interpretation of in vivo experiments observing neutrophil motion in capillaries, a neutrophil was defined as “stopped” if it required $\geq$1 s to enter a segment. Using a similar definition, Gebb et al. (14) observed that 46% of neutrophils pass through the capillary network from arteriole to venule without stopping. As shown in Fig. 13A, our model predicts that 46% of neutrophils pass through without stopping, 51% stop once, and 3% stop at least twice. In Fig. 13A, the Ptp is 5 cmH₂O, Ptm in the arteriole is 10 cmH₂O, and the arteriolar-to-venular pressure drop is 8 cmH₂O. Figure 13B shows the effects on neutrophil transit time of reducing Ptp from 5 to 3 cmH₂O, whereas Fig. 13C shows the effects of increasing arteriolar Ptm from 10 to 14 cmH₂O. Comparing Figs. 13B and 13A, decreasing Ptp had little effect on the number of stops that neutrophils made. However, comparing Figs. 13C and

Fig. 10. Percentage of the capillaries perfused at different capillary pressures. Ptp values are 2 and 10 mmHg.
13A, increasing arteriolar pressure caused many more neutrophils to pass through the capillary networks without stopping because of the relatively large capillary diameters at the higher Ptm values.

Nondeformable microsphere transit through networks. It has been assumed in these calculations that, if the neutrophil has a greater cross-sectional area than the capillary segment, it is delayed while it deforms to fit through and then retains that reduced cross section for the duration of its trip through the capillary network. A microsphere is rigid, however, and will be arrested when it first encounters a capillary with a major or minor diameter smaller than its own, even if the cross-sectional area of the capillary happens to be greater. Moreover, once the microsphere stops, it remains so because, unlike a neutrophil, it cannot deform under such low pressures. Therefore, the min-

Fig. 11. Red blood cell (RBC) transit time distributions. A: Ptp = 5 cmH2O and Ptm in the arteriole = 10 cmH2O. B: Ptp = 3 cmH2O and Ptm in the arteriole = 10 cmH2O. C: Ptp = 5 cmH2O and Ptm in the arteriole = 14 cmH2O. The pressure drop from the arteriole to the venule for all cases is 8 cmH2O. Left: distributions after passage through 1 of 6 networks in Fig. 3; right: distributions after passage through all 6 networks. All RBCs enter the first network at time 0.

Fig. 12. RBC transit time distributions before and after passage through 6 networks (Fig. 3). RBC concentration at the arteriole is as observed in Ref. 29. Ptp is 5 cmH2O, and the Ptm in the arteriole is 10 cmH2O. Pressure drop from arteriole to venule is 8 cmH2O. Vertical scale is determined such that the integral under each curve is unity.
imum diameter rather than the area of the capillary cross section determines microsphere passage.

We simulated the transit of microspheres with diameters of 3.08, 4.62, or 5.85 μm. Figure 14, A–C, shows the percentages of the sizes of microspheres that can pass through the six networks under the conditions of Ptp and Ptm shown in Fig. 13, A–C, respectively. These results show that all of the 3.08-μm microspheres passed through the six networks under all circumstances, although the distribution of trapping within the network differed. This can be compared with the experimental observations of Wiggs and colleagues (40), where 86% of the 3.08-μm beads and 15% of the 5.85-μm beads passed through the lungs (14 ± 2 and 85 ± 9% retention within the lungs of 3.08- and 5.85-μm microspheres, respectively).

In contrast, a large fraction (6–56%, depending on the conditions, Fig. 14) of microspheres that measure 4.62 μm in spherical diameter pass through the six networks. These data suggest that neutrophil deformability is critical in determining the transit time and/or that the cross-sectional area rather than the minimum diameter is the major determinant of neutrophil tran-

Fig. 13. Predicted no. of times a neutrophil stops during its transit from arteriole to venule. A: Ptp = 5 cmH2O, Ptm in the arteriole = 10 cmH2O; B: Ptp = 3 cmH2O, Ptm in the arteriole = 10 cmH2O; C: Ptp = 5 cmH2O, Ptm in the arteriole = 14 cmH2O. Pressure drop from arteriole to venule is 8 cmH2O for all 3 cases.

Fig. 14. Predicted percentages of microspheres [with diameters of 3.08 μm (solid bars), 4.62 μm (hatched bars), and 5.85 μm (open bars)] that pass through different nos. of septae. As in Fig. 12, A: Ptp = 5 cmH2O, Ptm in the arteriole = 10 cmH2O; B: Ptp = 3 cmH2O, Ptm in the arteriole = 10 cmH2O; C: Ptp = 5 cmH2O, Ptm in the arteriole = 14 cmH2O. Pressure drop from arteriole to venule is 8 cmH2O for all 3 cases.
sit. In addition, the transit of the 4.62-μm microspheres depended on the physiological conditions. At Ptp of 5 cmH₂O and arteriolar Ptm of 10 cmH₂O, 6% of the 4.62-μm microspheres and 46% of the neutrophils passed through without stopping; at Ptp of 3 cmH₂O and arteriolar Ptm of 10 cmH₂O, 28% of the 4.62-μm microspheres and 42% of the neutrophils passed through without stopping; and at Ptp of 5 cmH₂O and arteriolar Ptm of 14 cmH₂O, 56% of the 4.62-μm microspheres and 86% of the neutrophils passed through six networks without stopping. The increase in microsphere but not neutrophil passage with decreasing Ptp suggests that decreasing the size of the alveoli (and septae) may make the capillaries more circular in cross section without increasing their cross-sectional area. The greater percentage of neutrophils than microspheres that pass through the network at higher pulmonary arteriolar pressures is also likely due to the effect of cross-sectional shape. We acknowledge, though, that the complexity of the changes in diameter and pressure gradient across the segments that occurs on changing even one parameter weakens our conclusion, but the computational studies do lead to a testable hypothesis.

In another microsphere study, Ring et al. (33) observed that 0–20% of microspheres with diameter ≥8 μm could pass through the pulmonary circuit at higher capillary pressures. Our simulation of this experiment yielded 12% passage through the six networks at a mean transcapillary pressure of 18 mmHg (25 cmH₂O), consistent with the results of Ring et al. The differences between these results and those described above are attributable to the larger cross-sectional areas at the higher capillary pressures.

**Final aspect ratios of neutrophils.** The study by Gebb et al. (14) shows that 94% of neutrophils in arterioles have aspect ratios ≤1.25, which means that they are nearly circular (aspect ratio of a circle is 1.0) as they reach the pulmonary capillaries from the feeding pulmonary arterioles. Passage through the pulmonary capillaries elongates the neutrophils, which is measurable in the first postcapillary venules. Gebb and colleagues showed that, in venules, only 47% of neutrophils have aspect ratios ≤1.25, 17% are between 1.25 and 1.5, 10% are between 1.5 and 1.75, 10% are between 1.75 and 2.0, and 16% are elongated with aspect ratios >2. Figure 15A shows our predictions for the final neutrophil aspect ratio distribution after passage through six septal networks, which gives 46% of neutrophils with aspect ratios ≤1.25, 35% with the aspect ratios between 1.25 and 1.5, 8.5% with the aspect ratios between 1.5 and 1.75, and 9.5% with aspect ratios between 1.75 and 2. These results compare favorably with those of Gebb et al. As in previous sections, we also provide Fig. 15B and C, to illustrate the effects of Ptp and Ptm on the final aspect ratios of neutrophils. Similar to the observations of neutrophil stops in Fig. 13, decreasing Ptp from 5 to 3 cmH₂O had little effect on the aspect ratio, whereas increasing arteriolar Ptm from 10 to 14 cmH₂O resulted in many more circular neutrophils.

**Neutrophil transit time.** Neutrophil transit times are more difficult to evaluate than RBC transit time, in part because there is some ambiguity in determining how a neutrophil will change its shape when it enters a capillary with an elliptical cross section or what should be considered the critical effective diameter of a capillary. We took two approaches to calculate the effective diameter of the segment: 1) using the diameter of a circle with the same cross-sectional area as the segment as described in the Appendix, and 2) using the $h$ as the effective diameter, which results in a smaller
cross-sectional area than that of the original elliptical cross section. These two approaches represent approximate maximum and minimum effective segment diameters. In both simulations, the Ptp is 5 cmH₂O, the Ptm in the arteriole is 10 cmH₂O, and the pressure drop from arteriole to venule is 8 cmH₂O. Figs. 16 and 17 give the neutrophil transit time distributions after passage through one and six capillary networks using the cross-sectional area (Fig. 16) or h (Fig. 17) to determine the effective diameter. When cross-sectional area is used, all neutrophils pass through the entire network in <20 s (Fig. 16B). When h is used, 2.4% of neutrophils take longer than 1 min to pass, and 5.5% become entrapped and never pass through (Fig. 17B).

_Sensitivity analysis._ One of the useful functions of a model is that it allows one to ascertain which of the various features of the real system exert a significant effect on its behavior or, conversely, which features are largely irrelevant. We have selected several parameters from the many in Table 1 that are of particular interest and performed a sensitivity analysis varying each by ±10%. The results are summarized in Table 2 in terms of the parameters of greatest interest, namely, overall flow, RBC transit time, and neutrophil transit time. Of the parameters varied, the mean h exhibits the strongest influence, although neutrophil radius is also influential in determining neutrophil transit times. Thus it appears that the dimensions of the structure and the cells are most critical and that the effects of compliance, either in the model for capillary distension or the effects on capillary dimension arising from variations in pressure, are secondary.

In the last row of Table 2, we consider the effect of using a different model for the viscosity of whole blood, one by Pries et al. (32) developed based on observations in vivo. This presumably takes into account factors present in vivo but not in glass capillary tubes and more than doubles the transit time for both RBCs and neutrophils.

**DISCUSSION**

In this study, we developed a unique method to computationally generate geometrically realistic pulmonary capillary networks that have complex interconnected structures. The important ideas and methods developed here can also be used in other physiological network generations. Based on these structurally realistic capillary beds, we developed a
computational model of pulmonary blood flow, which was used to simulate RBC and neutrophil transit through the pulmonary microvasculature. Using this model, we can estimate blood flow, distribution of hematocrit within the capillary segments, distribution of pressure gradients through the segments, capillary blockage, and cellular transit, as well as evaluate the effects of Ptp and Ptm on network structure, flow behavior, and cellular transit. The model can provide insight into the bases for previous observations and suggest new experiments to broaden our understanding of these critical phenomena.

Fung and Sobin (9, 12, 13) developed a model of blood flow in the pulmonary capillaries in which blood flow is viewed as passing 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. It was reassuring to us that, despite the completely different basis for our model, which is based on the interconnected tubular anatomy, we found strong agreement between the two approaches in cases in which a direct comparison could be made (e.g., in the relationship between $h$ and the Ptm). In terms of its underlying basis, the present model is more closely related to other models of the systemic microcirculation (28, 31, 36, 37). The main differences lie in the structure of the microvascular beds, with the pulmonary capillaries being much shorter and more highly interconnected, factors that account for neutrophil margination. The model confirmed and extended the results of others, including our laboratory's previous model, which did not incorporate the anatomy of the capillary bed to the degree to which the present model does (1), namely that blood flow, hematocrit, and pressure gradients along the capillary segments are highly variable between segments. This variability leads to the formation of preferential pathways within the alveolar septa, due to variability in resistance to blood flow and to the geometric arrangement of the capillary bed.

This study also evaluated the effect of blocking a capillary segment on the flow, hematocrit distribution, and the distribution of pressure gradients along segments. When neutrophils reach a capillary segment that is smaller than their diameter, they temporarily obstruct the segment while they deform and elongate. This blockage has been suggested to lead to changes in blood flow and pressure gradients that may facilitate their passage through the pulmonary capillaries. This study demonstrates that neutrophils temporarily blocking segments while undergoing deformation are very likely to induce large changes in the distribution of blood flow among segments, in the variability of hematocrit, and in the distribution of pressure gradients. In particular, the pressure gradient across a capillary segment is thought to be the major driving force for neutrophils to deform and pass through segments that are narrower than neutrophils when spherical. In many cases, the pressure gradient across unobstructed capillary segments is insufficient to cause neutrophil deformation and passage. However, an obstructing neutrophil appears able to increase the local pressure gradient by 100–300%, to a level that facilitates its passage through the segment. Thus relatively small changes in physiological parameters, for example, arteriolar pressure, can significantly alter the lung's tendency to capture or release neutrophils.

The results of our studies of pulmonary capillary RBC transit times show that the computed transit times closely mimic the RBC transit times obtained during in vivo studies using video microscopy. This comparison suggests that this model may simulate the realities of capillary blood flow within the lungs. Our studies extend previous work to demonstrate that both decreasing Ptp by 2 cmH$_2$O and increasing pulmonary arterial pressure by 4 cmH$_2$O each lead to decreased RBC transit times to similar degrees. They suggest that different mechanisms may underlie these changes in resistance and blood flow; changes in alveolar size, particularly shortening the capillary segments, underlie the decreased RBC transit times induced by decreased Ptp, whereas increased diameters may be more important when pulmonary arterial pressures are increased. In that no experimental data exist to either confirm or refute these predictions, they constitute a testable hypothesis that can be used to further assess the validity of the model and, if inconsistencies are found, to suggest ways in which the model might be made more realistic.

It should be noted that our predictions of RBC transit are based on estimates using the expression for viscosity obtained by Kiani and Hudetz (20) from in vitro measurements. However, when a different equation is used, based on in vivo measurements by Pries et al. (32), blood flow rates are markedly reduced and the transit times for RBCs and neutrophils are consequentially increased. In fact, the estimates of RBC transit times are considerably longer than those observed in vivo. This raises important issues concerning the nature of blood-endothelial interactions in the lung microcirculation, compared with the systemic microcirculation, that need to be addressed by further experiments in vivo.

Although the model, in its present form, considers flows at a single, static lung volume, the results can also be used to infer the behavior during breathing. Because the capillaries are relatively rigid compared with the neutrophil, as lung volume changes with each breath, the capillary dimensions will change accordingly with little effect due to the presence of neutrophils. As a consequence, neutrophils encountering a narrow capillary segment near end expiration will have a slightly easier time passing than those arriving at end expiration. However, even if it is trapped at a time of low lung volume, a neutrophil may be released as lung volume increases. Large excursions in lung volume would have a more noticeable effect, potentially causing a surge of neutrophil release at the end of a deep inspiration. These predictions suggest important studies to be pursued in vivo.

Finally, this paper presents the first simulated results for neutrophil transit through the pulmonary...
capillaries, incorporating flows, resistances, pressure gradients, and transit times. The agreement between the computed predictions and the experimental observations is excellent for the percentage of neutrophils that do not stop and the final aspect ratio of neutrophils after passage through the capillary bed. Interestingly, with the use of the same model and the same parameters as for RBC transit, the percentage of neutrophils that stop and their final aspect ratio do not change with a 2-cmH2O decrease in Ptp, in contrast to the predicted decrease in RBC transit times. These observations also suggest that capillary length is a less important determinant of neutrophil transit than pressure drops or capillary segment diameters. The observation that a 4-cmH2O increase in pulmonary arterial pressure does decrease neutrophil transit supports the importance of capillary diameters in this process.

Reliable estimates of neutrophil transit times are difficult to make, as there are few data on which to base predictions of neutrophil deformation. In particular, estimating the diameter (or the cross-sectional shape) to which the neutrophil must deform is not possible based on current knowledge. In addition, the in vivo data examining neutrophil transit times are limited and, with only one exception, are not available as a transit time distribution, as in the case of RBCs. There have been several estimates of the average transit times for neutrophils, however, to which our predictions can be compared. We used two approaches that are based on the minimum and the maximum limits to which the neutrophil must deform. When a neutrophil is assumed to fill the whole cross-sectional area as it enters a narrow capillary with an elliptical cross section, the transit times are shorter than predicted, based on the available literature. When the neutrophil is assumed to remain circular in cross section (perpendicular to the capillary axis) and to deform until its diameter is equal to the height of the capillary segment, the transit times are long, that is, somewhat longer than the experimental values. Furthermore, very few neutrophils pass through the network without stopping when this assumption is made. These results can be compared with those of Lien and co-workers (24), who determined the distribution of transit times in subplural capillary beds using videomicroscopy. Their distribution of transit times differed from those presented in Fig. 17 in that a higher fraction of neutrophils in the experiment passed through in very short (<2 s) times. Their median transit time of 26.1 s (mean, 366 s) was, however, quite close to that of our second model (median, 20.1 s). Mean neutrophil transit times have also been determined, by the use of radio-labeled neutrophils, to be in the range of 190 s (mean) (18) and have also been reported to average 5.4 times that required for RBC transit. The first two measurements lie closer to our estimates when the segment height is used rather than the cross-sectional area (Fig. 17), although there is some ambiguity in how our infinite time blockages should be treated in computing mean transit times. These results do demonstrate, however, that the shape of the capillary cross section can be nearly as important as its cross-sectional area in determining its passage characteristics. It seems likely that, after entering a narrow capillary with an elliptical cross-sectional area, the neutrophil will change its cross-sectional shape to be an ellipse whose minor axis equals the  and whose major axis is larger than the  and smaller than the capillary width. This would lead to predicted transit times between the two cases depicted in Fig. 17 and somewhat shorter than the reported measurements.

These simulations reveal the key roles played by structures and mechanical properties of capillaries and neutrophils in modulating neutrophil transit and lead to a better understanding of the mechanisms of blood flow and cellular transit through the lungs. They also demonstrate the complexities of neutrophil transit through the lungs and point out a role for neutrophils in regulating the flow patterns of RBC and plasma, which has been poorly described to date. Finally, they point out the importance of the nature of the shape change that occurs in neutrophils in preparation for their transit through the many narrow capillary segments of the lungs.

**APPENDIX**

**Glossary**

- \( a \): Length of tissue portion of the circumference of a capillary cross section at zero Ptm
- \( a^* \): Major axis of an elliptical capillary cross section
- \( A_c \): Local cross-sectional area of capillary segment
- \( A_s \): Average septal area
- \( a_0 \): Length of tissue portion of the circumference of a capillary cross section at zero Ptp and zero Ptm
- \( a_1 \): Length of tissue portion of the circumference of a capillary cross section at nonzero Ptp and Ptm
- \( b \): Parameter in the hematocrit distribution model
- \( b^* \): Minor axis of an elliptical capillary cross section
- \( C \): Length of membrane segment of the circumference of a capillary cross section
- \( c_{i,j} \): Percentage of RBCs passing through the \( j \)th pathway of the \( i \)th network
- \( C_{i,m} \): RBC fraction passing through the \( m \)th pathway from the entrance of the first network to the exit of \( i \)th network
- \( C_{tt} \): Ratio of RBC transit time to plasma transit time in capillaries
- \( C_0 \): Length of membrane segment of the circumference of a capillary cross section at zero Ptm
- \( d \): Distance between two capillaries
- \( D \): Diameter of a circular capillary cross section
- \( D_{ev} \): Diameter of corner vessel
- \( D_h \): Hydraulic diameter
- \( D_m \): Diameter of the smallest vessel that a RBC can pass through
**PULMONARY CAPILLARY MODEL**

- $D_{mean}$ Mean hydraulic diameter of the capillaries
- $E$ Elastic coefficient of septal wall
- $f_d$ Darcy friction factor
- $h$ Height of capillary cross section
- $H_d$ Vessel hematocrit
- $H_{dout,i}$ Hematocrit in the $i$th daughter vessel
- $k_i$ Stiffness of the capillary wall
- $l$ Capillary length
- $L$ Side length of alveolar septum; cell length inside the vessel at time $t_e$
- $L^*$ Dimensionless cell length inside the vessel at time $t_e$
- $L_m$ Maximum cell length after entrance into a narrow vessel
- $L_{m^*}$ Dimensionless maximum cell length after entrance into a narrow vessel
- $l_0$ Length between a capillary entrance to the position at which the capillary has the same radius as that of the cell
- $L_0$ Side length of an alveolar septum at zero $P_{tp}$
- $m$ Coefficient in linearized theoretical model of neutrophil deformation
- $N_{s}$ Average number of septa between arteriole and venule
- $N_{seg}$ Number of segments in an average pathway
- $P_{cv}$ Minimum pressure required to aspirate a neutrophil into a micropipette
- $P_i$ Local pressure in the $i$th junction
- $P_{in}$ Pressure at the entrance of the capillary network
- $P_{j1}$, $P_{j2}$ Pressures at the junctions connecting the $j$th segment
- $P_{out}$ Pressure at the exit of capillary network
- $P_{trans}$ Transmural (or transcapillary) pressure
- $P_{tp}$ Transpulmonary pressure
- $Q$ Flow rate
- $Q_{ev}$ Flow rate in corner vessel
- $Q_{i,j,n}$ Flow rate in the $n$th capillary of the $j$th pathway in the $i$th network
- $Q_{in}$ Total inflow rate in a junction
- $Q_{ip}$ Flow rate in the $j$th segment connecting the $i$th junction
- $Q_{j}$ Flow rate in the $j$th capillary segment
- $Q_{mean}$ Average flow rate in septal capillaries
- $Q_{n}$ Flow rate in the $n$th capillary
- $Q_{nl,i,j,n}$ Total flow rate entering the upstream junction of the $n$th capillary of the $j$th pathway in the $i$th network
- $Q_{out,i}$ Outflow rate from the $i$th daughter vessel
- $Q_{RBC(out)}$ Inflow volumetric flux of RBCs in a junction
- $Q_{RBC(out,i)}$ Outflow volumetric flux of RBCs in the $i$th daughter vessel
- $r$ Flux cutoff parameter, which defines the minimal fractional blood flow required to draw RBCs into a daughter branch
- $R$ Resistance per unit length of capillary
- $R_{c}$ Instantaneous radius of the portion of the cell lying outside the vessel when a cell is partly drawn into a vessel
- $R_c$ Radius of cell
- $R_{(in)}$ Radius of the cell inside a capillary
- $R_{(out)}$ Resistance per unit length of corner vessels
- $R_{Dh}$ Reynolds number based on hydraulic diameter
- $R_{junc1}$, $R_{junc2}$ Resistances of the two junctional regions of a capillary
- $R_{mean}$ Average resistance per unit length of septal capillaries
- $R_{mask}$ Radius of microsphere
- $R_{p}$ Radius of suction pipette
- $R_{seg}$ Flow resistance of capillary segment
- $R_n$ Initial value of dimensionless cell radius before the cell enters a capillary segment
- $R_1$, $R_2$ Radii at the entrance and exit of a capillary segment, respectively
- $S_{seg}$ Surface area of capillary segment
- $S_{junc1}$, $S_{junc2}$ Surface areas of the two junctional regions of a capillary
- $S_{trans}$ Neutrophil transit time
- $T_e$ Time required for a neutrophil to enter a narrow capillary (entrance time)
- $T_{e,j,n}$ Total RBC transit time for the $n$th capillary segment of the $j$th pathway in the $i$th network
- $T_{l,m}$ RBC transit time for the $m$th pathway from the entrance of the first network to the exit of $i$th network
- $t_{n}$ RBC transit time in the $n$th capillary
- $t_p$ Passing time, the time neutrophil takes to pass through the capillary from one end to the other
- $T_s$ Force in the septal wall per unit length
- $u$ Local mean velocity
- $u_{blood}$ Bulk blood velocity
- $u_{neu}$ Neutrophil velocity
- $V$ Alveolar volume
- $V_n$ Volume of the $n$th capillary
- $V_0$ Alveolar volume at zero $P_{tp}$
- $\Delta P$ Pressure difference between the entrance and the exit of one segment; aspiration pressure
- $\Delta P_{a,v}$ $\theta$ Angle (see Fig. 2)
- $\mu$ Fluid viscosity
- $\mu_{app}$ Apparent viscosity
- $\mu_c$ Cytoplasmic viscosity
- $\mu_p$ Viscosity of plasma
- $\rho$ Fluid density
- $\tau_0$ Average tension in cell cortex

**Construction of the capillary networks.** To perform the simulation in a geometrically realistic structure, we developed a method and software to generate pulmonary capil-
lary networks loosely based on measured data supplemented by plausible assumptions concerning alveolar septal structure. A capillary network is composed of many junctions and segments. Among the parameters needed to generate a network are the size of the alveolar septum, the number of junctions or segments, the probability of three-way or four-way junctions, and the lengths and cross-sectional dimensions of capillaries. From photomicrographs of a typical microscopic field in dog lungs (24), one can roughly estimate that there are six septa between the arteriole and venule. In vivo observations have shown considerable interspecies variability in the number of segments in an average pathway: 60 in dogs (16), 45 in rabbits (3), and 90 in humans (17). If we consider the average number of segments in the blood pathways between the arteriole and venule to be 50, it gives the average number of segments in each individual flow pathways within one septum to be about eight. This number can be used to determine the number of junctions in a network. Lamm et al. (22) show that a rectangular region of the lung (400 × 500 μm) contains an average of 10 alveolar septa, which gives an average septal area of 2 × 10^4 μm^2. This value is used in our simulation as the septal area at a physiological Ptp, which yields, using Eq. 2 below, the length of one side of a septum at zero Ptp to be L_0 = 70 μm. Based on observations of the rat pulmonary capillary bed, we set bounds on the minimum and maximum capillary length, two-thirds and four-thirds the mean capillary length, respectively. Experimental observations show that most junctions connect three segments, whereas a few connect four.

Based on these anatomic data, we can computationally generate many geometrically realistic capillary networks. Figure 1A shows the three-dimensional structure of a network. Figure 1, B and C, shows the top views of two networks. These capillary networks are used in our pulmonary blood flow and cellular transit simulations.

Model for the dimensional changes of the capillary cross section. A tissue-membrane structure model (Fig. 2) is developed to describe the geometric changes of capillary cross section with Ptp and Ptm. The following assumptions are made. 1) The circumference of a pulmonary capillary cross section can be divided into two parts: one adjacent to septal wall tissue (bottom) and one composed of the membrane (top). 2) Ptp is assumed to influence capillary cross-sectional area only through its effect on the length of the bottom (septal wall). 3) Changes in length of the bottom due to Ptp are proportional to the change in overall septal dimension L. 4) Top (membrane) segment length increases linearly with increasing hoop tension T_c. To estimate changes in septal length and stress under a Ptp, we approximate a single septum as a square plane and an alveolus as a cube. First, consider the pure Ptp effects on the capillary cross-sectional area by setting Ptm = 0. When transpulmonary pressure increases from zero to Ptp, alveolar volume increases from V_0 to V, the side length from L_0 to L, and the length of any given membrane segment of a capillary from a_0 to a (= a_0L/L_0). We use measurements of Mercer et al. (25) of rat alveolar volumes during inflation and deflation to obtain the relationship between V and Ptm

\[ V = V_0 + (A - V_0)e^{-L/PtpM} \]  

where \( A = 2.90 \times 10^5 \mu m^3 \), \( B = 6.43 \text{ cmH}_2\text{O} \), and \( M = 2.14 \) for inflation, and \( A = 3.07 \times 10^5 \mu m^3 \), \( B = 3.42 \text{ cmH}_2\text{O} \), and \( M = 1.03 \) for deflation. Assuming the side length \( L \) varies as \( V^{1/3} \), one has

\[ L = L_0 \left[ 1 + \left( \frac{A}{V_0} - 1 \right) e^{-(B/PtpM)} \right]^{1/3} \]  

A force balance in an alveolus yields the following

\[ 2T_cL = PtpL^2 \]  

develops the force per unit length. Rewriting Eq. 3 in a stress-strain form

\[ T_c = E(Ptp) \left( \frac{L}{L_0} - 1 \right) \]  

we can define a pressure-dependent elastic coefficient \( E \)

\[ E(Ptp) = \frac{\sqrt{2}PtpL}{L - L_0} \]  

When Ptm increases, the length of tissue segment \( a \) increases to \( a_e \), and the length of membrane segment increases from \( C_0 \) to \( C \). A force balance and geometric relationships give

\[ \text{Ptm}h = T_c + E(a_1 - a) \left[ \frac{1}{a} + \frac{1}{d - a} \right] \]  

\[ T_c = \text{Ptm}R \]  

\[ a_1 = 2R \sin \theta \]  

\[ h = R(1 - \cos \theta) \]  

\[ C = 2R\theta \]  

where \( d \) is the distance between two capillaries, \( R \) and \( h \) are the radius and height of the cross section, respectively, and \( \theta \) is the angle shown in Fig. 2.

\[ R = \frac{C_0}{2\theta - \text{Ptm} \sin \theta} \]  

From Eqs. 6, 7, 9, 10, and 12 one obtains an equation for \( \theta \)

\[ c_1\theta + c_2 \cos \theta + c_3 \sin \theta + c_4 = 0 \]  

where

\[ c_1 = 2aE^* \]  

\[ c_2 = -C_0Ptm \]  

\[ c_3 = -2CE^* \]  

\[ c_4 = aE^*Ptm \]  

\[ E^* = E \left( \frac{1}{a} + \frac{1}{d - a} \right) \]  

Solving Eq. 13 to obtain \( \theta \) at the given Ptp and Ptm, one can calculate \( R \) using Eq. 12 and then \( a_1 \), \( h \), and \( C \) using Eqs. 9, 10, and 11, respectively.

Flow model in a single capillary. A “segment” is defined as the portion of a capillary between two “junctions.” Therefore, a capillary consists of one segment with a junction at either end. We first establish the flow model in the segment and then estimate the effects of junctions on flow resistance. As in
Dhadykawal et al. (1), an approximate equation is used to evaluate the flow resistance of a capillary segment (7), \( R_{\text{seg}} \)

\[
R_{\text{seg}} = \frac{\Delta P}{Q} = \frac{\mu_{\text{app}} R_{\text{Dh}} f_d}{2 A D_h} ds
\]

where \( \Delta P \) is the pressure difference between the entrance and the exit of one segment, \( Q \) is flow rate, \( \mu_{\text{app}} \) is the apparent viscosity, \( A \) is the local cross-sectional area of the segment at a location \( s \) along its axis, \( D_h \) is its hydraulic diameter \( (D_h = 4A/\text{perimeter}) \), \( R_{\text{Dh}} \) is the Reynolds number based on \( D_h \), and \( f_d \) is the Darcy friction factor defined by

\[
f_d = \frac{1}{2 \rho u^2} \frac{dP}{D_h}
\]

where \( u \) is the local mean velocity and \( \rho \) is fluid density. To simplify the calculation, we approximate the local cross section of the segment as an ellipse with a minor axis \( b^* = h/2 \) and a major axis \( a^* \), which is calculated by equating the perimeter of the ellipse to \( C + a_1 \). Under this approximation, \( R_{\text{Dh}} \) and \( f_d \) can be well approximated by a polynomial

\[
R_{\text{Dh}1,2} = 80.2 - 30.3 \left( \frac{b^*}{a^*} \right)^{3.45} + 16.6 \left( \frac{b^*}{a^*} \right)^2 - 168 \left( \frac{b^*}{a^*} \right) + 502.2
\]

In Eq. 14, the apparent viscosity is used to represent the increase in flow resistance due to the deformation of RBCs as they pass through narrow capillaries. It is calculated from Hogg (16) to be

\[
\mu_{\text{app}} = \mu_p \left[ 1 - \left( 1 - \frac{\mu_p}{\mu_c} \right) \left( 1 - D_{\text{m}} / D_h \right)^{1/2} \right]
\]

where \( \mu_p = 1.2 \) cP is the viscosity of plasma; \( \mu_c = \exp(0.48 + 2.35 H_d) \) cP, where \( H_d \) is the vessel hematocrit; \( D_{\text{m}} = 2.7 \) \( \mu \)m is the diameter of the smallest RBC that a capillary can pass through; and \( D^* = 2.03 - 2.0 H_d \) \( \mu \)m. This expression is based on experiments in glass tubes with circular cross section and is assumed to be approximately valid in the present situation. Because the capillaries are taken to be elliptical, we use the hydraulic diameter. In pulmonary capillary networks, junctions and segments have comparable dimensions. Therefore, the contributions of junctions to the total flow resistance should be important. However, in practice, it is difficult to calculate the resistance of junctions due to their complex geometry and flow patterns. For our purposes, we consider one junction to comprise \( N \) parts associated with its \( N \) connecting capillaries. In each part, the flow direction should be similar to that in its connecting segment. As an approximation, we assume that the flow resistance associated with a capillary consisting of the segment with its two connecting junctions is proportional to the total surface area and scales with surface area in the same manner as the segment alone. Under this assumption, we calculate the total flow resistance of a capillary by multiplying the resistance of the segment (see Eq. 18) by the ratio of total surface area (segment plus junctions) to the surface area of the segment

\[
R = R_{\text{seg}} + R_{\text{junc1}} + R_{\text{junc2}} = \left( 1 + \frac{S_{\text{junc1}} + S_{\text{junc2}}}{S_{\text{seg}}} \right) R_{\text{seg}}
\]

where \( S_{\text{junc1}} \) and \( S_{\text{junc2}} \) are the surface areas of the two junctions, and \( S_{\text{seg}} \) is the surface area of the segment.

**Model for corner vessels.** Corner vessels are located along the boundaries of each alveolar septum. Unfortunately, we know of no published anatomic data on their dimensions or on the flow rate they carry. We, therefore, make the following plausible assumptions: that all corner vessels are circular in cross section, and that each corner vessel conveys an amount of blood flow equal to the average flow rate in the septal capillaries \( (Q_{\text{mean}}) \) multiplied by the number of adjoining septae. Typically, three septa share one corner vessel so that

\[
Q_{\text{cv}} = 3Q_{\text{mean}} \quad \text{or} \quad R_{\text{cv}} = \frac{1}{3} R_{\text{mean}}
\]

where \( Q_{\text{cv}} \) is the resistance per unit length of a corner vessel and \( R_{\text{mean}} \) is the average resistance per unit length of septal capillaries. For a tube with a circular cross section and diameter \( D \), the resistance per unit tube length is

\[
R = \frac{128 \mu}{\pi D^4}
\]

where \( \mu \) is the fluid viscosity. Therefore

\[
(\frac{D_1}{D_{\text{mean}}} \frac{D_2}{D_{\text{mean}}})^4 = \frac{R_{\text{mean}}}{R_{\text{cv}}} = 3
\]

which yields

\[
D_{\text{cv}} = 1.32 D_{\text{mean}}
\]

where \( D_{\text{mean}} \) is the mean hydraulic diameter of the capillaries.

**Network flow model.** For a network with \( m \) junctions and \( n \) segments of septal capillaries and corner vessels, there exist \( m + n \) unknowns; these are the junction pressures \( P_i \), \( i = 1, 2, \ldots, m \) and the segment flow rates \( Q_{\text{cv}} \), \( j = 1, 2, \ldots, n \). Therefore, we require \( m + n \) governing equations as well as boundary conditions at the network entrance and exit. If the number of branches at the \( i \)th junction is \( q(i) \), mass conservation at each junction requires that

\[
\sum_{j=1}^{q(i)} Q_{ij} = 0 \quad i = 1, 2, \ldots, m
\]

where \( Q_{ip} \), \( p = 1, 2, \ldots, q(i) \) are the flow rates in the segments connected to the \( i \)th junction. Using the relationship for \( P \), \( Q \), and \( R \) across each segment, we have

\[
\frac{P_{ij} - P_{ij}}{Q_{ij}} = R_j \quad j = 1, 2, \ldots, n
\]

where \( P_{ij} \) and \( P_{ij} \) are the pressures at the junctions associated with the \( j \)th segment. Considering a square network with an entrance at one corner of the square area and an exit at the opposite corner, the entrance and exit pressures must be specified as boundary conditions

\[
P = P_{\text{in}} \quad \text{at} \quad (x, y) = (0, 0)
\]

\[
P = P_{\text{out}} \quad \text{at} \quad (x, y) = (L, L)
\]

Solving Eqs. 23 and 24 with boundary conditions (Eq. 25), the local pressure at each junction and flow rate through each segment can be obtained.

**Hematocrit distribution.** At each bifurcation, RBCs preferentially enter the daughter branches with higher flow (10, 35), leading to nonuniform hematocrit (Hd) distributions. The nonuniform distribution of Hd will, in turn, alter the local flow resistance and thereby the pressure and flow rate distributions. To calculate the hematocrit distribution and take
into account its effect on flow resistance, we introduce the model described in Levin et al. (23), from which we obtain
\[
\frac{Q_{\text{out}/i}}{Q_{\text{in}}} = \left\{ \begin{array}{ll}
\frac{G(Q_{\text{out}/i}/Q_{\text{in}})}{G(Q_{\text{out}/j}/Q_{\text{RBC/ini}})} & 0 \leq Q_{\text{out}/i}/Q_{\text{in}} \leq r \\
1 + \left( \frac{1 - [Q_{\text{out}/i}/Q_{\text{in}} + r]}{Q_{\text{out}/i}/Q_{\text{in}}} \right)^{1/r} & r \leq Q_{\text{out}/i}/Q_{\text{in}} \leq 1 - r \\
1 & 1 - r \leq Q_{\text{out}/i}/Q_{\text{in}}
\end{array} \right.
\]
where
\[
G(Q_{\text{out}/i}/Q_{\text{in}}) = \frac{1}{1 + \left( \frac{1 - [Q_{\text{out}/i}/Q_{\text{in}} + r]}{Q_{\text{out}/i}/Q_{\text{in}}} \right)^{1/r}}
\]
(26)

The hematocrit in the ith daughter branch is given by
\[
H_{d,\text{out}/i} = \frac{Q_{\text{RBC/ini}}}{Q_{\text{out}/i}}
\]
(28)

Here, \( Q_{\text{RBC}} \) is the volumetric flow rate of RBCs in a vessel segment, the subscripts (in) and (out) represent inflow and outflow, respectively, and the index \( i = 1, 2, \ldots \) denotes the outflow branch. Two parameters must be specified: \( b = 1.15 \), as determined by Klitzman and Johnson (21), and \( r \), the flux cutoff parameter that defines the minimal fractional blood flow required to draw RBCs into the daughter branch. When \( Q_{\text{out}/i}/Q_{\text{in}} \leq r \), no RBCs enter the ith daughter branch. Otherwise, its value can be estimated using \( r = 0.4/D \) (31), where \( D \) is the diameter of the parent branch measured in micrometers.

For pulmonary capillaries, the mean diameter is similar to the dimension of the neutrophil. If we consider all possible paths and the fraction of RBCs that follow each path, this information, the entire transit time distribution can be computed.

**Neutrophil transit time.** The estimation of neutrophil transit time is more difficult. While all RBCs behave in the same way within a given capillary and, therefore, experience the same transit time under a given flow condition, neutrophil transit time depends on its entrance diameter, which may vary depending on the diameters of capillaries that it previously encountered. That is, neutrophils with different entrance diameters, relating to their earlier “transit history,” will have different transit times in the same capillary under the same pressure gradient.

In this simulation, neutrophil transit time is computed in two steps: the entrance time \( t_e \), which is the time for neutrophil deformation to enter a narrow capillary, and passing time \( t_p \), which is the time it takes to pass through the capillary from one end to the other. The total transit time \( t \) is the sum of the entrance time and passing times
\[
t = t_e + t_p
\]
(34)

Capillary cross-sectional area exerts a strong influence on entrance time. To simplify the calculation, we consider the neutrophil initially to be a sphere and approximate the cross section of the segment to be a circle with effective radius \( R \), which is determined by maintaining the original cross-sectional area.

\[
R = \sqrt{a \cdot b}
\]
(35)

Our model for neutrophil entrance into a capillary segment is based on studies of leukocyte aspiration into a micropipette. As observed in granulocyte suction experiments (4–6), the pressure difference across a micropipette entrance must exceed a “critical pressure” \( P_{cr} \) to initiate granulocyte flow.
into a pipette. The following equation describes the dependence of the critical pressure on pipette diameter (6)

$$P_{cr} = 2 \frac{\sigma_0}{R_p} \left( \frac{R_e}{R_p} - 1 \right)$$

(36)

where \(\sigma_0 = 0.035\) dyn/cm is the average tension in the cell cortex, and \(R_p\) and \(R_e\) are the radii of the suction pipette and cell (before aspiration), respectively. For cases in which the pressure difference across the capillary segment exceeds \(P_{cr}\), the present model draws from an analysis by Yeung and Evans (41) along with the experimental results of Fenton et al. (8) to calculate neutrophil transit times for different values of the cell-to-vessel radius ratio. Yeung and Evans (41) developed a theoretical model for micropipette aspiration in which the cell is approximated as a uniform liquid core encapsulated by a distinct cortical shell. Their analysis predicted a dependence of aspiration time on both driving pressure and radius ratio. In contrast, the experiments of Fenton et al. (8) suggested that entrance time has no significant dependence on aspiration pressure, at least over the relatively narrow range of differential pressures tested (200–400 Pa), and that \(\log(t_e)\) is a linear function of the cell-to-vessel radius ratio. We combine the results from these two studies by using a linearized version of the Yeung and Evans model (41) for small values of \(R_e/R_c\)

$$\frac{dt_e^*}{dL^*} = m \left( 1 - \frac{1}{R^*} \right)$$

(37)

where \(t_e^* = t_e(\Delta P - P_{cr})/\mu_c\) is a dimensionless time, where \(\Delta P\) is the aspiration pressure and \(\mu_c\) is the cytoplasm viscosity; \(L^* = LR_c\), where \(L\) is the cell length inside the vessel at time \(t_e^*\) and \(R_c\) is the capillary radius as defined in Eq. 35; \(R^* = r/R\), where \(r\) is the instantaneous radius of the portion of the cell lying outside the vessel; and \(m = 6\). By conservation of volume for a cell with hemispherical, cylindrical, and spherical segments, we have

$$R_e^3 - 1 + (R_e^2 + \frac{1}{2})(R_e^2 - 1)^{1/2} = \frac{1}{2}(L_m - L^*)$$

(38)

where \(L_m = L_m/R_c\), where \(L_m\) is the maximum cell length corresponding to the fully aspirated cell. Equations 37 and 38 give

$$\frac{dt_e^*}{dR^*} = -\frac{1}{2}m[(3R_e^2 - 3R^*) + 2(R^* - 1)(R_e^2 - 1)^{1/2} + (R^* - 1)(R_e^2 + \frac{1}{2})(R_e^2 - 1)^{-1/2}]$$

(39)

Solving this equation with the conditions

$$R^* = R_0^* = \frac{R_e}{R} \quad \text{at} \quad t^* = 0$$

$$R^* = 1 \quad \text{at} \quad t^* = t_e^*$$

(40a)

we have

$$t_e^* = m \left( \frac{1}{2} + \frac{1}{2} R_0^* R_e^2 - R_0^* R_e^2 + \frac{1}{2}(R_e^2 - 1)^{3/2} + (R_e^2 - 1)^{1/2} \right.$$  

$$- R_0^* \sin \left( \arccos \left( \frac{1}{R_e} \right) \right)$$

$$+ \frac{R_0^* \sin \left( \arccos \left( \frac{1}{R_e} \right) + \frac{R_e^2}{R_0^*} \right)}{R_0^* + (R_e^2 - 1)^{1/2}} \right)$$

(41)

$$+ \ln \left( \frac{R_0^*}{R_e} \right)$$

from which the dimensionless entrance time can be computed as

$$t_e = \frac{\mu}{\Delta P - P_{cr}} t_e^*$$

(42)

Fenton et al. (8) gave a relationship of a different form based on their experimental measurements for aspiration pressure in the range of 200–400 Pa

$$\log t_e = 3.68 R_0^* - 4.77$$

(43)

Comparing Eqs. 42 and 43 at \(\Delta P - P_{cr} = 200\) Pa, one finds that they match very well for \(R_0^* = 1.2\). For other values of \(\Delta P\), the slopes of the curves at \(R_0^* = 1.2\) are also in reasonable agreement. This led us to construct a pressure-dependent entrance time model based on Eqs. 42 and 43 of the form

$$t_e = \left\{ \begin{array}{ll}
\frac{\mu}{\Delta P - P_{cr}} t_e^* & R_0^* < 1.2 \\
0.107 \frac{m \mu}{\Delta P - 33} 10^{0.68(R_0^* - 1.2)} & R_0^* \geq 1.2
\end{array} \right.$$  

(44)

obtained by matching the two expressions at \(R_0^* = 1.2\), where \(t_e^*\) is given by Eq. 41.

Considering a capillary with a radius of \(R_1\) at the entrance and \(R_2\) at the exit, we assume that the radius varies linearly in between so that

$$R(x) = R_0 + \frac{R_2 - R_1}{l} x$$

(45)

where \(l\) is the capillary length. We also have the following expression from Fenton et al. (8) for the ratio of neutrophil velocity \(u_{neu}\) to bulk velocity \(u_{blood}\)

$$\frac{dx}{dt} = \frac{Q}{\pi R^2(x)} \left[ \frac{2}{1 + \left( \frac{R_{c(x)}}{R(x)} \right)^{2/3}} \right] \quad t(x = 0) = 0, \quad t(x = l) = t_p$$

(46)

where \(R_{c(x)}\) is the radius of the cell inside the capillary. Combining these expressions and integrating along the length of the capillary we obtain for the passage time

$$t_p = \frac{l}{2} \left[ 1 + \left( \frac{R_{c(x)}}{R(x)} \right)^{2/3} \right]$$

(47)

$$R_{c(x)} = R_1 \quad \text{if} \quad R_1 \leq R_2 \quad \text{or} \quad R_1 > R_2$$

if \(R_1 = R_2\), then defining \(R_{min} = \min(R_1, R_2)\) we obtain

$$\frac{R_{c(x)}}{R(x)} = 1$$

(48)

for \(R_c \leq R_{min}\).

For \(R_c > R_{min}\), there are two cases. First, if \(R_1 > R_2\)

$$R_{c(x)} = \begin{cases} R_1 & \text{if} \quad x \leq l_0 \\
R(x) & \text{if} \quad x > l_0 \end{cases}$$

(49)

where \(l_0 = x(R = R_c)\). Second, if \(R_1 \leq R_2\)

$$R_{c(x)} = \frac{R_{min}}{R(x)} = \frac{R_1}{R(x)}$$

(50)

Solving Eq. 46 with Eqs. 48, 49, and 50 [where \(R(x)\) is given by Eq. 45], we have

$$t_p = \frac{\pi}{2Q} \frac{l}{(R_2 - R_1) \left[ \frac{1}{2} (R_2^3 - R_1^3) + I \right]}$$

(51)
Equations 44 and 51 give the neutrophil passing time for each case.

Neutrophil-induced segment blockage. When a neutrophil diameter is greater than the segment it encounters, the segment will become blocked, at least temporarily. This neutrophil-induced blockage will change the flow pattern in the network and increase the pressure drop across the blocked segment. Considering the resistance of a blocked segment to be finite, one can recalculate the local volume flow rate \( Q \), hematocrit \( H_d \), and pressure \( P \) for all other segments using Eqs. 23–28. The higher pressure drop across this blocked segment is then used to compute neutrophil entrance time.

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