Blood Flow in Microvascular Networks
Experiments and Simulation

A.R. Pries, T.W. Secomb, P. Gaechtgens, and J.F. Gross

A theoretical model has been developed to simulate blood flow through large microcirculatory networks. The model takes into account the dependence of apparent viscosity of blood on vessel diameter and hematocrit (the Fahraeus-Lindqvist effect), the reduction of intravascular hematocrit relative to the inflow hematocrit of a vessel (the Fahraeus effect), and the disproportionate distribution of red blood cells and plasma at arteriolar bifurcations (phase separation). The model was used to simulate flow in three microvascular networks in the rat mesentery with 436, 583, and 913 vessel segments, respectively, using experimental data (length, diameter, and topological organization) obtained from the same networks. Measurements of hematocrit and flow direction in all vessel segments of these networks tested the validity of model results. These tests demonstrate that the prediction of parameters for individual vessel segments in large networks exhibits a high degree of uncertainty; for example, the squared coefficient of correlation between predicted and measured hematocrit of single vessel segments ranges only between 0.15 and 0.33. In contrast, the simulation of integrated characteristics of the network hemodynamics, such as the mean segment hematocrit or the distribution of blood flow velocities, is very precise. In addition, the following conclusions were derived from the comparison of predicted and measured values: 1) The low capillary hematocrits found in mesenteric microcirculatory networks as well as their heterogeneity can be explained on the basis of the Fahraeus effect and phase-separation phenomena. 2) The apparent viscosity of blood in vessels of the investigated tissue with diameters less than 15 μm is substantially higher than expected compared with measurements in glass tubes with the same diameter. (Circulation Research 1990;67:826–834)

In recent years, the fast development of new methods in microcirculatory research has made it possible to determine a large number of rheologically and functionally relevant parameters in individual microvessels down to the capillary level. On the other hand, it is still very difficult to predict the functional behavior of a tissue or organ from processes observed on the level of individual vessels. For example, if it were known from intravital microscopic observation in a given tissue that following an ischemia-reperfusion procedure 20% of the capillary vessels of a certain diameter are plugged by leukocytes, what would be the expected increase in overall resistance to blood flow?

Such questions, which relate to the influence of the angioarchitecture of a network on its hemodynamic and rheological properties, cannot easily be answered by direct in vivo investigation alone, especially in large networks in which it is impractical to measure all relevant quantities. In contrast, a conceptual framework is needed that would take into account the effects of the various elementary rheological and hemodynamic factors and processes within a complex network and their interactions. Such a framework can be realized in the form of theoretical models that simulate blood flow through microcirculatory networks and are based on available experimental information on elementary rheological phenomena. However, any model that simulates blood flow through the microcirculation must be validated by comparison with experimental results before it can be used to predict the behavior of the network under varying functional conditions.

Therefore, the present study was aimed at developing a theoretical flow model and testing it in a tissue that allows the observation of complete microcirculatory networks. The experimental database consists of complete sets of topological, morphological, and hemodynamic parameters for all vessel segments in networks that extend from the main input and output vessels to the capillary level. This

From the Department of Physiology, Freie Universität Berlin (A.R.P., P.G.), FRG, and the Department of Physiology, University of Tucson (T.W.S., J.F.G.), Ariz.

Supported by National Institutes of Health grants HL-17421 and HL-34555 and the Deutsche Forschungsgemeinschaft (Pr 271/1-1 and Pr 271/1-2).

Address for correspondence: Dr. A.R. Pries, Freie Universität Berlin, Department of Physiology, Arnimallee 22, D-1000 Berlin 33, FRG.

Received November 6, 1989; accepted May 17, 1990.
allows a comparison of measured data with those obtained from the corresponding simulation, thereby providing a critical test of the assumptions underlying the theoretical modeling of blood flow. Therefore, the present study represents a major improvement in comparison with previous investigations in which complete sets of morphological, hemodynamic, and rheological parameters were not available and the topological organization of the networks was not precisely defined.

Materials and Methods

Network Flow Simulation

Several simulations of blood flow in microvessel networks have been reported. One method, involving tracking of individual blood cells, was developed by Schmid-Schönbein et al. Subsequently, it was used by Fenton et al. to analyze the effect of white blood cell entrance times in a model for the hamster cremaster muscle microcirculation and by Furman and Olbricht, who simulated the motion of individual red and white blood cells through a small network. An alternative approach was described by Papenfuß and Gross, who simulated blood flow in a seven-segment microvascular network. They used a continuum model, in which the red blood cell content of each segment was represented by a uniform hematocrit. Hematocrit varied from segment to segment due to the effect of phase separation (uneven partition of hematocrit) at diverging bifurcations, whereas apparent viscosity and the Fahraeus effect varied as functions of tube diameter, hematocrit, and flow rate, according to those in vitro experimental data. The continuum approach was also used by Levin et al. to investigate the effects of phase separation at bifurcations on the distribution of hematocrit in stochastic networks.

Papenfuß and Gross and Secombe et al. modified and extended the original approach to allow simulation of much larger networks and to incorporate more recent data concerning the rheological behavior of blood. In the present study, simulations that make use of these developments are reported.

The network flow simulation provides predictions of flow rate and hematocrit in each segment, given information on network architecture and rheological behavior of blood. In addition, the inflow and outflow conditions must be defined either by the flow rate or the pressure at the terminal node for each segment entering or leaving the network, as discussed in detail below. The numerical method consists essentially of two procedures, which are carried out alternately until the solution to the governing equations is reached. The first procedure ("linear analysis") involves computation of the flow in each segment and the pressure at each node, assuming that the rheological parameters are known, including the apparent viscosity in each segment. This is a linear problem of standard type, and the governing equations are as follows. The segment conductance \( J = Q/\Delta P \), where \( Q \) is flow rate and \( \Delta P \) is pressure drop, is given by Poiseuille’s law. Since the sum of the inflows minus the sum of the outflows at a node must equal zero, the following condition is satisfied at any node at which three segments meet:

\[
Q_1 + Q_2 + Q_3 = 0 = J_1(p_1 - p_0) + J_2(p_2 - p_0) + J_3(p_3 - p_0)
\]

where \( p_0 \) is the pressure at the node; \( p_1, p_2, \) and \( p_3 \) are the pressures at the adjacent nodes; \( Q_1, Q_2, \) and \( Q_3 \) are the corresponding segment flows (negative for outflows from the node); and \( J_1, J_2, \) and \( J_3 \) are the corresponding conductances. These relations, when applied at every node in the network, yield a system of linear equations in which the unknowns are the pressures at the nodes. This system is large, but sparse, and is solved efficiently using the iterative method of successive overrelaxation. At the first application of this procedure, a uniform apparent viscosity is assumed throughout the network. Subsequently, the final result of the previous linear analysis is used as the starting condition for the iteration.

The second procedure ("rheological analysis") involves computation of the hematocrit and apparent viscosity in each segment, using the flow rates and pressures from the linear analysis. The assignment of hematocrits is carried out in terms of discharge hematocrits. Conservation of red blood cell and plasma flow rates is applied at every node, and the hematocrit in each segment entering the network is specified as described below. In addition, a relation is applied that describes the disproportionate distribution of red blood cells and plasma at nodes corresponding to diverging bifurcations (phase separation). This relation gives the hematocrits in the two daughter segments as a function of the hematocrit in the parent segment, the flow rates, and the segment diameters. Since the hematocrit in each segment depends on the phase separation at all upstream bifurcations, the hematocrits at a given node cannot be computed until all upstream nodes have been considered. To guarantee this, we first perform a partial sorting of the nodes satisfying the condition that any two connected nodes appear in order of decreasing pressure. The nodes are then considered from high to low pressures along every flow pathway. Once the discharge hematocrit has been computed in each segment, the apparent viscosity is deduced according to an empirical relation for the Fahraeus-Lindqvist effect. The tube hematocrit is estimated from the discharge hematocrit according to another empirical relation for the Fahraeus effect.

The two procedures (linear and rheological analysis) are applied alternately ("outer" iteration) until satisfactory convergence is achieved, typically after 20–30 iterations. These procedures were implemented using PASCAL language on a personal computer. Simulation of flow in a 913-segment network required several minutes of computer time.

Empirical Data Input

Network data. Male Wistar rats were prepared for intravital microscopy as described in detail previously.
(Pries et al). Mesenteric areas of 50–80 mm² were scanned in about 40 minutes, taking both video recordings and photographs from each field of view. During that time, no change in microvessel diameters due to change in vascular tone or vasomotion was observed. The photographs were assembled into photomontages of the entire networks (up to 300 fields of view) and were used to determine diameter and length for each vessel segment between two bifurcations.

From the corresponding video recordings, tube hematocrit and discharge hematocrit values were determined using a microphotometric method. In those cases where the photographs allowed identification of individual red blood cells (mostly in the diameter range below 10 μm), the tube hematocrit was calculated from the number of red blood cells counted in a vessel segment of known length. This value was then converted into the discharge hematocrit using compiled literature data on the Fahraeus effect. The video recordings also served to determine flow direction in every vessel segment.

The topological structure of the network was recorded by labeling each vessel segment and branching point (node) in the network and generating a list of all segments together with the connecting nodes. On the basis of the flow directions in the individual vessel segments, the network was subdivided into arterial and venous vessel trees. The vessel segments connecting arterial and venous vessel trees were classified as arteriovenous segments. Each segment within the trees was assigned a generation number equal to the number of branch points between that segment and the main vessel feeding or draining the tree plus one.

Network simulations were performed on the basis of data obtained from three microvessel networks in the rat mesentery. These networks consisted of 913, 546, and 436 segments, respectively, and were each fed predominantly by one major arteriole (diameter ~35 μm). The inflow hematocrits for the two larger networks were 0.56 and 0.54; for the smaller network, the inflow hematocrit was 0.31, due to isovolemic hemodilution of the animal with hydroxyethyl starch solution (60 g/l, molecular weight 450,000, Plasmaher, Bad Homburg, FRG).

**Boundary conditions.** Although the region scanned during intravital microscopy was chosen to include fairly self-contained microvessel networks, a number of small vessels, in addition to the major feeding arterioles and draining venules, inevitably crossed the boundaries of the selected area. The total number of nodes connected to inflow or outflow segments (boundary nodes) was 65, 36, and 50 for the three networks, respectively. To carry out the simulation, values of flow or pressure for the input and output segments are required. Since these qualities were not measured, appropriate values had to be estimated. While the absolute values of pressures and flows in the network segments depend on the assumed input and output values, the distribution of these parameters throughout the network is quite independent of these assumptions. Furthermore, the main conclusions drawn from the analysis do not critically depend on the values chosen, due to the large number of segments in each network.

In each network, a pressure of zero was assigned to the main venular draining segments. Volume flow was assigned to the main arteriolar input segment according to its diameter, assuming a linear relation between internal diameter (D, in micrometers) and average blood flow velocity (v, in millimeters per second):

\[
v = 0.4 \cdot D - 1.9
\]

This equation was designed to provide values corresponding approximately to experimental data obtained in the cat mesentery. For other inflow and outflow segments, volume flows were assigned by calculating the average volume flow in the arteriovenous segments supplied by the main arteriolar feeding vessel (flow rate in the main arteriole/number of arteriovenous segments supplied) and multiplying that value with the number of arteriovenous segments supplied or drained by the respective inflow or outflow.

The choice of boundary conditions was checked with runs of the simulation, assuming zero hematocrit in all input nodes, to exclude the influence of the laws that were applied for the Fahraeus-Lindqvist effect and phase-separation effect. By use of the above-described procedure to define boundary conditions, a substantial number of nodes with negative pressure values (\(N_{\text{NEG}}\) in Table 1) and segments in which calculated and observed flow direction did not agree (\(N_{\text{INV}}\) in Table 1) were found. The negative pressure values were obviously due to an inappropriate choice of boundary conditions, with excessively high volume flows assigned to some output segments. Therefore, these flows were reduced by multiplying

---

**Table 1. Evaluation of Boundary Conditions in Three Microvascular Networks in the Rat Mesentery**

<table>
<thead>
<tr>
<th>Network</th>
<th>No. of segments</th>
<th>No. of nodes</th>
<th>No. of boundary nodes</th>
<th>(N_{\text{NEG}}) Starting conditions</th>
<th>(N_{\text{NEG}}) After modification of boundary conditions</th>
<th>(N_{\text{INV}}) Starting conditions</th>
<th>(N_{\text{INV}}) After modification of boundary conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>913</td>
<td>652</td>
<td>65</td>
<td>41</td>
<td>0</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>B</td>
<td>546</td>
<td>389</td>
<td>36</td>
<td>101</td>
<td>0</td>
<td>39</td>
<td>24</td>
</tr>
<tr>
<td>C</td>
<td>436</td>
<td>325</td>
<td>50</td>
<td>27</td>
<td>4</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

\(N_{\text{NEG}}\) nodes with negative pressure values; \(N_{\text{INV}}\), segments in which calculated and observed flow direction did not agree.
with factors between 0.85 and 0.2. Flow had to be changed in approximately 10% of the output segments to reduce the number of nodes with negative pressures to a satisfactory level (Table 1). This procedure also reduced the number of segments with inverted flow direction to 1–4% of the total number of segments. Extensive tests with additional changes of boundary conditions with both the assumption of zero hematocrit as well as the use of measured hematocrit levels for the input segments were performed to achieve a further significant reduction in \( N_{\text{INV}} \). However, this turned out to be impossible since the remaining segments with inverted flow directions were disseminated over the entire network area. Although the flow direction in each of these segments could individually be changed by appropriate adjustments of boundary conditions, these manipulations were accompanied by the generation of additional segments with inverted flow in the adjacent network areas leading to an increase in \( N_{\text{INV}} \).

The Fahraeus effect. To simulate blood flow through a network, assumptions about the rheological characteristics of blood must be made. In the present model, the Fahraeus effect, the Fahraeus-Lindqvist effect, and the phase-separation effect (disproportionate distribution of red blood cells and plasma at bifurcations) were taken into account. A parametric description of the reduction of tube hematocrit (\( H_T \)) relative to discharge hematocrit (\( H_D \)) (Fahraeus effect) was developed on the basis of data referring to experiments in which human red blood cell suspensions were perfused through glass tubes with different diameters (\( D \)).

\[
\frac{H_T}{H_D} = H_D + (1 - H_D) \left( 1 + 1.7 e^{-0.415D} - 0.6 e^{-0.011D} \right)
\]

(1)

This equation has been adapted to rat blood by scaling the diameter-dependent exponents with the cube root of mean red blood cell volume (human: 92 fl, rat: 55 fl) (Figure 1).

The Fahraeus-Lindqvist effect. It is known from in vitro experiments that the apparent viscosity of blood in small tubes is a function of both hematocrit and tube diameter. Literature data obtained with human blood were used to define a parametric equation for the variation of relative apparent viscosity (\( \eta_{\text{rel}} \)) with \( H_D \) and \( D \) in rat blood:

\[
\eta_{\text{rel}} = 1 + \frac{e^{\frac{H_D}{0.45} - 1}}{e^{\frac{H_D}{0.45} - 1} - 1} \left( 110 e^{-1.424D} + 3 - 3.45 e^{-0.035D} \right)
\]

(2)

with

\[
\alpha = 4 \left[ 1 + e^{-0.593(D - 6.74)} \right]
\]

(3)

This relation is graphically shown in Figure 1. According to this equation, relative viscosity increases exponentially with hematocrit for larger tubes (\( D > 15 \, \mu m \)); for small diameters (\( D < 5 \, \mu m \)), the hematocrit dependence of viscosity is approximately linear.

Phase-separation effect. The fraction of the total red blood cell flow in the feeding vessel of a bifurcation that enters one of the daughter branches (\( F_{Q_B} \)) is not necessarily equal to the fractional blood flow entering that branch (\( F_{Q_B} \)) (Figure 2). Fractional flow is defined as the flow into a daughter branch divided by the flow in the parent vessel of the bifurcation. This phase-separation effect has been investigated in the rat mesentery, and the following empirical relation was developed to describe the distribution of blood and cell flows at an individual bifurcation (Figure 2):

\[
\text{logit } F_{Q_B} = A + B \log \left( \frac{F_{Q_B} - X_0}{1 - 2X_0} \right)
\]

where logit \( x = \ln[x/(1-x)] \), \( X_0 \) defines the minimal fractional blood flow required to draw red blood cells into the daughter branch, \( B \) denotes the nonlinearity of the relation between \( F_{Q_B} \) and \( F_{Q_B} \), and \( A \) describes the difference between the relations derived for the two daughter branches.

By use of the data obtained by Pries et al. in 65 microvascular bifurcations, relations between the parameters \( A, B, \) and \( X_0 \) of the logit fits and relevant experimental variables (diameter \( D_F \) and hematocrit \( H_D \) in the feeding branch, diameters \( D_a \) and \( D_b \) of the daughter branches) could be established:
hematocrits in all vessel segments ($r^2_{H_D}$). Table 2 shows the values of these parameters under six different sets of input conditions. When the rheological behavior of blood was simulated using the above described representations of the Fahraeus effect, the Fahraeus-Lindqvist effect, and the phase-separation effect (condition 1), $N_{INV}$ was found to vary between 3.0% and 5.5% in all nodes in the network, whereas $r^2_{H_D}$ ranged from 0.06 to 0.177.

These results indicate substantial discrepancies between observed and predicted behavior for which two potential sources can be identified. The viscosity law underlying the calculations of pressure and flow could be wrong, or the description of flow behavior at bifurcations could be incorrect, leading to errors in the calculation of individual vessel hematocrits. Due to the interdependence of viscosities and hematocrits, errors in either rheological assumption would lead to errors in both the predicted hematocrits and the predicted flows.

The influence of the bifurcation law on the results was tested by setting the discharge hematocrits in all vessel segments to the values measured experimentally (Table 2, condition 4). In all three networks, this approach caused $N_{INV}$ to increase compared with condition 1 in Table 2. This indicates that the observed discrepancies in flow do not primarily originate from an inaccurate prediction of hematocrits due to a faulty bifurcation law.

Therefore, we investigated whether the discrepancy between predictions and observations resulted from incorrect assumptions concerning the dependence of flow resistance on hematocrit and vessel diameter. Simulations were carried out in which this dependence was modified relative to the behavior observed in vitro. For convenience, these modifications are expressed in terms of altered apparent viscosity although geometrical factors may also be involved. Simulations in which viscosity was set equal in all vessel segments independent of hematocrit and diameter (Table 2, conditions 2 and 5) showed better results than the initial conditions both in terms of $N_{INV}$ as well as $r^2_{H_D}$. If compared with the in vitro viscosity law, the assumption of uniform viscosity leads to an elevation (or decreased reduction) of resistance in the smaller vessel segments. It was

$$A = -6.96 \ln \left( \frac{D_a}{D_\beta} \right) / D_F$$

(4)

$$B = 1 + 6.98 \left( \frac{1 - H_D}{D_F} \right)$$

(5)

$$X_0 = \frac{0.4}{D_F}$$

(6)

These equations result from linear regression analysis with the offset fixed to zero (Equations 4 and 6) and 1 (Equation 5), respectively.

**Model Evaluation**

For the evaluation of the modeling process, two parameters were used: the number of segments in which the predicted flow direction was inverted relative to observation ($N_{INV}$), and the squared coefficient of correlation between predicted and measured discharge

<table>
<thead>
<tr>
<th>Condition</th>
<th>$H_D$</th>
<th>Viscosity law</th>
<th>$N_{INV}$</th>
<th>$r^2_{H_D}$</th>
<th>$N_{INV}$</th>
<th>$r^2_{H_D}$</th>
<th>$N_{INV}$</th>
<th>$r^2_{H_D}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Predicted</td>
<td>In vitro</td>
<td>44 (4.8%)</td>
<td>0.060</td>
<td>30 (5.5%)</td>
<td>0.133</td>
<td>13 (3.0%)</td>
<td>0.177</td>
</tr>
<tr>
<td>2</td>
<td>Predicted</td>
<td>Uniform</td>
<td>25 (2.7%)</td>
<td>0.080</td>
<td>24 (4.4%)</td>
<td>0.163</td>
<td>7 (1.6%)</td>
<td>0.226</td>
</tr>
<tr>
<td>3</td>
<td>Predicted</td>
<td>Modified</td>
<td>15 (1.6%)</td>
<td>0.148</td>
<td>25 (4.6%)</td>
<td>0.183</td>
<td>2 (0.5%)</td>
<td>0.333</td>
</tr>
<tr>
<td>4</td>
<td>Measured</td>
<td>In vitro</td>
<td>69 (7.6%)</td>
<td>...</td>
<td>47 (8.6%)</td>
<td>...</td>
<td>22 (5.0%)</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>Measured</td>
<td>Uniform</td>
<td>25 (2.7%)</td>
<td>...</td>
<td>24 (4.4%)</td>
<td>...</td>
<td>7 (1.6%)</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>Measured</td>
<td>Modified</td>
<td>20 (2.2%)</td>
<td>...</td>
<td>29 (5.3%)</td>
<td>...</td>
<td>3 (0.7%)</td>
<td>...</td>
</tr>
</tbody>
</table>

$H_D$, discharge hematocrit; $N_{INV}$, segments in which the predicted flow direction was inverted relative to observation; $r^2_{H_D}$, the squared coefficient of correlation between predicted and measured discharge hematocrits in all vessel segments. $H_D$ was either predicted from the phase-separation effect or measured in vivo.
therefore tested whether further improvement of the simulation could be obtained with a viscosity law that assumes an increase in apparent viscosity with decreasing vessel diameter, particularly in the range below approximately 15 μm (η\textsubscript{rel}). Within the range of viscosity relations tested, the best model results were achieved by multiplying η\textsubscript{rel}, as calculated with Equations 2 and 3, with a diameter-dependent factor:

\[
\eta_{rel}' = \eta_{rel}\left(\frac{D^4}{D-W}\right) \tag{7}
\]

For the three networks analyzed, the optimal values of the constant W were found to be 4 μm (network A) and 3.4 μm (networks B and C), irrespective of whether hematocrits were set to the measured values or predicted by the model (Table 2, conditions 3 and 6). The resulting relation between η\textsubscript{rel} and vessel diameter for W=3.5 μm is given in Figure 3. A comparison with the original viscosity law (Figure 1) shows a marked viscosity increase in the low diameter range. It should be cautioned, however, that this viscosity relation cannot be considered as a precise, quantitative representation of effective blood viscosity in vivo. Model results with comparable values of N\textsubscript{INV} and r\textsubscript{HD} could be achieved with a number of viscosity relations that exhibit significant quantitative differences to those described by Equation 7. All these relations, however, are qualitatively similar in predicting a viscosity increase with decreasing vessel diameter below about 15 μm. The results presented in the following will be based on the modified law for apparent viscosity described in Equation 7, using optimized values for W.

Although the use of the modified viscosity law reduces N\textsubscript{INV} to an average of only 2% of the total number of segments, the values of r\textsuperscript{2}HD, though higher than in the previous conditions, are still fairly low. Accordingly, the plots of predicted discharge hematocrits versus measured hematocrits exhibit considerable scatter (Figure 4). In contrast, global parameters describing the hematocrit distributions (Figure 5), such as the mean and coefficient of variation, show a high degree of similarity between simulation and measurements (Table 3). This difference in the quality of global and local predictions is not unexpected since errors (e.g., in the bifurcation law) will accumulate at consecutive arteriolar generations, making predictions for individual segments increasingly uncertain as the venous tree is approached. The effect of error accumulation is demonstrated for network A by the fact that r\textsuperscript{2}HD increases from 0.148 to 0.281 if, instead of all vessel segments, only arterioles and arteriovenous segments are considered and rises further to 0.334 and 0.403 if segments only up to generation 12 and 6, respectively, are included in the calculation.

Another example of the ability of the model to simulate global network behavior is provided by the results shown in Figure 6, which gives the variation of flow velocities in the arteriovenous vessels with generation number. The distribution, as predicted by the model, is very similar to the results obtained by direct measurements in a previous study.17
Discussion

In modeling blood flow through microvascular networks, a high degree of idealization of the original experimental situation is necessary. In most cases, these idealizations reflect the limited quantitative knowledge of rheological phenomena on which the model simulation has to be based. Two areas where such limitations are of major importance for the validity of any flow simulation are the distribution characteristics of red blood cells and plasma at bifurcations and the apparent viscosity of blood in small vessels.

The results presented here indicate that the description of phase-separation phenomena as derived from in vivo experiments is adequate to predict the distribution of cells and plasma to the different flow pathways through microcirculatory networks. This was tested by comparing measured and predicted values for hematocrit and flow direction in microvessel segments. The low hematocrit values reported for the capillaries in a number of tissues have created a discussion of whether this phenomenon is due solely to cell and volume flow distribution in vessels and networks or whether additional effects are involved.10,18–23 Such effects could result from hypothetical intravascular fluid regions, for example, with restricted flow due to wall-adherent macromolecules or irregular vessel shapes. For the rat mesentery, however, the agreement between measured and predicted hematocris presented here indicates that the hematocrit distribution within the network can be explained on the basis of the Fahraeus effect observed in vitro and the bifurcation law.

Although the bifurcation law used was derived from in vivo measurements, the initial description of apparent viscosity as a function of vessel diameter and hematocrit had to be based on results obtained in vitro. The available direct measurements of viscosity in vivo24 do not provide enough information for a parametric description of blood viscosity, especially in the vessel diameter range below 20 μm. The use of a viscosity law derived from in vitro investigations, however, implies the representation of a blood-perfused mesenteric microvessel network by an array of smooth cylindrical tubes perfused with red blood cell suspension. The model evaluation strongly suggests that this simplification leads to a systematic error in the calculation of the pressure-flow relation in microvessels. Flow resistance in vessels with diameters below approximately 15 μm seems to be substantially higher than is estimated from in vitro measurements of apparent viscosity, and this difference increases with decreasing diameter. In addition, these results imply a stronger change of viscosity with hematocrit in small microvessels.

Since these findings are in contrast with current views of microvascular blood flow, the pressures predicted by the model on the basis of the modified viscosity relation were tested against simulations using the original viscosity law, and both data sets were compared with direct pressure measurements in

**Table 3. Comparison of Measured and Predicted Hematocrit Levels in Three Microvascular Networks in the Rat Mesentery**

<table>
<thead>
<tr>
<th>Network</th>
<th>Measured H₀</th>
<th>Predicted H₀</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>A</td>
<td>0.494</td>
<td>0.166</td>
</tr>
<tr>
<td>B</td>
<td>0.454</td>
<td>0.156</td>
</tr>
<tr>
<td>C</td>
<td>0.285</td>
<td>0.125</td>
</tr>
</tbody>
</table>

H₀, discharge hematocrit; SD, standard deviation; CV, coefficient of variation. H₀ was either measured in vivo or predicted from the phase-separation effect.

**Figure 5.** Graphs showing comparison of measured and predicted hematocrit distributions for network A (upper panel) and network C (lower panel) in Table 1.

**Figure 6.** Graph showing average flow velocity versus generation level for arteriovenous (AV) segments. The variation of flow velocity with generation number predicted by the model simulation for network A (Table 1) agrees well with previous measurements.17 The similarity of the absolute velocity levels is not indicative of the simulation quality, since it depends on the assumed flow velocity in the main feeding arteriole (see "Materials and Methods").
the cat mesentery\textsuperscript{25,26} In spite of the large differences in the assumed viscosity for the narrowest vessels between the two simulations, the resulting pressure distributions are surprisingly similar and agree rather well with the in vivo measurements (Figure 7). This rather low sensitivity of pressure distribution to the difference in vessel segments of a given diameter class.\textsuperscript{27,28} Therefore, the slope of the pressure-diameter relation given in Figure 7 cannot be interpreted as a direct expression of vessel resistance. Since a vessel segment of a given diameter may be coupled in parallel to a vessel segment of a lower or higher diameter category, an alteration of viscosity only in this segment will not lead to a proportional change of its pressure drop. Diagrams of the type shown in Figure 7 can therefore be misleading, because they suggest series-coupled arrangements of the consecutive diameter classes that in strict form probably do not exist in any tissue. With this limitation in mind, Figure 7 may be interpreted to demonstrate that the modeling results presented here are not inconsistent with the existing in vivo measurements of pressure distributions within microvascular networks.

The unexpected discrepancy between the optimized viscosity relation and in vitro measurements implies that a combination of geometrical and rheological effects not present in perfusion experiments in vitro acts to elevate effective flow resistance in the smallest microvessels. These hypothetical effects are listed in Figure 8: 1) In contrast to straight cylindrical glass tubes, living microvessels may exhibit considerable irregularity of the lumen contour. 2) Macromolecular structures associated with the glycocalyx of the endothelial surface might act to impede flow in the marginal flow regions and thereby reduce the cross-sectional area of the vessel available for free flow. In contrast to the original concept, which was put forward by Desjardins and Duling,\textsuperscript{22} the present results indicate that such a hypothetical vessel wall-associated zone does not lead to an exclusion of red blood cells and a concomitant reduction of tube hematocrit. 3) The radial distribution of red blood cells flowing through microvessels is often more asymmetric\textsuperscript{1,29} and less stable than observed in vitro. This is partially due to the presence of bifurcations and may lead to increased energy dissipation in changes of cell shape and a localized reduction of the lubrication layer between cells and vessel wall. 4) Finally, white cells, which are removed in most in vitro experiments, may increase flow resistance in vivo, due to interactions with the vessel wall, train formation, or even transient occlusion of single capillaries.

Present knowledge of these phenomena does not allow a definitive conclusion whether any or all of these mechanisms would suffice to account for the increased flow resistance in small microvessels deduced from the present results. However, the model evaluation suggests that a direct application of in vitro viscosity measurements may lead to significant and systematic misinterpretation of the flow situation in vivo.

References

2. Fenton BM, Wilson DW, Cokelet GR: Analysis of the effects of measured white blood cell entance times on hemodynamics in a computer model of a microvascular bed. *Pflugers Arch* 1985;403:396–401


**Key Words** • microvascular networks • microvessel hematocrit • Fahraeus-Lindqvist effect • Fahraeus effect
A R Pries, T W Secomb, P Gahtgens and J F Gross

*Circ Res.* 1990;67:826-834
doi: 10.1161/01.RES.67.4.826

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/67/4/826

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org//subscriptions/