Special Article

Vascular Wall Shear Stress: Basic Principles and Methods

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The investigation of various mechanical forces and the tissue deformations they induce have been extensively studied for over three centuries. The basic principles concerning the relationship between mechanical stress and strain of various materials were demonstrated by Robert Hooke (1635-1703) and proved to be essential for the improvement of bio-materials and the understanding of pathophysiological mechanisms in the vascular bed. Subsequently, the ground-breaking studies of Jean Poiseuille (1799-1869) led to the development of mercury manometers for blood pressure measurement and resulted in theories describing the flow inside a cylindrical conduit, widely known as Poiseuille's law.

The present work aims to describe and provide an interpretation of basic mechanical and haemodynamic phenomena related to forces applied to arterial walls and especially shear stresses.

Basic principles and definitions

In physics, *stress* is the internal distribution of forces within a body that balance and react to the external loads applied to it. Stress is a 2nd. order tensor. A tensor is a mathematical quantity that is defined by the *order* and the number of its *components*. In Euclidian space (three dimensions) the components of a tensor are 3^n, where n is the order of the tensor. Thus stress, which is a 2nd. order tensor, consists of $3^2 = 9$ components (terms); six tangential (parallel) and three normal ones. As an example, pressure or temperature is a *gradient* quantity with zero order and one component, while *force or velocity* is a *vector* quantity of one order and three components.

Strain is defined as the mechanical deformation of a physical body under the action of applied forces. Depending on the direction of the applied force there is a different kind of deformation. Shear strain is defined as the deformation of an object in which parallel planes remain parallel but are shifted in a direction parallel to themselves, as opposed to normal stress or force, which when applied to an object induces normal (direct) deformation (Figure 1). For a one-dimensional object, deformation is either lengthening or shortening. For a two-dimensional object, there are a total of four strain components: normal strain along the x or y axis, and shear strain causing distortion of the shape along the x or y axis.

The haemodynamic conditions inside blood vessels lead to the development of superficial stresses near the vessel walls, which can be divided into two categories: a) *circumferential stress* due to pulse pressure variation inside the vessel; b) *shear stress* due to blood flow. It should be noted that intravascular hydrostatic pressure

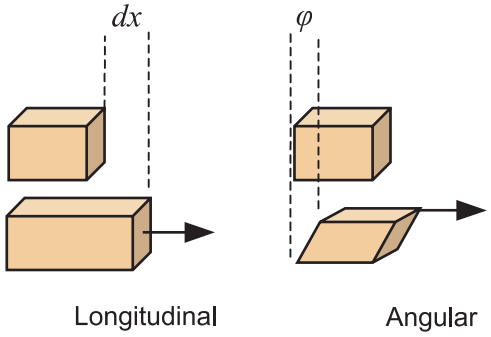

Figure 1. Deformations induced by normal and shear forces.

produces not only circumferential but also normal tensions. The direction of the shear stress vector is determined by the direction of the blood flow velocity vector very close to the vessel wall. Shear stress is applied by the blood against the vessel wall. On the other hand, the force applied to the blood by the wall is considered as *friction* and has a direction opposite to the blood flow. The tensions acting against the vessel wall are likely to be determined by blood flow conditions. Shear stresses during turbulent flow, regions of flow recirculation or flow separation, develop more complicated local characteristics.

Normal stresses due to blood pressure are transferred to all vessel wall layers (intima, media and adventitia). On the other hand, shear stress is applied mainly to the inner layer of the arterial wall in contact with the blood, the vascular endothelium. The normal stresses applied (directly), as well as shear stresses (indirectly), regulate blood vessel diameter depending on vascular wall elasticity (distensibility) and endothelial function (endothelial induced vasodilatation), respectively. Arterial distensibility is one of the most important mechanical properties of the arterial walls, and deserves a more extensive analysis, which, however, is beyond the scope of the present review.

Shear rate

The notions of shear rate and fluid viscosity should be first clearly apprehended, since they are crucial for the assessment and development of shear stress. Shear rate is defined as the rate at which adjacent layers of fluid move with respect to each other, usually expressed as reciprocal seconds. The size of the shear rate gives an indication of the shape of the velocity profile for a given situation.

The determination of shear stresses on a surface is based on the fundamental assumption of fluid mechanics, according to which the velocity of fluid upon the surface is zero (no-slip condition).[1] This leads to the establishment of velocity gradient. Thus, as the fluid particles "travel" parallel to the wall, their velocity increases from zero at the wall to a maximum value at some distance from the wall (Figure 2).

If we consider a blood vessel as a straight, cylindrical tube with rigid walls then the velocity gradient $\dot{\gamma}$ (shear rate) will be given by the relation:

$$\dot{\gamma} = \frac{du}{dr} \qquad (1)$$

where u is the fluid velocity and r the radius of the tube. Figure 2 illustrates two cases with different velocity profiles corresponding to flows with different velocity gradients. Assuming that the blood is an ideal Newtonian fluid with constant viscosity, the flow is steady and laminar and the vessel is straight, cylindrical and inelastic, Poiseuille's law could be applied to determine shear rate as follows:

$$\dot{\gamma} = \frac{8 \cdot u}{d} \qquad (2a)$$

or

$$\dot{\gamma} = 32 \frac{Q}{\pi \cdot d^3} \qquad (2b)$$

where u is the average velocity, Q the mean volumetric flow and d the vessel diameter. Under these conditions a parabolic velocity profile could be assumed.

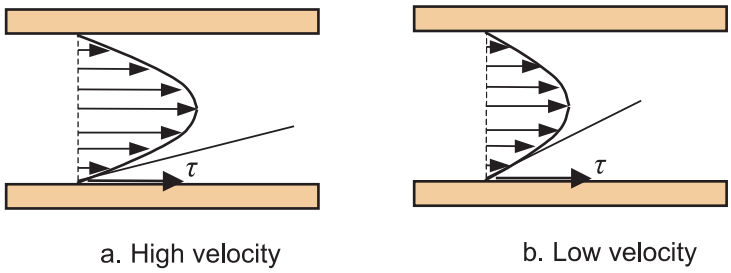

Figure 2. Velocity profiles in cylindrical tubes with different shear rates.

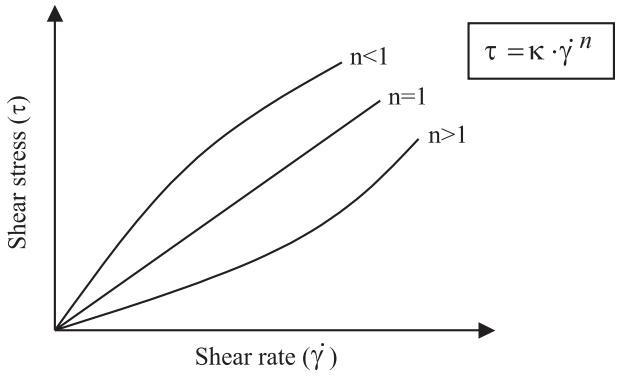

Figure 3. Shear stress-rate relationship for Newtonian (n=1) and non-Newtonian (n >1 or n <1) fluids.

Determination of shear stress

Shear rate and viscosity are directly related to the properties of the fluid. Non-Newtonian fluids are governed by a non-linear relationship between shear stress and shear rate (Figure 3). In this case (non-Newtonian fluid), the slope of the shear stress-rate curve, which is equal to fluid viscosity, depends on pressure, temperature and shear rate. In contrast, the viscosity of Newtonian fluids is independent from shear rate, as indicated by the linear relation between shear stress and shear rate (Figure 3).

For non-Newtonian fluids shear stress (τ) is defined by the Ostwald de Waele equation:

$$\tau = \varkappa \cdot \dot{\gamma}^{n} \qquad (3)$$

where $\dot{\gamma}$ is the shear rate (sec^{-1}), n and k are indices of fluid internal properties, i.e. adhesion, cohesion.[1]

For Newtonian fluids flowing upon a planar surface, shear stress is determined according to Newton's law by the equation:

$$\tau = \mu \cdot \frac{du}{dy} \qquad (4)$$

where μ is the kinetic viscosity, u the fluid velocity, y the distance from the surface and du/dy the velocity gradient, namely the shear rate $\dot{\gamma}$ (sec^{-1}).

For blood flow within a vessel (inelastic, cylindrical and straight), shear stress is defined by the Haagen-Poisseuille equation:

$$\tau = 32 \cdot \mu \cdot \frac{Q}{\pi \cdot d^{3}} \qquad (5a)$$

or

$$\tau = 8 \cdot \mu \cdot \frac{u}{d} \qquad (5b)$$

where Q is the mean volumetric flow rate, u the mean velocity, and d the vessel diameter.

It should be emphasised that the Haagen-Poisseuille equation is applied in vivo only after the following assumptions have been made:

- The blood is considered as a Newtonian fluid.
- The vessel cross sectional area is cylindrical.
- The vessel is straight with inelastic walls.
- The blood flow is steady and laminar.

The Haagen-Poisseuille equation indicates that shear stress is directly proportional to blood flow rate and inversely proportional to vessel diameter.

Blood viscosity

Viscosity is an internal property of a fluid that offers resistance to flow. It is measured in centipoise (cP). Viscosity is a characteristic property of fluids and is a measure of the combined effects of adhesion and cohesion. Viscosity of fluids increases as temperature decreases. Blood viscosity (non-Newtonian fluid) depends on shear rate, which is determined by blood platelets, red cells, etc.

Lipowsky et al investigated the changes of blood viscosity in relation to changes in: a) shear rate for different levels of haematocrit and b) haematocrit for different shear rates.[2,3] It was shown that blood viscosity is slightly affected by shear rate changes at low levels of haematocrit. In contrast, as haematocrit increases, the effect of shear rate changes on blood viscosity becomes greater. Additionally, at low shear rates (~ 54 sec^{-1}) haematocrit variations induce greater changes in blood viscosity. Consequently, in arteries where high shear rates (~ 300 sec^{-1}) are present (e.g. the aorta) blood viscosity is approximately 3.5 cP (for 45% haematocrit), while in vessels with lower shear rates (~ 5 sec^{-1}) such as the veins, blood viscosity is markedly higher (~ 10 cP). Therefore, for large arteries the assumption of 3.5 cP blood viscosity is commonly made. Blood viscosity measurement is required for the accurate calculation of shear stress in veins or microcirculation. Viscosity is measured with various types of viscometer at a specified constant temperature, typically 25°C.

Relation of vessel diameter with haematocrit

It has to be emphasised that the dependence of blood viscosity on haematocrit is more pronounced in the microcirculation than in larger vessels, due to haematocrit variations observed in small vessels (lumen diameter <100 μm). The significant change of haematocrit in relation to vessel diameter is known as the

Fahraeus-Lindquist phenomenon.[4] This phenomenon is associated with the tendency of red blood cells to travel closer to the centre of the vessels. Thus, the greater the decrease in vessel lumen, the smaller the number of red blood cells that pass through, resulting in a decrease in blood viscosity.

Methods of shear stress measurement at vascular walls

Shear stress on arterial walls has been estimated in numerical models, in vitro, in animals and in humans. In many cases approximations and assumptions are necessary in order to calculate shear stress; they may thus sometimes diverge from the real flow phenomenon.

Mathematical models often require a specific description of geometrical characteristics and the flow conditions of the vessel studied. The distribution of shear stresses in a vessel area can be calculated by resolving the mathematical equations describing the flow velocity in the vessel.[5,6]

In vitro models have been used previously to investigate shear stresses applied to endothelial cells under various flow conditions:

- Steady, laminar flow using parallel planar or conical moving surfaces.[7]
- Unsteady, pulsatile, laminar flow by using peristaltic pumps which allow the study of time varying shear stresses.[8]
- Oscillatory, turbulent flow.[9]

In vitro estimation of shear stresses is achieved by determination of flow velocity profiles (e.g. by flow visualisation techniques). Advanced experimental techniques also exist that allow the 3-D analysis of shear stresses and deformation of endothelial cells.[10,11]

In vivo estimation of shear stress often requires fewer assumptions and approximations than do the numerical or in vitro models. Detailed geometric characteristics and specific flow conditions are particularly variable under in vivo conditions. Shear stress measurement requires only the estimation of shear rate values and blood viscosity for a specific area of a vessel (considering the blood as a Newtonian fluid). Estimation of local velocity gradient along a cross sectional area of a vessel can be realised by various techniques.

Assessment of shear stress with Doppler echocardiography can be performed using equation 5, by calculating the mean or maximum blood flow velocity within a vessel of known diameter, considering blood as a Newtonian fluid. In most cases where measurement of blood viscosity is not feasible, the value 3.5 cP can be used instead. This value is based upon the assumption that blood acts like a Newtonian fluid in large vessels.

Magnetic resonance imaging (MRI), by applying various flow quantification methods (phase contrast, phase velocity mapping, Fourier velocity mapping, etc.), has been used for shear rate evaluation, with rather direct estimation of the flow velocity distribution in the cross-section of a vessel.[12]

Phase contrast MRI is somewhat superior to other imaging techniques, providing better image resolution and contrast, while it allows measurement of blood velocity at various points within a given cross-sectional vessel area. Every pixel of the recorded image corresponds to a specific value of velocity. The determination of velocity gradient is made using various methods. A simple method is to consider a linear velocity change between two adjacent points on the vessel's diameter. In this case shear rate is determined as follows:

$$\dot{\gamma} = \frac{\Delta u}{\Delta r} \qquad (6)$$

It has been found that shear rates calculated by eq. 6 are overestimated by approximately 10-45%.[13] Nonlinear models describing the velocity profile more realistically have also been used,[14] without, however, increasing the accuracy of shear rate measurement, especially in regions very close to the arterial wall. More sophisticated models have also been proposed for the estimation of shear rate regardless of a vessel's geometric details or diameter velocity distribution.[15]

One of the major shortcomings of imaging techniques for the accurate estimation of wall shear stresses is the inability of accurate arterial wall tracking. This, however, is expected to be overcome by imaging systems with more advanced spatial and temporal resolution.

To date, in clinical practice there is no single commonly used technique of shear stress determination, something that is also evident with respect to the measurement of other physical variables such as the arterial mechanical properties. This renders it difficult to perform a comparison and interpretation of data between various clinical studies.

Shear stress and vascular endothelium

Endothelium responds to shear stress through various pathophysiological mechanisms depending on the kind and the magnitude of shear stresses. More specifically, the exposure of vascular endothelium to shear forces in

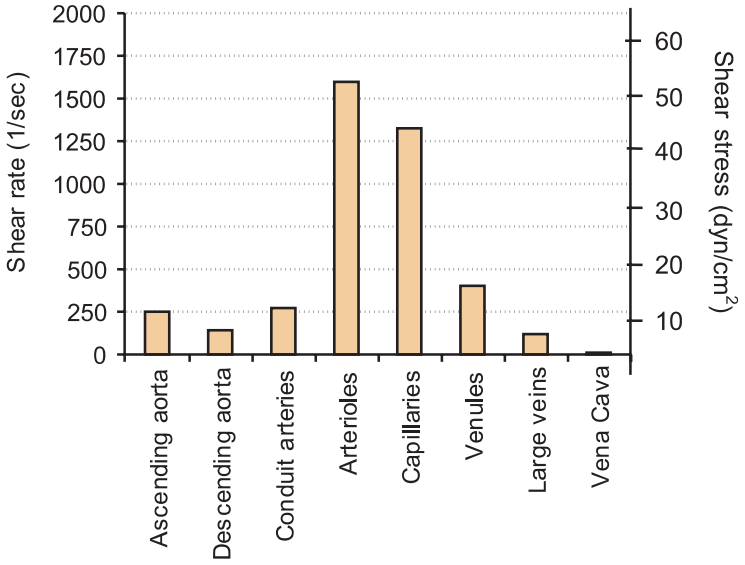

Figure 4. Shear stress values in various vessels according to data reported by Lipowsky et al.[2,3]

the normal value range stimulates endothelial cells to release agents with direct or indirect antithrombotic properties, such as prostacyclin,[16] nitric oxide (NO)[17], calcium[18], thrombomodulin[19], etc. Further insights concerning the interaction of shear stress and endothelium can be found elsewhere[8,20,21].

How the mechanical forces are detected and are transformed into biological signals that stimulate intravascular processes remains unresolved. The possible existence of so-called "mechanoreceptors" has provoked a number of research groups to localise those receptors which "translate" mechanical forces into biological signals. Two models of mechanotransduction have been demonstrated so far:

a) The localised model, where the mechano-receptor, like other receptors, is considered to be located in cellular membrane. Possible channels also located in membrane, such as those of potassium, sodium and calcium, respond to shear stress alteration.[9]

b) The decentralised model, where shear stress forces acting on a cell's surface are transmitted through a cytoskeleton, allowing the activation of several mechano-receptors within the cell. Integrines connected with cytoskeleton have been related to the aforementioned mechanism of mechanoreception.

Shear stress in clinical practice

Under normal conditions, shear stresses maintain their direction and their magnitude within a range of values that impedes atherogenesis, thrombosis, adhesion of leukocytes, smooth muscle proliferation and endothelial apoptosis.

The arterial and venous vascular tree is exposed to different levels of shear stress, a fact that is determined by flow velocity characteristics. Shear stress at arterial walls ranges between approximately 10 and 70 dynes/cm^2, whereas the corresponding normal values for veins are considerably lower, from 1 to 6 dynes/cm^2. Higher shear stress values have been observed in the vasculature, especially in regions with an anatomy/geometry promoting turbulent flow or increased flow velocity (e.g. arteries with strong curvature such as the aortic arch, bifurcations, anastomoses, etc). In those cases, shear stress shows increased values, while the direction may also change due to retrograde flow, which depends on the haemodynamic conditions.

Indicative values of shear stress and shear rate for several vessels are outlined in figure 4, based on previously published data.[22,23] The estimation of these values requires the mean volumetric flow and velocity of blood in the specific vessel, the vessel diameter and the blood viscosity, which in this case was considered to be equal to 3.5 cP.

Under normal shear conditions, endothelial as well as smooth muscle cells have a rather low rate of proliferation. Changes in shear stress magnitude activate cellular proliferation mechanisms as well as vascular remodelling processes. More specifically, a high grade of shear stress increases wall thickness and expands the vessel's diameter,[24] so that shear stress values return to their normal values. In contrast, low shear stress induces a reduction in vessel diameter and leads

to intima-media hyperplasia. Consequently, shear stresses stimulate vasoregulatory mechanisms which, together with alterations of arterial diameter, attempt to maintain a mean shear stress level of approximately 15 dynes/cm^2.[25,26]

The presence of low shear stresses is frequently accompanied by unstable flow conditions (e.g. turbulence flow, regions of blood recirculation, "stagnant" blood areas). Such conditions are often observed in the aorta or at arterial bifurcations.[27-29]

Atherogenesis

Shear stress with a low mean or maximum value and varying direction (*oscillating shear stress*) has been associated with development of atherosclerotic impairment in arteries.[27-29]

Grafts - anastomoses

In regions of anastomoses, thrombosis or intimal hyperplasia has been reported, mainly due to the presence of low shear stresses.[30]

Aneurysms

Shear stresses play an important role in the pathogenesis of aneurysms. Vessel wall remodelling as a result of shear stress alteration is accompanied by synthesis and secretion of NO, growth factors and metalloproteins, which contribute to aneurysm pathogenesis. Shear stress has been also associated with the rupture of aneurysms.[31]

In-stent restenosis

Low shear stress has also been linked to in-stent restenosis.[32]

Conclusions

The pivotal role of shear stresses in vascular endothelial function and in various pathological conditions renders shear stress investigation a matter of particular importance at the molecular and clinical levels. Shear stress assessment in clinical practice may serve in the investigation of many pathological conditions and mechanisms affecting the cardiovascular system and the vascular endothelium. Understanding and development of the existing techniques and methods for shear stress measurement may contribute greatly towards this goal.

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