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Microcirculatory blood flow: functional implications of a complex fluid

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Blood is a complex fluid with two major hemodynamic components, plasma and blood cells. The diameters of typical blood vessels in the microcirculation cover a range from about 300 µm down to about 4 microns. In comparison, the largest diameter of an unstressed red blood cell is 7 to 8 µm. Thus, the particulate nature of blood cannot be neglected in assessing blood flow in microvessels and with decreasing vessel size, homogeneous continuum models get less adequate in describing microvascular hemorheology.

The main rheological phenomena resulting from in the particulate nature of blood are the Fåhraeus-Lindqvist effect, the Fåhraeus effect and the phase separation at microvascular bifurcations[1-6].

The Fåhraeus-Lindqvist effect describes the dependence of apparent blood viscosity (η)

$$\eta = \frac{\pi}{8} \cdot \frac{r^4}{l} \cdot \frac{\Delta P}{Q}$$

of blood with a given hematocrit during tube flow on the tube diameter. Experimental findings show a substantial decrease from about 3.2 times the viscosity of the suspending medium (η_{rel}) for a hematocrit of 0.45 in large tubes (diameter > 1000 µm) down to only 1.3 in the capillary range from 5 to 10 µm[7]. This allows transport of blood through these vessels at nearly the same energy cost as for plasma.

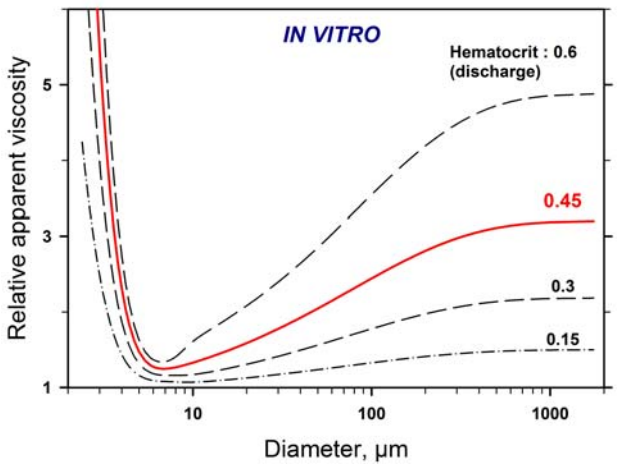

Figure 1: Relative apparent viscosity (η_{rel}) for tube flow of blood as a function of tube diameter and discharge hematocrit (modified after [7])

However, apparent microvascular blood viscosity is also influenced by specific properties of the microvessels themselves. Vessels are lined by endothelial cells that present a specialized surface to flowing blood. In the last two decades, it has been shown that endothelial cells towards the vessel lumen are covered by an endothelial surface layer (ESL, also called endothelial glycocalyx)[7-10]. The ESL is a relatively thick (0.5 to 1 µm or more) layer of macromolecules that has a very low hydraulic conductance and restricts access of blood cells and macromolecules to the anatomical endothelial surface, i.e. the plasma membrane.

Only preliminary concepts exist with respect to the chemical composition of the ESL. As show on Figure 2 the layer is anchored to the plasma membrane by glycosylated transmembrane molecules of the typical endothelial glycocalyx, the proteoglycans with long unbranched sugar side chains and the glycoproteins with short and branched side chains.

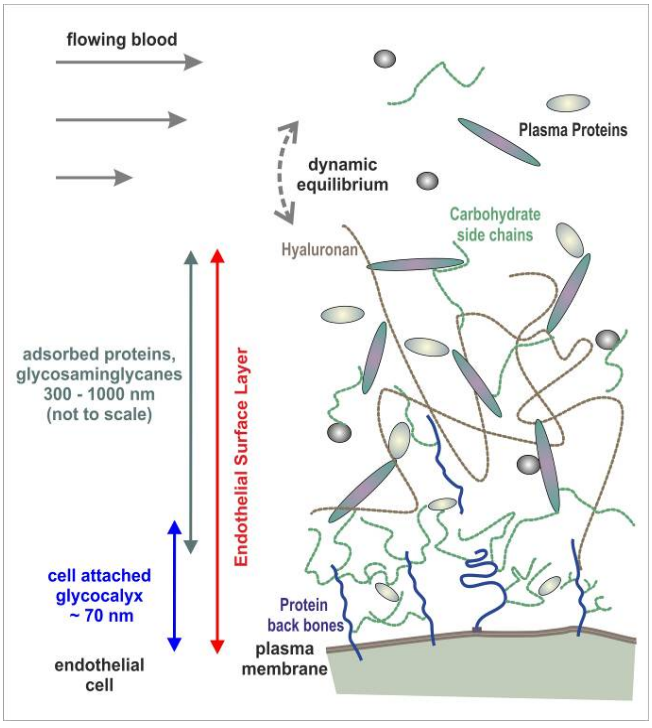

Figure 2: Hypothetical composition of the endothelial surface layer (modified after [4, 11])

However, this layer is very thin (about 50-100 nm) and only by adsorption of additional components, possibly including hyaluronan, a very long linear polysaccharide, and plasma proteins, the full thickness may be generated. Also, experimental data indicate that the layer is in a continuous equilibrium with the flowing blood.

Due to its properties the ESL reduces the effective microvascular diameter (Figure 3) resulting in an increased flow resistance [12, 13].

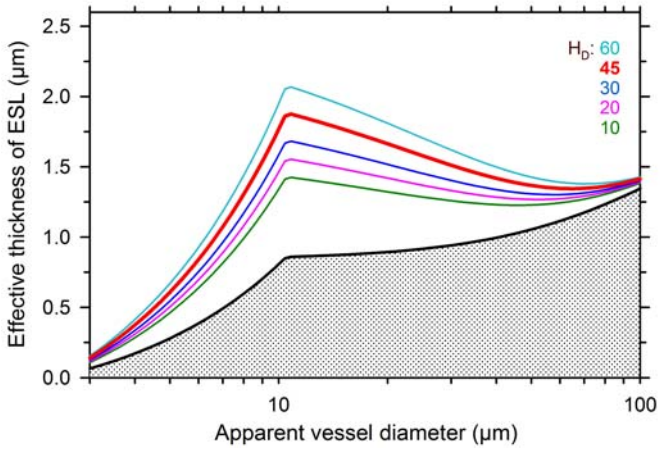

Figure 3: Estimated thickness of the endothelial surface layer as a function of vessel diameter (modified after [14]). The estimates were obtained by flow simulations for microvascular networks for which the angio-architecture and the flow velocity in each vessel segment had been obtained by intravital microscopy. Assumptions for ESL thickness were tested by comparing predicted with measured flow velocities. The thick black line and grey area give the basic thickness of the ESL. The agreement between predicted and measured velocities could be further improved, if an additional hematocrit dependent effect of the layer was assumed. This effect, which is descripted here as an increased layer thickness, is probably due to the increased interaction of red blood cells with the layer with increasing hematocrits. Especially at a diameter around 10 µm, red cells passing each other will have a tendency to push each other in a radial direction into the layer.

The different areas where this layer has biological impacts are still not fully understood, but probably include regulation of coagulation, inflammation, and exchange. In addition, the viscoelastic layer modifies stresses exerted on flowing blood cells during their passage through narrow capillaries [15, 16]. The investigation of the layer, its chemical composition, its generation and decay and its mechanical properties is, however, still hampered due to limited possibilities for its investigation in suitable test systems in vitro.

It is also of central importance to appreciate the heterogeneity of microvascular networks. Arterio-venous flow pathways differ substantially with respect to their morphological and topological properties[17]. This leads to large variations in hemodynamic conditions (e.g. flow velocity, pressure, hematocrit) which necessitate caution in the use of standardized representations (e.g. the 'typical capillary' approach)[18]. For example, the Fåhraeus effect and the phase separation at microvascular bifurcations lead to a situation where the average microhematocrit in capillaries is only about 55% of systemic values, but shows a coefficient of variation (CV=STD/mean) of 0.6[18, 19]. The CV for capillary red cell flow is even higher (approx. 1.9).

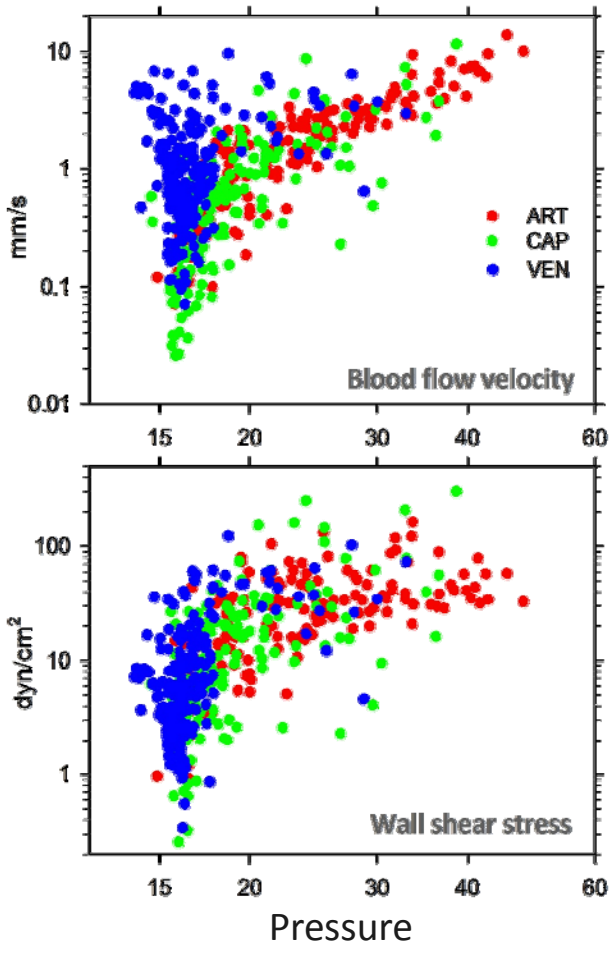

Figure 4: Distributions of blood flow velocity and wall shear stress for arterioles, capillaries and venules (together 546 vessel segments) in a microvascular network of the rat mesentery. In addition to the general trends along the pressure scale, substantial heterogeneity is observed at each pressure level and for each vessel class (modified after [18].

For many relevant hemodynamic parameters, the vessel-to-vessel variability is larger than the typical relation of these parameters to other structural or functional characteristics, e.g. the vessel type or the vessel diameter (Figure 4) [20].

In any attempt to understand or to model the hemodynamic behavior of blood in terminal vascular beds, the particulate nature of the blood and the heterogeneity of the microcirculation need to be addressed.

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