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Wall shear stress revisited

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Summary *In vivo* measurements of wall shear stress (WSS), a determinant of endothelial cell function and gene expression, have shown that theoretical assumptions regarding WSS in the arterial system and its calculation are invalid. In humans mean WSS varies along the arterial tree and is higher in the carotid artery (1.1–1.3 Pa; 1 Pa = 10 dyn cm^{-2}) than in the brachial (0.4–0.5 Pa) and femoral (0.3–0.5 Pa) arteries. Also in animals mean WSS is not constant along the arterial tree. In arterioles mean WSS varies between 2.0 and 10.0 Pa and is dependent on the site of measurement. In both arteries and arterioles, velocity profiles are flattened rather than fully developed parabolas. Across species mean WSS in a particular artery decreases linearly with increasing body mass, in the infra-renal aorta from 8.8 Pa in mice to 0.5 Pa in humans. The observation that mean WSS is far from constant along the arterial tree indicates that Murray's cube law on flow-diameter relations cannot be applied to the whole arterial system. The exponent of the power law varies from 2 in large arteries to 3 in arterioles. The *in vivo* findings imply that in *in vitro* investigations an average calculated shear stress value cannot be used to study effects on endothelial cells derived from different vascular areas or from the same artery in different species. Sensing and transduction of shear stress are in part mediated by the endothelial glycocalyx. Therefore, modulation of shear stress sensing and transduction by altered glycocalyx properties should be considered.

Introduction

It has been well established that wall shear stress (WSS), i.e., the drag of the flowing blood exerted on endothelial cells, is an important determinant of arteriolar and arterial diameters by modifying the production of vasoactive mediators by endothelial cells[1–5] and of endothelial gene expression.[6–12] Endothelial genes can be transiently or more permanently up-regulated by shear stress.[7] WSS can be estimated as the product of wall shear rate (WSR) and local blood viscosity, WSR being defined as the radial derivative of blood flow velocity distribution at the wall.

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The vast majority of the experiments on shear stress and endothelial gene expression are performed *in vitro*, exposing the cells to an average calculated shear stress, no matter the area in the vascular system or the species they are derived from. In *in vivo* studies on shear stress and arterial diameter adaptation and endothelial gene expression, shear stress is calculated by assuming the velocity profile to be a fully developed parabola. In these approaches it is assumed that Poiseuille's law can be applied, WSS is constant along the arterial tree according to Murray's law of minimal energy discharge[13,14] at a level of about 1.5 Pa (1 Pa = 10 dyn cm^{-2})[15] and WSS in a particular artery is similar across species. *In vivo* measurements of WSS, however, have shown that these assumptions regarding WSS in the arterial system and its calculation are far from valid.[16,17] This does have consequences, among others, for the *in vitro* experiments on shear stress and endothelial gene expression and our ideas concerning the design of the arterial system.[18]

In this survey we will address the assessment of wall shear stress *in vivo*, the data as found in arterioles and arteries, the discrepancies of these findings with theory and the implications thereof, and the differences in WSS across species. Because there are indications that the glycocalyx plays a role in the interaction between WSS and endothelial cell function we will briefly discuss its part in sensing and transferring shear forces.

WSS *in vivo*

Arterioles

In mesenteric arterioles WSS has been determined directly by means of measured[19] or calculated[20] pressure up and downstream, and length and diameter measurements, or from WSR, as derived from recorded velocity profiles,[21] and plasma viscosity.[22] In cremaster muscle arterioles shear stress was calculated from blood flow, radius and viscosity, assuming Poiseuille flow conditions.[23]

Originally fluorescently labelled blood platelets were used as velocity tracers to assess velocity profiles in arterioles.[21] These velocity tracers cannot come closer to the wall than 0.5 μm.[24] More recently fluorescently labelled nanometer particles are in use as velocity tracers, which come as close to the wall as 0.2 μm.[25,26] Originally, the velocity of the tracers and their position were determined manually, a rather time-consuming procedure, but recently a two-dimensional correlation technique has been developed to measure displacement and position of the velocity tracers,[26] automatically providing velocity profiles.[27] The velocity tracers approach the vessel walls closely, especially the nanometer particles. Therefore, plasma viscosity can be taken to convert WSR to WSS, especially because the plasma layer is likely to be a few micrometers thick.[28] Plasma viscosity can be accurately determined *in vitro* by means of glass capillary viscometry systems. The velocity profiles in arterioles are flattened parabolas rather than fully developed ones.[21]

In mesenteric arterioles mean WSS was found to be on the average 1.8 Pa in rabbits, 4.7 Pa in cat and 5.0 Pa in rat in the larger arterioles and >10 Pa in the smaller ones (Table 1). The variation in WSS values can likely be explained by the non-regulatory properties of mesenteric arterioles[29]; variations in blood flow are not or inadequately compensated for by changes in arteriolar diameter. Variations in shear stress along the vascular tree were also found in cremaster muscle arterioles, varying on the average from 3.0 Pa in the proximal part to 2.1 Pa in the more distal part (Table 1).

Large arteries

In large arteries WSS can be estimated from WSR and whole blood viscosity, WSR being derived from velocity profiles recorded with either Ultrasound or Magnetic Resonance Imaging (MRI). In our studies we have chosen Ultrasound, because of its better spatial and especially temporal resolution compared to MRI. We use a 7.5 MHz 2D imaging device combined with a dedicated system as developed in our institute.[30,31] This system captures along the M-line of observation through the centre of the vessel (sample rate 20 MHz) the RF signals induced by artery wall displacement and the moving red blood cells. After eliminating the high amplitude low frequencies generated by the moving wall by means of adaptive filtering, the time-dependent velocity distribution in the artery is determined by means of a modelled cross-correlation technique.[32] By calculating the mean velocity for each RF segment a 3D velocity profile is obtained (Fig. 1). The length of the RF-segments is about 300 μm with a spacing of 150 μm (50% overlap). This is the best spatial resolution attainable for a system operating effectively at 6 MHz. The shear rate distribution in the artery is obtained by determining the radial derivative of blood flow velocity at each site and each time instant (Fig. 2). WSR is high near the wall and low in the centre of the vessel, which is consistent with a flattened parabolic velocity profile, a shape found in most large arteries.[16] Because blood flow velocities cannot be determined at the wall, the maximum value of the radial derivative of the velocity profile is considered as the estimate of instantaneous WSR. From the shear distribution mean WSR, the time-averaged shear rate over one cardiac cycle, and peak WSR, the value at peak systole, can be determined. In large arteries whole blood viscosity is used to calculate WSS, because the plasma layer of a few micrometers in thickness[28] can be ignored relative to the size of the sample volume of the ultrasound system (250–300 μm). It should be realized that no average whole blood viscosity value can

Table 1 Average mean wall shear stress in animal arterioles.

	Diameter (μm)	WSS (Pa)
Mesentery		
Cat[19]	10–58	4.7
Rabbit[22]	17–32	1.8
Rat[20]	>15	5.0
	6.0	>10.0
Rat cremaster muscle[23]		
Proximal	179	3.0
Distal	203	2.1