Motion of red blood cells in a capillary with an endothelial surface layer: effect of flow velocity

T. W. SECOMB,1 R. HSU,1 AND A. R. PRIES2
1Department of Physiology, University of Arizona, Tucson, Arizona 85724-5051; and
2Department of Physiology, Freie Universität Berlin, D-14195 Berlin, Germany

Received 6 June 2000; accepted in final form 14 March 2001

Secomb, T. W., R. Hsu, and A. R. Pries. Motion of red blood cells in a capillary with an endothelial surface layer: effect of flow velocity. Am J Physiol Heart Circ Physiol 281: H629–H636, 2001.—Interior surfaces of capillaries are lined with macromolecules forming an endothelial surface layer (ESL). A theoretical model is used to investigate effects of flow velocity on motion and axisymmetric deformation of red blood cells in a capillary with an ESL. Cell deformation is analyzed, including effects of membrane shear and bending elasticity. Plasma flow around the cell and through the ESL is computed using lubrication theory. The ESL is represented as a porous layer that exerts compressive forces on red blood cells that penetrate it. According to the model, hydrodynamic pressures generated by plasma flow around the cell squeeze red blood cells into narrow elongated shapes. If the ESL is 0.7 μm wide, with hydraulic resistivity of $2 \times 10^8$ dyn·s·cm$^{-4}$, and exerts a force of 20 dyn/cm$^2$, predicted variation with flow velocity of the gap width between red blood cell and capillary wall agrees well with observations. Predicted gap at a velocity of 0.1 mm/s is $\sim 0.6 \mu$m vs. $\sim 0.2 \mu$m with no ESL. Predicted flow resistance increases markedly at low velocities. The model shows that exclusion of red blood cells from the ESL in flowing capillaries can result from hydrodynamic forces generated by plasma flow through the ESL. 

Apparent viscosity; blood flow resistance; glyocalyx; hematocrit; microvessels

The interior surfaces of blood vessels are lined with a glyocalyx, consisting of bound and adsorbed macromolecules. Electron-microscopic studies have typically revealed a layer several tens of nanometers thick. In vivo investigations of blood flow in capillaries have shown the presence of a much thicker layer, estimated to be $\sim 0.4–1$ μm thick, known as the endothelial surface layer (ESL) (10), which excludes red blood cells and impedes plasma flow. This layer is believed to be a major factor leading to the low tube hematocrits observed in capillaries (9) and levels of flow resistance in microvessels that are substantially higher than in glass tubes with corresponding diameters (11). Further evidence for the existence of such a relatively thick layer was provided by the experiments of Vink and Duling (21), who measured the widths of the columns of red blood cells and labeled dextran-70 in capillaries in the hamster cremaster muscle. The widths of these columns increased 0.8–1 μm after a light-dye treatment, without observable changes in capillaries’ anatomic diameters. These results were interpreted to show that disrupting the glyocalyx (ESL) by a photodynamic process increased the space available for red blood cell motion and plasma flow.

Vink and Duling (21) also examined the effect of red blood cell velocity on the width of the zone at the endothelial surface from which red blood cells were excluded. They found that the width of the zone decreased with decreasing cell velocity below $\sim 200$ μm/s. When motion of red blood cells ceased, red blood cells expanded to fill the capillary, such that no space could be detected between the red blood cell surface and the anatomic wall of the capillary at the widest part of the red blood cell. This observation is of interest, because it suggests that the physiological effects of the ESL, such as its effects on oxygen transport, may vary with red blood cell velocity. Also it provides possible indications of the biophysical nature of the ESL.

Feng and Weinbaum (5) proposed that fluid dynamic lubrication forces generated within the ESL are responsible for the exclusion of flowing red blood cells from the ESL. Because the lubrication forces are generated by fluid flow, such forces cease when flow stops. This provides a possible explanation for the observation (21) that stationary red blood cells expand to fill capillaries. In the theoretical analysis (5), the red blood cell is treated as an object with a prescribed shape. Other previous theoretical studies considered the motion of rigid spherical particles (2, 23) or deformable red blood cells (1, 17) through cylindrical tubes lined with a porous wall layer but did not consider cases in which the red blood cell penetrates or compresses the layer substantially.

In the present study, a modified version of a previously developed theoretical model (17) is used to analyze the motion and deformation of red blood cells in capillaries lined with an ESL as a function of red blood cell velocity. The mechanical properties of the red blood cell, including the elastic resistance of the cell mem-

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brane to shear and bending deformations, are included in the model. The ESL is assumed to be compressible and permeable to water and to exert a small radial force resisting penetration by red blood cells. With this approach, quantitative relationships can be established between the biophysical properties of the ESL and the velocity-dependent deformation of red blood cells within a capillary.

**FORMULATION OF THE MODEL**

*Red blood cell mechanics.* Single-file flow of mammalian red blood cells is considered, and fluid mechanical interactions between red blood cells are neglected. Axisymmetric red cell shapes are assumed. The red blood cell is represented as a viscoelastic membrane containing an incompressible viscous fluid. Our previous model (17) included the elastic resistance of the red cell membrane to shear deformation but neglected bending resistance of the membrane. Although the bending resistance is small, its effects may be significant at very low red cell velocities, when fluid mechanical forces are very small, and so effects of bending resistance are included here. The elastic resistance of the red cell membrane to area changes is very large, so it is assumed to deform without area change. Transient changes of red cell shapes are considered, and so the viscous resistance of the membrane to shear deformation is included. Previous studies of red cell motion in capillaries with variable diameters (15) have shown that the energy dissipation in the cell interior associated with transient changes in cell shape is much less than the dissipation in the membrane, and such internal dissipation is neglected here. The hydrostatic pressure is therefore considered to be uniform within the cell, and internal shear stresses are neglected.

The previous model (17) assumed that the cell membrane was unstressed in a spherical reference shape. In that model, the choice of the stress-free configuration was not an important factor. However, the outward radial force exerted by a red blood cell within a capillary depends on the assumed stress-free configuration, and this is an important consideration in the present model, because it is responsible for the widening of the red blood cell at very low velocities. The biconcave shape of freely suspended red blood cells is not necessarily stress free, but some evidence (6) suggests that a biconcave shape is more appropriate than a spherical configuration, and that assumption is made here. The axis of the reference biconcave disk shape is assumed to coincide with the capillary axis. This assumption is necessary to preserve the axisymmetry of the configuration.

Cylindrical polar coordinates \((\rho,\phi,z)\) are defined traveling with the cell, with origin at the front of the cell and \(z\) increasing toward the rear (Fig. 1). A material coordinate \(\sigma\) is defined as arc length measured along the cell from the origin in the reference shape. The radial position of a material element in the reference shape is denoted \(r_0(\sigma)\). The position of material point \(\sigma\) is given by \((\rho,\phi,z(\sigma))\). Other variables are as follows: \(s(\sigma)\), arc length measured along the cell from the origin; \(\theta(\sigma)\), angle between the normal to the membrane and the axis; \(k_s(\sigma)\) and \(k_0(\sigma)\), membrane curvatures; \(m_s(\sigma)\) and \(m_0(\sigma)\), bending moments in the membrane; \(t_s(\sigma)\) and \(t_0(\sigma)\), components of membrane tension; and \(q_s(\sigma)\), shear force per unit length (18). The subscript \(s\) denotes components in a plane containing the axis (i.e., along the cell), and the subscript \(\phi\) denotes azimuthal components (i.e., around the cell).

Following the analysis of Evans and Skalak (Ref. 4, p. 109), the bending moments in the cell membrane are assumed to be isotropic and proportional to the change in total curvature of the surface

\[
m_s = m_0 = Bkh_0 - (k_s + k_0) \tag{1}
\]

where the curvatures are given by

\[
k_s = \theta/\rho \quad \text{and} \quad k_0 = \sin \theta/r \tag{2}
\]

where \(B\) is the bending modulus and subscript 0 denotes the reference shape. The extensions (stretch ratios) of the membrane in the axial and circumferential directions are \(\lambda_s = ds/d\sigma\) and \(\lambda_0 = r_0/\rho_0\). Because the membrane deforms without change in area, \(\lambda_s\lambda_0 = 1\). The axial and circumferential components of membrane tension are (4)

\[
t_s = t_0 - t_d \quad \text{and} \quad t_0 = t_0 + t_d \tag{3}
\]

where

\[
t_d = (\mu_m/\lambda_0)\partial k_0/\partial t + h(\lambda_s^2 - \lambda_0^2) - m_s(k_s - k_0)/2 \tag{4}
\]

Here, \(t_0\) is the isotropic part of the membrane tension, and \(\mu_m\) and \(h\) are the shear viscosity and the elastic shear modulus of the membrane. The first and second terms on the right-hand side of Eq. 4 represent the viscous and elastic contributions to membrane stress resulting from in-plane shear deformation of the membrane. The third term is added according to an analysis of the mechanics of bilayer membranes (13) showing that, under the assumptions leading to Eq. 1 for the bending moments in the membrane, bending the membrane also generates in-plane shear stresses.
For a thin axisymmetric shell, the equations of equilibrium of normal stress, tangential stress, and bending moments in the membrane are (20)

\[
\begin{align*}
    r^{-1}d(rq_r)/ds &= p + f + k_c t_s + k_m t_b \\
    r^{-1}d(rq_t)/ds &= r^{-1}t_s \cos \theta - k_c q_t - \tau \\
    r^{-1}d(rm_b)/ds &= r^{-1}m_b \cos \theta + q_s
\end{align*}
\] (5)

where \( p \) is the hydrostatic pressure difference across the membrane (external minus internal) and \( \tau \) is the viscous shear stress due to the external fluid. The additional term \( f \) in Eq. 5 represents the force exerted by the ESL on the cell (see below).

**Plasma flow mechanics.** The flow of plasma around the exterior of the cell and through the ESL is described by invoking the approximations used in lubrication theory, which results in a simpler form of the equations governing fluid flow in a narrow space between two surfaces when the Reynolds number is very small. In this theory, the fluid pressure \( p \) is assumed to be uniform across the gap between the cell and the wall, including the ESL (2, 17). The ESL is modeled as a porous matrix. The hydraulic resistivity, i.e., the pressure gradient divided by the mean flow velocity in the matrix, is denoted by \( K(p) \). This assumption leads to the following equation for the axial component of plasma velocity (\( v_z \))

\[
\mu \rho \frac{\partial}{\partial \rho} \left( \rho \frac{\partial v_z}{\partial \rho} \right) = \frac{\partial p}{\partial z} + K(p)v_z
\] (8)

where \( \mu \) is the fluid viscosity and the solid fraction of the matrix is assumed to be small. The boundary conditions are as follows: \( v_z = 0 \) when \( \rho = D/2 \), where \( D \) is the capillary diameter, and \( v_z = V_{rbc} \) when \( \rho = r \), where \( r \) is the cell radius and \( V_{rbc} \) is the cell velocity. In the previous study (17), \( K(p) \) was assumed to vary smoothly with distance from the wall, with a parameter \( L \) describing the width of the diffuse boundary of the layer. However, the results were found to be relatively insensitive to the value of \( L \). For simplicity, therefore, a sharp boundary to the layer is assumed here; i.e., \( K(p) = K_0 \) when \( \rho > D/2 - w \) and \( K(p) = 0 \) otherwise, where \( w \) is width of the ESL. Possible increases in \( K_0 \) with compression of the ESL (5) are neglected.

Under these assumptions, Eq. 8 can be solved exactly in terms of modified zeroth-order Bessel functions of the first and second kind (2). When \( r < D/2 - w \), solutions are obtained in the regions within and outside the ESL and matched with continuous velocity and shear stress at the interface \( \rho = D/2 - w \). From this solution, the flow rate in the gap and the shear stress acting on the membrane can be obtained as a linear function of cell membrane velocity and pressure gradient for a given gap width. The condition of conservation of fluid volume is then obtained, and this, together with the equations of membrane equilibrium above, constitutes the system of governing equations. A time-dependent form of these equations is used here (15) to permit analysis of transient changes in red cell shape with changing driving pressures. The cell shape is described by the coordinates \( [r(t), z(t)] \) of 200 nodal points fixed in the cell membrane. The system of differential equations is solved for \( dr/dt, dz/dt, p, \) and \( t_b \) by a finite difference method; then the cell shape at the next time step is computed. To improve the stability, a partially implicit approach is used. At each time step, membrane curvature \( (k_m) \) and its spatial derivatives are calculated on the basis of the updated shape, and the shape is then adjusted iteratively until the system of equations is satisfied within a prescribed tolerance. Steady-state solutions are obtained by imposing a steady driving pressure and following the solution until transient changes are negligible.

**ESL stiffness.** Two types of evidence suggest that the ESL has a finite resistance to compression. First, a structure with no resistance to compression would be flattened by the shear stress exerted by flowing blood (10). Second, the ESL in a capillary regains its width in \( \sim 1 \) s after being flattened by a passing white blood cell (22). This shows the existence of a force tending to restore the layer thickness after compression. The biological origin of this force is not known. One hypothesis (12) is that it results from colloid osmotic forces generated by plasma proteins adsorbed to the glycolyx. According to this hypothesis, the colloid osmotic pressure within the ESL is increased by an amount \( \Delta p_c \) above that of free plasma, and this additional pressure is balanced by tension in membrane-bound glycoprotein chains (19). An applied mechanical force tending to compress the ESL, such as that exerted by a red blood cell, relieves the tension in the chains and must therefore exert force against the increment in colloid osmotic pressure within the layer to reduce its width.

The present model is based on this hypothesis. It is assumed that the ESL exerts a pressure on the red cell membrane, in addition to the hydrostatic pressure, given by \( f(r) = \pi_r \) when the red blood cell penetrates the ESL (i.e., \( r > D/2 - w \) and \( f(r) = 0 \) otherwise, where \( r \) is the radial position of a point on the membrane. This force acting normal to the membrane is included in Eq. 5. The pressure exerted by the ESL is assumed to be independent of the compression of the layer. In reality, the pressure may increase when the layer is compressed, and the consequences of such behavior are considered in the discussion. For simplicity, the analysis of red blood cell motion through the ESL neglects the disturbance of the layer resulting from passage of preceding red blood cells (22). Possible effects of such disturbance are considered below. Compression of the ESL by passing red blood cells implies, by conservation of fluid volume, that fluid is squeezed out of the ESL and reabsorbed when the ESL returns to its original width. The analysis of plasma flow mechanics, as already described, allows for such exchange of fluid between the ESL and free plasma.

**Parameter values.** Red blood cells are assumed to have volume of 90 \( \mu \)m\(^3\) and area of 135 \( \mu \)m\(^2\). The membrane is assumed to have \( \kappa = 0.006 \) dyn/cm and \( \mu_m = 0.001 \) dyn·s·cm\(^{-1}\). \( B \) is estimated to be 1.8 \( \times \)
viscosity ($\mu$) of 0.01 dyn·s·cm$^{-2}$ is assumed. In comparisons with experimental data from hamsters, the observed vessel diameters are scaled up according to the cube root of the ratio of the assumed volume to the mean volume (61 $\mu$m$^3$) of hamster red blood cells (21), i.e., by a factor of 1.14. Plasma viscosity ($\mu$) of 0.01 dyn·s·cm$^{-2}$ is assumed.

Most estimates of the thickness ($w$) of the ESL have been in the range 0.4–1 $\mu$m, and values in that range are considered here. The hydraulic resistivity ($K_0$) of the ESL has not been measured directly. At least $\sim 10^8$ dyn·s·cm$^{-4}$ is required to account for observed levels of flow resistance in rat mesentery, even when other mechanisms, such as capillary irregularity and the presence of white blood cells, are taken into account (17). Most other water-permeable tissues have higher resistivities, and a range of values is considered. The radial force ($\Delta \pi_r$) exerted by the layer also has not been measured directly. In our previous model (17), it was assumed that the force was sufficient to exclude red blood cells, and 200 dyn/cm$^2$ was used. However, the ability of stationary red blood cells to invade the ESL suggests that the actual value is much smaller. Typical wall shear stresses in microvessels are on the order of 20 dyn/cm$^2$, and simple mechanical arguments (10) suggest that the actual value is much smaller. Typical wall shear stresses in microvessels are on the order of 20 dyn/cm$^2$, and simple mechanical arguments (10) suggest that the actual value is much smaller. Typical wall shear stresses in microvessels are on the order of 20 dyn/cm$^2$, and simple mechanical arguments (10) suggest that the actual value is much smaller.

The sensitivity of the results to the parameter values is indicated in Fig. 3B, which shows results for $w = 0.6$, 0.7, and 0.8 $\mu$m. In each case, $K_0$ was chosen to give approximately the same average gap width at a velocity of 100 $\mu$m/s as observed experimentally. Although best agreement with the experimental data is seen with $w = 0.7$ $\mu$m, the results for the other two cases are probably within the experimental uncertainty of the experimental results.

Theoretical predictions of gap width and rheological parameters over a wide range of velocities are summarized in Fig. 4 for the case when $w = 0.7$ $\mu$m and $K_0 = 2 \times 10^8$ dyn·s·cm$^{-4}$. Corresponding results in the absence of an ESL are shown by dashed lines. The discontinuity in slope of the results with ESL corresponds to the velocity at which the cell starts to ride above the ESL, i.e., $\sim 300$ $\mu$m/s. Figure 4B shows a strong variation in the Fahraeus effect with cell velocity. The Fahraeus effect is expressed as

$$\frac{H_T}{H_D} = \frac{V}{V_{rbc}}$$

where $H_T$ is the tube hematocrit, $H_D$ is the discharge hematocrit, $V$ is the mean flow velocity, and $V_{rbc}$ is the velocity of the red blood cells. At very low cell velocities, the cell almost fills the capillary, and so $V_{rbc} \approx V$. At
higher velocities, the red blood cell moves with the plasma lying outside the ESL, and the plasma within the ESL is almost stationary, so \( V_{\text{rbc}} > V \).

In this model, interactions between red blood cells are neglected, and so flow resistance varies linearly with hematocrit

\[
R = R_0(1 + K_T H_T) \quad (10)
\]

where \( R_0 \) is the resistance at zero hematocrit and \( K_T \) is the apparent intrinsic viscosity. Here, \( R \) is expressed as a relative apparent viscosity, i.e., the viscosity that would lead to the same flow resistance as a Poiseuille flow in the absence of red blood cells and an ESL. With an ESL present but no red blood cells, \( R_0 = 2.54 \), while \( R_0 = 1 \) in the absence of both red blood cells and an ESL. The resistance at discharge hematocrit 45% \((R_{45})\) is given by

\[
R_{45} = R_0(1 + 0.45K_T H_T/H_D) \quad (11)
\]

\( K_T \) and \( R_{45} \) decrease substantially with increasing flow velocity (Fig. 4, C and D). This reflects two factors. First, at low velocities, the cell membrane is inclined to the tube axis along much of the length of the cell, and the normal force exerted by the ESL on the membrane has a component opposing the cell's motion. Second, at high velocities, the increasing width of the plasma layer between the cell and the ESL leads to a reduction in flow resistance.

In comparison with the results in the absence of an ESL (dashed curves in Fig. 4), the ESL is predicted to cause a stronger Fåhraeus effect (lower \( H_T/H_D \)) and increased flow resistance (higher \( R_{45} \)) at corresponding velocities. The increase in \( R_{45} \) reflects the increased \( R_0 \) in the absence of red blood cells resulting from the ESL and the increased proportional effect of red blood cells on resistance (higher \( K_T \)), which together more than compensate for the reduced tube hematocrit in the presence of an ESL.

The model can also be used to investigate the transient changes in red blood cell shape when flow is suddenly started. This process is modeled by assuming that the driving pressure is suddenly increased from an extremely low value, corresponding to a cell velocity of 1 \( \mu \)m/s, to one corresponding to a given steady-state cell velocity. Predicted sequences of cell shapes are shown in Fig. 5 for final velocities of 0.1 and 1 mm/s. In each case, the corresponding steady driving pressure (113 and 558 dyn/cm²) is imposed over a 30-\( \mu \)m length of the capillary containing the cell. The predicted variation of cell shape with distance traveled is similar in both cases. After traveling \( \sim 4 \) \( \mu \)m, the cell temporarily takes on a conical shape unlike any of the steady-state shapes shown in Fig. 2. The time taken by the cell to approach its final steady-state shape depends on the eventual velocity and is \( \sim 200 \) ms for a final velocity of 0.1 mm/s and \( \sim 40 \) ms for a final velocity of 1 mm/s. However, the distance traveled when the cell has nearly attained its final shape is approximately the same in each case and is \( \sim 20 \) \( \mu \)m.

**DISCUSSION**

The principal result of this study is that fluid dynamical pressures generated within the ESL can lead to variation of red cell shape and gap width with flow velocity in capillaries, consistent with the observations of Vink and Duling (21). This mechanism was proposed by Feng and Weinbaum (5) in a model in which the red blood cell was represented by an inclined plane riding over a planar surface coated with a porous layer. The present model, which includes the deformability of the red blood cell, predicts more complex cell shapes in which the angle between the cell membrane and the vessel wall varies significantly over the length of the cell. The theory of Feng and Weinbaum takes into account increased hydraulic resistivity of the layer when it is compressed. In the present model, the resistivity of the layer was assumed to be constant, independent of compression. Consequently, the lubrication pressures predicted by this model are less than would
be predicted by the model of Feng and Weinbaum but are still sufficient to account for the observed variation in gap width. Significant variation of gap width with red blood cell velocity is predicted over a wide range of velocities, from \(1 \text{ mm/s} \) to \(1 \text{ mm/s} \) (Fig. 4). This corresponds to the range of red cell velocities observed in capillaries in vivo.

In the absence of an ESL, the fluid dynamical forces generated in the lubrication layer cause an increase in the average gap width with increasing velocity. However, the predicted gap width in that case is less than half of that observed experimentally. In contrast, a much wider gap is predicted in the presence of an ESL. This result provides further evidence supporting the existence of an ESL that exerts substantial effects on the motion of plasma and red blood cells.

The key parameters defining the properties of the ESL in this model are \(w\), \(K_0\), and the outward force (i.e., \(\Delta \pi_p\)) that it exerts on red blood cells that penetrate it. According to the results shown in Fig. 3B, reasonable agreement between the model predictions and the experimental results (21) is obtained for \(w = 0.6–0.8 \mu\text{m}\) and \(K_0 = 10^8–10^9 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-4}\). These estimates are similar to those obtained by Secomb et al. (17). With the assumed scaling of radial dimensions by a factor of 1.14 from hamster to human taken into account, these results suggest that \(w\) in the experiments (21) was 0.5–0.7 \(\mu\text{m}\). However, relatively small changes in the experimental data could lead to estimates of \(w\) and \(K_0\) outside these ranges. The other key parameter, \(\Delta \pi_p\), is assumed to be 20 \text{ dyn/cm}^2. In further simulations, \(\Delta \pi_p\) was varied. When \(\Delta \pi_p\) was decreased to 10 \text{ dyn/cm}^2, the predicted gap width decreased slightly. When \(\Delta \pi_p\) was increased to 40 \text{ dyn/cm}^2, the gap width did not approach zero as cell velocity decreased. These results suggest that 20 \text{ dyn/cm}^2 is an approximate upper bound on \(\Delta \pi_p\). An argument based on the ability of the ESL to withstand shear stress exerted by flowing blood (10) suggests that the force has about this magnitude.

In the model, the outward force (\(\Delta \pi_p\)) is assumed to be independent of the degree of compression of the layer. Compression of the layer might be expected to lead to an increase in \(\Delta \pi_p\). However, assuming a substantial increase in \(\Delta \pi_p\) with decreasing layer thickness leads to predicted gap widths that do not approach zero as cell velocity decreases, and such behavior is not consistent with the observations (21).

In the model, the unstressed shape of the red blood cell membrane is assumed to be a biconcave disk, the axis of symmetry of which coincides with the capillary axis. Assuming that the membrane is unstressed in a spherical shape with the same area (17) would lead to an underestimate of the outward force exerted by the red blood cell on the layer. However, observations (7) suggest that red blood cells actually enter capillaries “edge on,” i.e., with the axis of the disk perpendicular.
to the capillary axis. A red blood cell entering a narrow capillary edge requires less deformation than one entering “face on.” Thus, for a cell entering edge on, the outward force may vary around the circumference of the capillary and be lower on average than that assumed here. In that case, the red blood cell shape is not axisymmetric, and prediction of the shape would require a fully three-dimensional analysis, which is beyond the scope of the present model. The cell shapes predicted by the present model represent axisymmetric approximations to the actual shapes taken by cells entering capillaries edge on. The model cannot predict details such as the asymmetric concavity or cleft often seen at the rear of cells traveling along capillaries.

The predictions of the model also depend on the assumed mechanical properties of the red blood cell membrane, i.e., $k$ and $B$. Further simulations were carried out in which $B$ was varied, showing that $B$ determines the membrane curvature in the sharply curved region at the rear of the cell but otherwise has little effect on cell shape (16). However, the model predictions are sensitive to $k$. For a given cell shape, the outward force exerted by the red blood cell on the surrounding ESL or fluid is proportional to $k$. At very low velocities, the compression of the ESL by the cell is determined mainly by the ratio of $k$ to $\Delta p_c$, while the cell shapes predicted at higher velocities depend mainly on the ratio of $k$ to $\mu V_{rbc}$.

According to the model, the changes in cell width with increasing velocity are accompanied by decreasing flow resistance and increasing Fåhraeus effect (i.e., decreasing $H_T/H_D$). As shown in Fig. 4, C and D, the predicted flow resistance increases markedly with decreasing flow velocity, as the red blood cell increasingly enters the layer rather than flowing outside it. The Fåhraeus effect vanishes ($H_T/H_D = 1$) at extremely low velocities (Fig. 4B), because the cell completely fills the capillary cross section, and cell velocity necessarily equals mean flow velocity in the capillary. However, at velocities above $\sim 10 \mu m/s$, the Fåhraeus effect is much more marked than would be the case in the absence of the ESL (Fig. 4, dashed line).

The question arises whether the model predicts flow cessation in capillaries at positive driving pressures, as observed experimentally (14). For this to occur, the slope of a log-log plot of flow resistance vs. velocity must be $-1$ or more negative at low velocities (14). The slope of the graph in Fig. 4D at low velocities is approximately $-0.6$, and so flow cessation is not predicted. Flow cessation may occur when red blood cells encounter irregularities in capillary cross section (14). In that case, the presence of the ESL would increase the minimum driving pressure needed to sustain flow.

Several other effects, not included in the model, may influence the behavior of red blood cells flowing in a capillary with an ESL. The present model does not include effects of interactions between red blood cells. In particular, each red blood cell is assumed to encounter an unperturbed ESL, with the specified nominal thickness. At low velocities, according to the model, each passing cell significantly compresses the layer. According to Vink et al. (22), the layer takes $\sim 1 s$ to recover its initial width after compression. If a following red blood cell arrives before recovery is complete, it may encounter a significantly compressed ESL, and so the gap between the cell and the capillary wall would be smaller than predicted by the present model. This could occur when the red cell flux exceeds $1/s$, which corresponds to a red cell velocity of $10 \mu m/s$, for the assumed parameter values. Conversely, at higher flow velocities, about $\sim 300 \mu m/s$, the red blood cells are predicted to ride above the layer. Thus, for flow velocities of $10–300 \mu m/s$, the present theory may overestimate the gap between red blood cell and vessel wall, leading to underestimates of tube hematocrit and flow resistance. Model predictions corresponding to this range are shown as dotted lines in Fig. 4 to indicate
that they are subject to this uncertainty. Another effect not included in the model is the possible compression of the ESL resulting from wall shear stress at high flow rates (10). If these phenomena are significant, the actual width of the layer may be larger than deduced here (i.e., 0.5–0.7 μm) to explain the experimental results (21). Inclusion of these effects would lead to altered estimates of parameter values, including $K_0$, for agreement between predicted and observed velocity-dependent gap width but would not lead to qualitatively different predicted dependence of flow resistance and hematocrit on velocity.

In summary, this model shows that the exclusion of red blood cells from the ESL in flowing capillaries can be explained by hydrodynamic forces generated by plasma flow through and adjacent to the ESL, as first proposed by Feng and Weinbaum (5). Comparison of model predictions with experimental observations (21) leads to approximate bounds on key parameters characterizing the mechanical properties of the ESL. According to the model, the ESL causes a substantial increase in flow resistance at low velocities, and this may play a role in flow cessation in capillaries at low driving pressures.

This work is supported by National Heart, Lung, and Blood Institute Grants HL-34555 and HL-07249 and Grant Deutsche Forschungsgemeinschaft Pr 271/5-4. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

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