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## AN ALTERNATIVE VIEW ON BLOOD PLASMA IN THE VASCULATURE

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## **Abstract**

Blood plasma is not only a suspending medium for blood cells but exerts important further tasks in the vasculature. It couples RBC flow with its own flow, lubricates blood flow, and contributes to the endothelial and erythrocyte (RBC) surface layers. It was long believed exhibiting a pure Newtonian behaviour, but recent developments highlight an elastic nature that is reinforced at small scale. This surprising finding is attributed to careful dynamic mechanical tests optimizing the interfacial interactions between blood plasma and surfaces of the rheometry setup. In this frame, to approach the boundary conditions of blood biophysics in flow, we coated the surfaces with a hydrogel composed of extracellular matrix proteins to mimic a dissected aortic wall. We evidence for native whole blood a shear elastic plateau at about 30 mPa for frequencies within 0.3 and 0.6 rad s<sup>-1</sup> and gap of 0.7 mm. Such behaviour indicates that the blood oscillates in the gap as a whole. We conclude that the slow flow of blood plasma observed close to the vessel wall can generate a stationary plasma layer that contributes to the functional width of surface layers in vessels. In endothelial cells, this layer uptakes the shear stress of flow first. The shear stress term calculated out of wall shear rate and blood viscosity becomes imprecise if it does not include this utmost important intermediate layer.

**Key words:** blood plasma, rheology, interfacial forces, boundary conditions, shear elasticity, endothelial surface layer

## Introduction

The liquid state is the most spread on the Earth's surface, it plays the most crucial role up to the ultimate scales of life. It is also the less understood. The microfluidics scale is certainly the scale at which these puzzling effects are the more visible. It is the scale at which mass flux occurs in the vasculature and it is therefore crucial for living bodies. The role of blood plasma in this regard appears to be still poorly explored in relation to studies on red blood cells (RBC), although plasma transmits the shear stress of flow to the RBC membranes forcing their mobility and deformation, and thus couples the RBC flow with its own flow [1]. Plasma also interacts with the vessel wall and forms the marginal cell-free layer that lubricates RBC flow [2][3]. In general, flowing red blood cells do not touch the wall, whether in vitro or in vivo, only in blood vessels the RBCs are farther away from the vessel wall; the RBC exclusion zone is larger in arterioles than in microfluidic systems of the same diameter [4]. The biophysics of this cell-free layer justifies investigations because of its impact on the flow resistance. This was documented in a meta-analysis of patient data [5] and also experimentally [6] by diluting blood or by changing its composition. The marginal plasma layer cannot be purely fluidic over its entire width. It contains a luminal part in which plasma flows with the RBCs, and a marginal part where plasma flow is retarded until a situation is reached where plasma becomes stationary. The presence of an immobile layer close to the endothelial cells was evidenced in early works by the differences between the inflow (tube hematocrit) and the outflow (discharge) hematocrit [7], and was visualized 15 years later in hamster cremaster muscle capillaries [8]. Typical properties of this layer [9][10][11] include the sieving of molecules [12], and the prevention of excessive fluid filtration into the interstitium [13][14]. The closest layer on endothelial cell surfaces (endothelial glycocalix layer; EGL) confines plasma within its fibrous network and generates a matrix. It protects the endothelium against the adherence of prothrombotic and inflammatory agents [15][16], and can be diminished in diseases [17]. Its stiffness is slightly more than  $0.3 \text{ pN nm}^{-1}$  [18], and its apparent Young's modulus is around 40 Pa [19]. On basis of the flow resistance the calculated hydraulic resistivity identifies it as a very dilute matrix of macromolecules [20]. To date it is not solved if the matrix layer exceeds lumenally through adsorption of macromolecules to generate the total width of the endothelial surface layer (ESL) [21]. The difficulty in deciding the composition of the immobile layer on vessel walls arises from the experimental difficulty in determining the length of the fragile glycocalix. Reported data range from several tens to several hundreds of nanometers wide [22]. The flow resistance, however, indicates an ESL width to be in the range of several micrometers [4], which strongly suggests a plasma layer so much retarded that it no longer flows.

Our motivation was to find gel-like properties in blood plasma. We carried out dynamic mechanical tests in which the conventional steel surfaces [23] were replaced by patented ceramic fixtures [24] to improve the interactions between the blood plasma and the substrate, and thus optimize the shear stress transmission across the gap. The principle of rheometry consists in measuring the time-dependent (versus frequency,  $\omega$ ) response transmitted by the fluid subjected to a dynamic mechanical shear stress. The fluid is confined between two surfaces, and the mechanical stress is transmitted via the interfacial interactions between fluid

and substrate, and therefore depends on the energy of interaction between blood plasma and the test surface in contact with the fluid.

Although the principle of rheometry is well-known, the boundary conditions between the substrate and fluids are often ignored [25]. By reinforcing the force of interaction of the fluid to the substrate using the excellent wetting properties of a high energy substrate (ceramic), we accessed the shear elasticity of blood plasma and showed that the elastic property was reinforced at small scales (few hundreds of microns) [26]. The consideration of interfacial forces [27][28] is recent and has revealed that the boundary conditions play a major role in the quality of the rheological measurements. The dynamic response of fluids (including viscous liquids) in total wetting conditions can be much stronger and makes a viscoelastic behaviour of solid-like type appear (see Figure 1 for the glycerol and reference therein). This identification of “static” shear elasticity in confined geometry challenges the classical viscoelasticity model (Maxwell's model) according to which the liquid differs from the solid by its lack of static shear elasticity:  $G'_{\omega \rightarrow 0} = 0$ . The impact of confinement and boundaries in the viscoelastic response demonstrates that fluids cannot be characterized by a universal viscoelastic signature [25]. The identification of shear elastic properties in blood plasma is in agreement with its role in forming an elastic layer on vertebrate RBCs. The halo that was detected in AFM-SCFS tests not only enlarged the functional cell size but also blunted the thermal input into the RBC membrane [29]. Plasma components can thus accumulate on several cell surfaces to create an elastic envelope.

## Materials and Methods

After recognizing the relevance of the boundary conditions, we expected that whole blood would also elicit an elastic property. For that, a typical viscoelastic measurement was carried out using a stress-controlled Physica MCR301 rheometer (Anton Paar, Austria) to impose the frequency, the shear stress and the gap thickness. The blood confined in between two parallel plates of 50mm diameter was submitted to a dynamic shear stress generated from the sinusoidal movement of the upper plate  $\sigma = \sigma_0 \cdot \sin(\omega.t)$  where  $\sigma_0$  is the imposed shear stress and  $\omega$  the frequency. By varying the frequency of the imposed sin wave stress, the impact of the incoming shear stress energy rate on the fluid dynamics can be analyzed in terms of shear elastic  $G'$  and viscous moduli  $G''$  in agreement with the conventional formalism:  $\sigma(\omega) = \sigma_0 \cdot \sin(\omega.t + \Delta\phi)$  with  $\sigma(\omega)$  is the imposed shear stress,  $\sigma_0$  the shear modulus, and  $\Delta\phi$  the phase shift between the input and the output waves. This equation can be also expressed in terms of shear elastic  $G'(\omega)$  and viscous  $G''(\omega)$  moduli:  $\sigma(\omega) = \gamma_0 \cdot (G'(\omega) \cdot \sin(\omega.t) + G''(\omega) \cdot \cos(\omega.t))$ , with  $\gamma_0$  the strain amplitude defined as the ratio of the displacement to the sample gap. It should be stressed that the formalism in terms of  $G'$  and  $G''$  supposes that the resulting stress wave keeps the shape of the imposed stress wave (sinusoidal-like). A constant 10 mPa shear stress was applied, the frequency varied from 0.3 to 30 rad/s and the chosen gap thickness was 0.7mm.

Due to the importance of flow inside the false lumen of a dissected aortic wall [30], we coated our plates with a hydrogel that mimics connective tissue. We used a purified and decellularized chorion-derived extracellular matrix hydrogel powder [31], diluted it in phosphate buffer (0.2%

powder concentration) and placed a portion of it on top of our rheometer plates (bottom fixture: borate glass; upper fixture: disposable plates fabricated of aluminium coated tinplate) and submerged the surfaces afterwards slowly in phosphate buffer at 37°C in a Petri dish. After two hours of incubation, the buffer was removed by placing the plates upright and letting the buffer drain into absorbent material, which was visible by a slightly opaque film on the glass surface. We mounted the plates, adjusted motor and inertia of the upper plate due to the additional weight, and performed frequency sweep tests of a native human blood sample (hematocrit: 42%). After giving informed consent (2114/2019, MedUni Vienna, Austria), blood was obtained from a healthy volunteer (female, 26y) by puncturing the antecubital vein with a 21G butterfly needle that was connected to a vacutainer system containing EDTA for anticoagulation. Conventional viscoelastic measurements using stainless steel substrates were carried out in the same conditions for reference and comparison. Both series of measurements were carried out at 37°C.

## Results and Conclusions

Figure 2 displays the frequency dependence of the shear elastic and the viscous moduli of a 0.7 mm human blood layer. The viscoelastic response obtained by hydrogel coating is compared with the conventional rheometry protocol using stainless steel surfaces under the same dynamic conditions. The results show that blood exhibited a shear elastic plateau around 30 mPa below 1 rad/s and oscillated as a whole in the gap, when it was in contact to extracellular matrix proteins. The absence of shear elasticity in the control experiment with steel plates exhibiting a viscous-like behaviour demonstrates the influence of the coating.

Defining the intimate contact area of the flowing blood suspension with the more stationary endothelium is extremely challenging. Blood always begins to flow at a certain distance away from the endothelial cell membrane, since there is a solid-like layer in between (see Figure 3). This layer reduces the available space for flow [3]. What first comes into mind is albumin coating due to its strong tendency to bind to cell surfaces [32][33]. Albumin coating is on one hand effective in protecting RBCs from lysis by hydrodynamic shear forces [34]. But on the other hand albumin alone will not generate the full length of a surface layer [35]. We showed that blood plasma - and not a concentration of the structures that it contains - can form a stationary layer when blood flow is retarded and when there is sufficient adhesion to the substrate below. We thus support the concept that the EGL can be extended luminally through the interaction with plasma components [21]. We also showed that the true nature of blood and blood plasma is gel-like. This finding is in agreement with recent experimental results [25] and new theoretical models integrating effects of the confinement [25][36]. We propose that stationary blood plasma contributes to the functional width of marginal surface layers in vessels (Figure 3). This layer uptakes first the flow shear stress and transmits it to the receptors on the bilayer to start the inwards mechanotransduction pathways [37][38]. The wall shear stress term calculated out of wall shear rate and blood viscosity [39] becomes therefore imprecise when it does not include the dynamic properties and width of this intermediate

layer. The shear force can on the one hand be buffered and at the same time be more easily transmitted to the membrane [21].

To conclude, we have evidenced that submillimeter thickness blood layers, confined between two thin sheaths of extracellular matrix proteins exhibit a finite elastic threshold. The identification of shear elasticity in blood has the immediate consequence that it is necessary to exceed a stress threshold so that blood can flow. This elastic threshold depends on the boundary conditions and it is likely physiologically favorable to fulfil an intermediate situation where the energy of the boundary conditions is not too strong to allow the flow and also non-zero (slippage conditions) without which no exchange is possible with the endothelial layer. Balance conditions are vital and probably determining. From a fundamental point of view, this dynamic study points out the importance of interfacial conditions, which certainly modify the flow in microchannels and open the question of personalization of hemodynamic models for practical applications [40][41].

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Figure 1:

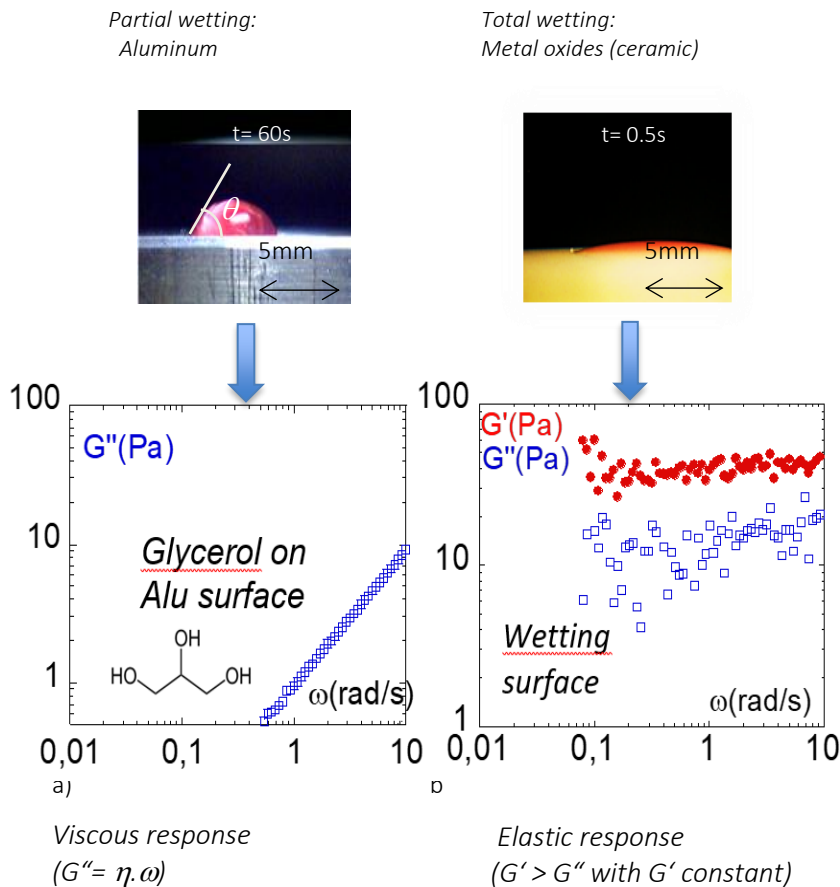


Figure 1: The wetting and the liquid elasticity: The top photographs show a different drop mechanism depending on whether the liquid (here a drop of glycerol colored in red) is deposited on a partial wetting (aluminum) and on a complete wetting (non-porous ceramic) surface. On a partial wetting substrate the contact angle ( $\theta$ ) reaches a stable angle ( $\theta \sim 35^\circ$ ). For total wetting,  $\theta$  is zero in less than 1 second due to the strong energy of adhesive forces. The wetting has also a strong impact on the viscoelastic characterization of the fluidic properties ( $G'$  is the shear elastic modulus and  $G''$  the viscous modulus measured as a function of oscillation frequency  $\omega$  on a  $40 \mu\text{m}$  glycerol layer). a) Poor (aluminum) surface-wetting conditions. With a lower energy of adhesion, the measurement accesses only to the viscous part with  $G''$  scaling linear with the frequency, in line with a purely viscous liquid. b) Good surface-wetting conditions (non-porous ceramic) access to higher viscoelastic moduli and lead to a dominant elastic response ( $G' > G''$ ; reproduced from [28]).

Figure 2:

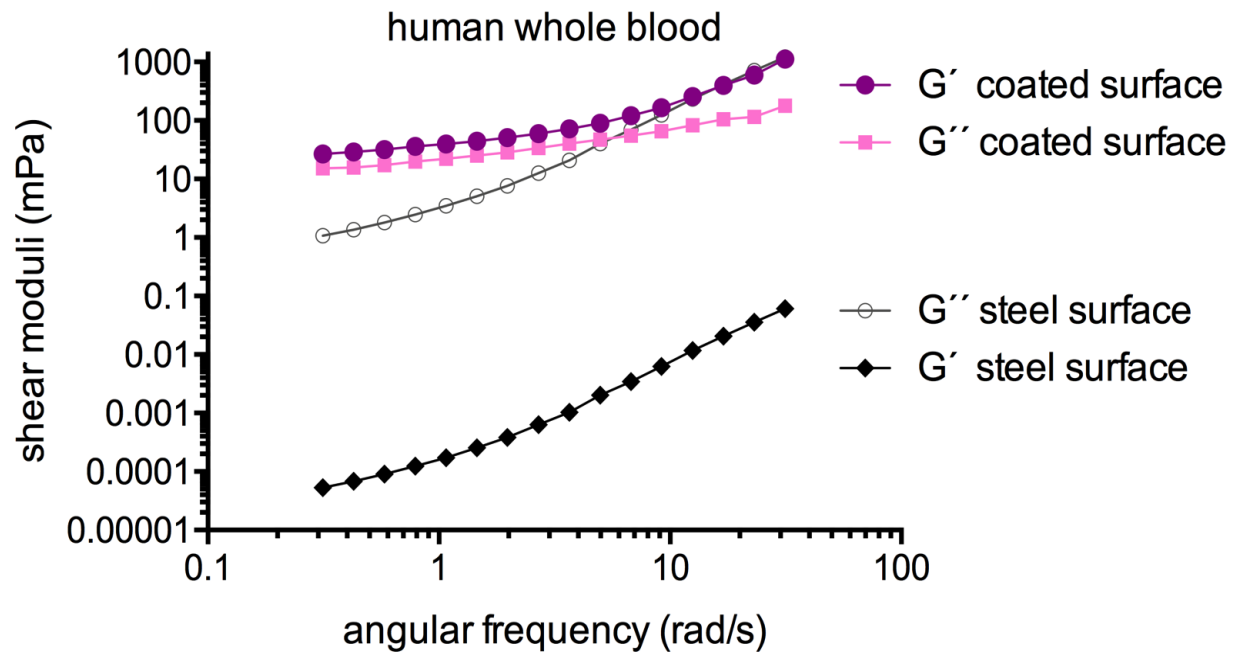


Figure 2: Comparison of shear stress versus frequency measurements exhibited by a native human blood sample using conventional stainless steel surface and a coated (bottom, stationary) surface. A low frequency elastic plateau is evidenced at 0.7 mm gap thickness using the coating surface ( $G' > G''$  with  $G'$  and  $G''$  nearly independent of the frequency) while the conventional measurements shows a viscous-like behavior ( $G'' \gg G'$  vanishing at low frequency). This coating measurement reveals that blood can resist to a shear stress exhibiting an elastic modulus of about 30 Pa (and does not flow under these conditions).

Figure 3:

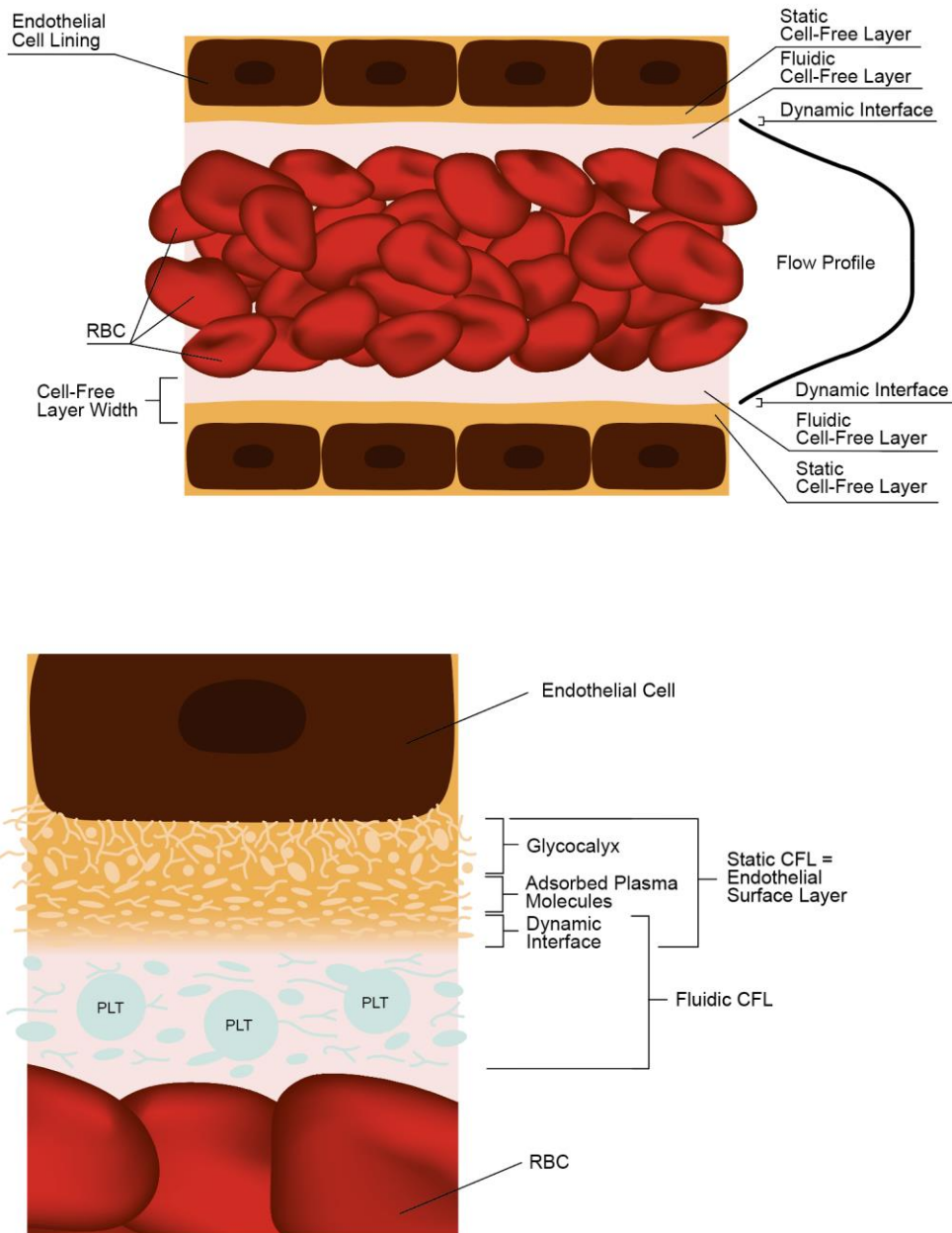


Figure 3: Scheme (detailed view at the bottom) of the proposed stationary and mobile layers adjacent to the endothelial cell lining in blood vessels, as proposed already earlier [21]. The cell-free layer (CFL) comprises a stationary part close to the endothelial cells and a flowing part lumenally to it, which carries the blood cells. The stationary part of the CFL consists of the endothelial glycocalyx layer plus a further layer composed of immobilized plasma proteins on top of it to compose the full length of the endothelial surface layer. The interface between the static and the fluidic part of the CFL is dynamic and its width varies with the blood flow velocity. The wall shear rate occurs on the boundary between the static and the fluidic layer and not on the endothelial cell itself.