THE ENDOTHELIAL SURFACE LAYER AS A MECHANICAL BUFFER: EFFECTS ON STRESSES EXPERIENCED BY ENDOTHELIAL CELLS AND RED BLOOD CELLS IN CAPILLARY FLOW

Timothy W. Secomb (1), Richard Hsu (1), Axel R. Pries (2)

(1) Department of Physiology
University of Arizona
Tucson, AZ

(2) Department of Physiology
Free University of Berlin
Berlin, Germany

INTRODUCTION

A large body of experimental evidence shows that the endothelial surfaces of microvessels are lined with a relatively thick layer of macromolecules, which has a substantial impact on the mechanics and hemodynamics of blood flow [1]. This layer, known as the glycocalyx or endothelial surface layer (ESL), has been estimated to be from 0.3 μm to more than 1 μm thick. Its hemodynamic effects include a marked reduction in tube hematocrit below expected levels, due to the exclusion of red blood cells from a zone near the vessel wall [2], and a significant increase in flow resistance [3]. Information about the mechanical properties of the ESL has been deduced from observations of blood flow in microvessels [2-4]. However, the physiological role of the ESL is not well established. Here, we explore its potential role in modulating the forces experienced by endothelial cells and red blood cells (RBCs) when blood flows through capillaries. In particular, we examine the effect on the ESL on the transient stresses resulting from the particulate nature of blood and from the irregularity of capillary cross-sections.

MECHANICAL PROPERTIES OF THE ESL

In order to exert the observed effects on microvessel hematocrit and flow resistance, the ESL must have a hydraulic resistivity of at least 10^8 dyn·s/cm^4 [5]. Such a resistance to fluid flow can be achieved by a very dilute structure, with a solid volume fraction of much less than 1%. The ability of the ESL to exclude RBCs can be accounted for by a hydrodynamic mechanism [6]. However, other observations, such as the restoration of layer thickness within about 1 s following its compression by a passing white blood cell [4], indicate that the layer has a finite resistance to compression. One proposed explanation [3] is that plasma proteins adsorbed to the ESL generate a colloid osmotic pressure that is slightly higher, by an amount $\Delta\Pi_p$, than that of free plasma. In the absence of external forces tending to compress the ESL, this effective pressure must be balanced by tension in membrane-bound glycoprotein chains. A value $\Delta\Pi_p = 20$ dyn/cm^2 is consistent with available information.

EFFECTS OF THE ESL ON STRESSES EXPERIENCED BY ENDOTHELIAL CELLS

The fluid shear stress acting on endothelial cells is proportional to the gradient in fluid velocity adjacent to the cell surface. The hydraulic resistivity of the ESL is sufficient to largely inhibit plasma flow within the layer, and so the fluid shear stress is correspondingly reduced [7]. Therefore, the ESL itself must be largely responsible for the transmission of wall shear stress to the endothelial cells [8], as indicated in Figure 1. The structural attachment points of the ESL to endothelial cells are therefore likely to play a crucial role in the transduction of shear stress.

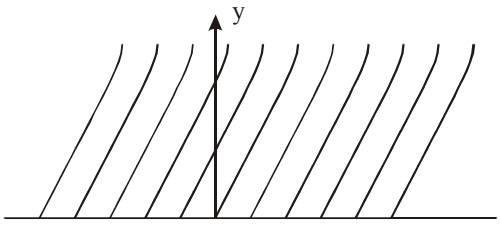

Figure 1. Schematic diagram showing transmission of shear stress to endothelial surface (y = 0) by tension in membrane-bound glycoprotein chains.

When RBCs flow along a tube with capillary dimensions, relatively large fluctuations in wall shear stress can be generated. We [8] analyzed the transmission of such fluctuations to the endothelial cells. Fluid motion within the layer was assumed to be governed by

$$\mu L^2\mathbf{u} = \nabla p + K(\mathbf{u} - \partial\mathbf{U}/\partial t) \quad \text{and} \quad \nabla\cdot\mathbf{u} = 0 \qquad (1)$$

where $\mathbf{u}$ is the fluid velocity, $\mathbf{U}$ is the velocity of the ESL matrix, $K = 2 \times 10^8$ dyn⋅s/cm^4 is the hydraulic resistivity and $\mu = 0.01$ dyn⋅s/cm^2 is the plasma viscosity. For traveling wave disturbances, this linear equation can be solved to estimate the fluctuation of shear stress at the endothelial surface resulting from a given fluctuation at the outer edge

of the layer. Results are shown in Figure 2, for a layer of width 1 μm. It is evident that the layer protects the endothelial surface from the relatively short-wavelength disturbances resulting for, example, from the passage of the leading or trailing edges of a red blood cell.

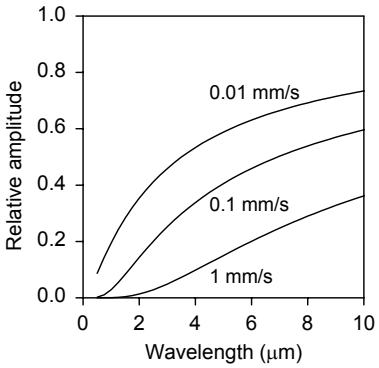

Figure 2. Relative amplitude of transient disturbances in shear stress transmitted to endothelial surface, for indicated disturbance velocities.

EFFECTS OF THE ESL ON STRESSES EXPERIENCED BY RED BLOOD CELLS IN IRREGULAR CAPILLARIES

During its lifetime, a RBC typically makes about 3×10^5 transits through the circulatory system. Capillaries are not uniform tubes: their lumens are irregular due, for example, to the nuclei of endothelial cells, which protrude from the cells. RBCs undergo frequent large deformations in traversing capillaries and in passing through capillary entrances and bifurcations. We therefore examined the effects of the ESL on the stresses experienced by RBCs passing through irregular capillaries [9]. Lubrication theory was used to describe the motion of plasma around RBCs and through the ESL. Axisymmetric RBC shapes were assumed, and the mechanical properties of the RBC membrane including its viscoelastic response to shear deformations and its elastic resistance to bending were included in the analysis [10]. A uniform ESL width of 0.7 μm was assumed. A typical configuration is shown in Figure 3. In a capillary with no ESL and diameter varying between 4 and 6 μm with a wavelength of 10 μm, RBCs experience large transient shear stresses. For a realistic flow rate of 2.5×10^{-9} cm^3/s, peak shear stress on the membrane exceeds 200 dyn/cm^2 (Figure 3). In a corresponding capillary with an ESL and with the same ESL-free luminal space, the peak stress on the RBC is about 30 dyn/cm^2. These results suggest that the ESL may protect RBCs traversing irregular capillaries from damage due to large, rapidly fluctuating stresses.

DISCUSSION

The physiological importance of the ESL remains unclear. Reduction in tube hematocrit and increase in flow resistance do not appear to be of obvious functional value. A more likely interpretation is that the ESL serves as an interface and a mediator of interactions between flowing blood and endothelial cells. Important aspects of this may include the control of access to endothelial cells of blood-borne cells and molecules. The results presented here suggest that it acts as a mechanical buffer in capillaries. It mediates the transmission of shear stress to endothelial cells, protecting them from large variations in shear stress generated by passing RBCs, and at the same time protects RBCs from large transient stresses resulting from irregular endothelial cell morphology.

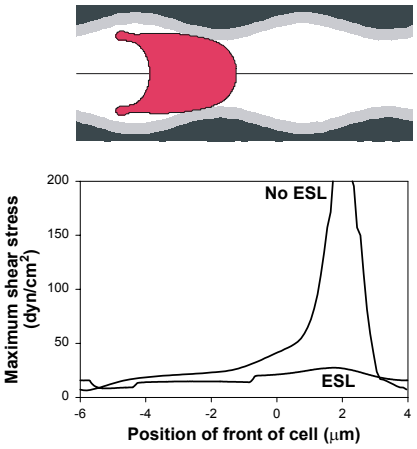

Figure 3. (Upper) Computed RBC shape in nonuniform capillary with ESL, shown in gray. (Lower) Variation of maximum fluid shear stress acting on RBC membrane with position of front of cell relative to a point of minimum width, compared with results with no ESL.

REFERENCES

1. Pries, A.R., Secomb, T.W., and Gaehtgens, P., 2000, "The endothelial surface layer," Pflügers Archiv: European Journal of Physiology, Vol. 440, pp. 653-666.
2. Desjardins, C., Duling, B.R., 1990, "Heparinase treatment suggests a role for the endothelial cell glycocalyx in regulation of capillary hematocrit," American Journal of Physiology, Vol. 258, pp. H647-H654.
3. Pries, A.R., Secomb, T.W., Jacobs, H., Sperandio, M., Osterloh, K., Gaehtgens, P., 1997, "Microvascular blood flow resistance: role of endothelial surface layer," American Journal of Physiology, Vol. 273, pp. H2272-H2279.
4. Vink, H., Duling, B.R., 1996, "Identification of distinct luminal domains for macromolecules, erythrocytes, and leukocytes within mammalian capillaries," Circulation Research, Vol. 79, pp. 581-589.
5. Secomb, T.W., Hsu, R. and Pries, A.R., 1998, "A model for red blood cell motion in glycocalyx-lined capillaries," American Journal of Physiology, Vol. 274, pp. H1016-H1022.
6. Feng, J., Weinbaum, S., 2000, "Lubrication theory in highly compressible porous media: the mechanics of skiing, from red cells to humans," Journal of Fluid Mechanics, Vol. 422, pp. 281-317.
7. Damiano, E.R., Duling, B.R., Ley, K., Skalak, T.C., 1996, "Axisymmetric pressure-driven flow of rigid pellets through a cylindrical tube lined with a deformable porous wall layer'" Journal of Fluid Mechanics, Vol. 314, pp. 163-189.
8. Secomb, T.W., Hsu R., and Pries, A.R., 2001, "Effect of the endothelial surface layer on transmission of fluid shear stress to endothelial cells," Biorheology, Vol. 38, pp. 143-150.
9. Secomb, T.W., Hsu, R. and Pries, A.R., 2002, "Blood flow and red blood cell deformation in nonuniform capillaries: effects of the endothelial surface layer," Microcirculation, Vol. 9, pp. 189-196.
10. Secomb, T.W., Hsu, R. and Pries, A.R., 2001, "Motion of red blood cells in a capillary with an endothelial surface layer: effect of flow velocity," American Journal of Physiology, Vol. 281, pp. H629-H636.