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The effects of spatial inhomogeneities on flow through the endothelial surface layer

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Abstract

Flow through the endothelial surface layer (the glycocalyx and adsorbed plasma proteins) plays an important but poorly understood role in cell signaling through a process known as mechanotransduction. Characterizing the flow rates and shear stresses throughout this layer is critical for understanding how flow-induced ionic currents, deformations of transmembrane proteins, and the convection of extracellular molecules signal biochemical events within the cell, including cytoskeletal rearrangements, gene activation, and the release of vasodilators. Previous mathematical models of flow through the endothelial surface layer are based upon the assumptions that the layer is of constant hydraulic permeability and constant height. These models also assume that the layer is continuous across the endothelium and that the layer extends into only a small portion of the vessel lumen. Results of these models predict that fluid shear stress is dissipated through the surface layer and is thus negligible near endothelial cell membranes. In this paper, such assumptions are removed, and the resultant flow rates and shear stresses through the layer are described. The endothelial surface layer is modeled as clumps of a Brinkman medium immersed in a Newtonian fluid. The width and spacing of each clump, hydraulic permeability, and fraction of the vessel lumen occupied by the layer are varied. The two-dimensional Navier–Stokes equations with an additional Brinkman resistance term are solved using a projection method. Several fluid shear stress transitions in which the stress at the membrane shifts from low to high values are described. These transitions could be significant to cell signaling since the endothelial surface layer is likely dynamic in its composition, density, and height.

Keywords: Endothelial surface layer; Glycocalyx; Mechanotransduction; Fluid shear stress; Matrix shear stress

1. Introduction

It has been known for many years that endothelial cells have a polysaccharide-rich outer coat, but it was Stanley Bennett in his 1963 paper who coined the term "glycocalyx" derived from Greek meaning *sweet husk* (Bennett, 1963). Although this definition may give the impression of a purely polysaccharide layer, the endothelial glycocalyx also includes large macromolecules such as proteoglycans, glycoproteins, glycolipids and associated glycosaminoglycans. Fibrinogen, albumin and other plasma proteins also attach to glycocalyx components creating an even more complex structure sometimes called the endothelial surface layer (ESL) (Henry and Duling, 1999). While the composition of the ESL is fairly well understood, its three-dimensional structure and the flow field within it are not. Furthermore, variations in the height and density of this layer have not been well characterized, and no mathematical or experimental studies have considered how such heterogeneities might alter flow. It is the purpose of this paper to explore how structural variations change flow velocities within this layer and alter the shear stresses that act on the underlying endothelial cells.

Since the ESL is the barrier between vascular endothelial cells and the blood, it serves a variety of important roles in the proper function and maintenance of the circulatory system. One important role of the ESL is to act as a protective layer between endothelial cells and blood-borne species. For example, this layer functions as a shield

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hindering adhesion of flowing leukocytes and platelets to endothelial cells by presenting a physical barrier between them (Mulivor and Liposky, 2002; Vink and Duling, 1996; Constantinescu et al., 2003). However, the ESL is dynamic and can also expose endothelial cells to particular macromolecules. During an inflammatory response, the ESL can be signaled chemically to shed some of its components and in doing so allow for the adhesion of leukocytes. The ESL also acts as a sieve for large macromolecules. This significantly affects oncotic pressures across the vessel wall (Henry and Duling, 1999; Michel and Curry, 1999; Hu and Weinbaum, 1999). It has been observed that the ESL contributes significantly to blood flow resistance through microvascular networks (Pries et al., 1997). Within the ESL that lines capillaries, large repulsive forces are thought to be generated to assist the movement of red blood cells by acting as a lubrication layer (Feng and Weinbaum, 2000; Secomb et al., 1998). In addition to physically protecting endothelial cells, the ESL has received much attention recently for its role as a mechanosensor (Weinbaum et al., 2003). Biochemical events in endothelial cells are initiated by signals generated by this mechanosensor. Blood flows over and possibly through the ESL, information is transduced across the cell membranes and signal transduction pathways inside the cell are activated. This last, but extremely important, role of the ESL has inspired recent theoretical and computational modeling to try to better understand not only the *in vivo* structure of this layer, but the fluid–structure interactions between a dynamic permeable matrix and flowing blood.

A number of *in vitro* experimental studies have illustrated the role the ESL plays in endothelial cell signaling through mechanotransduction. The release of vasodilators, such as nitric oxide (NO), is one example of mechanotransduction that has been studied by applying fluid shear stress or pressure to endothelial cells and measuring the resulting release of NO. The release of vasodilators, including NO, has been shown to depend on the specific glycocalyx constituents heparan sulfate proteoglycans and hyaluronan. Enzymatic treatments that specifically reduce the quantity of these species in the glycocalyx also lead to lower levels of NO release in untreated glycocalyx at the same level of fluid shear stress (Florian et al., 2003; Mochizuki et al., 2003). This shear-stress-mediated release of vasodilators has strong implications in the regulation of vessel diameter and, consequently, blood flow regulation and oxygen delivery. Fluid shear stress also affects alignment and stiffness of endothelial cells through the reorganization of their actin cytoskeletons. It is well known that exposure to flow causes endothelial cell actin microfilaments to change from banded to parallel fiber patterns (Davies, 1995). These flow studies were performed both in the absence and presence of an ESL and revealed that without specific glycocalyx components, mechanotransduction and subsequent cytoskeletal rearrangement did not occur (Thi et al., 2004; Yao et al., 2007). Mechanotransduction and the ESL may also play an important role during cardiogenesis; the ESL is already present at the wall of the vasculature during heart morphogenesis, when fluid shear stresses are needed for proper cardiac looping as well as valve and chamber formation (Hove et al., 2003; Manasek, 1976). These observations lead to the following questions: What is the relationship between the underlying structure of the ESL and flow? Do endothelial cells sense shear stress through specific glycocalyx components or directly at the cell membrane? Most studies done to address these questions have used theoretical and computational approaches.

In order to understand mechanotransduction via the ESL, one must first know what the flow environment is like in and around this layer and this in turn depends on the ESL's microstructure. Although many glycocalyx ingredients have been identified, the intact *in vivo* structure has yet to be determined. Previous modeling attempts have assumed uniform height and permeability of the layer as well as a zero Reynolds number flow regime. For example, Damiano (1998) studied the effect of the ESL on microvascular resistance and the motion and deformation of red blood cells in the capillaries. The ESL was modeled as being comprised of interacting fluid and solid constituents with a fixed height in the presence of deformable red blood cells. It was concluded that the presence of an ESL greatly reduces wall shear stresses and it was suggested that a possible role for the ESL is to maintain spatiotemporal uniformity of the fluid-mechanical forces felt at the membrane of endothelial cells. Secomb et al. (2001a, b) examined the transmission of shear stress using a theoretical model in which the ESL consisted of molecular chains of uniform height and spacing held upright due to tension from osmotic pressures. They considered both steady and unsteady Stokes flow through the ESL matrix and found that shear stress is greatest in the upper portion of the ESL and is low near the membrane itself. Weinbaum et al. (2003) found similar results by assuming that the microstructure of the ESL has a quasi-periodic organization of core glycocalyx proteins as first suggested by Squire et al. (2001). Under this assumption, Weinbaum et al. computed the volume fraction of core proteins and used results (Sangani and Acrivos, 1982) for flow through periodic arrangements of fibers to estimate a hydraulic permeability of the layer. They then assumed that the glycocalyx is a Brinkman layer with this hydraulic permeability and matched the flow through this layer to Stokes flow above the layer. They found that the majority of shear stress was imposed on the tip of the core proteins and relatively little was imposed at the membrane. They concluded that the core proteins rather than the fluid near the membrane transmit the fluid shear stress to the cells.

Several studies have also considered electrical potentials and ion distributions coupled to flow through the ESL. Damiano and Stace (2002) modeled the ESL as a deformable continuum made up of fluid, solid and charged ions. They found that when the ESL is mechanically compressed, electrochemical potential gradients within the