Expert Perspective

The Effect of Shear Stress on the Onset and Progression of Atheromatous Disease and on Restenosis Following Transluminal Therapies

Michail I. Papafaklis[1], Lampros K. Michalis[2]

[1]Michaelideion Cardiac Centre, [2]Cardiology Department, Medical School, University of Ioannina, Ioannina, Greece

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Address:
Lampros K. Michalis

Cardiology Department, Medical School, University of Ioannina 45110 Ioannina, Greece
e-mail:
lmihalis@cc.uoi.gr

Atheromatous disease is still the prime cause of morbidity and mortality in most western societies. A severe degree of atheromatous disease impedes blood flow, creating significant problems in various organs (e.g. myocardial ischaemia, myocardial infarction, cerebral ischaemia, etc.). In spite of the systemic nature of the risk factors related with atheromatosis (hypertension, hyperlipidaemia, diabetes mellitus), atheromatous disease is a site-specific disease with a tendency to develop in certain regions of the arteries: for example, at the outer wall of bifurcations or at the inner wall of arteries with a significant degree of curvature. For half a century now, haemodynamic forces have been proposed as factors controlling the structure of vessels (vascular wall remodelling) and the development of vascular pathology (onset and progression of atheromatous disease).[1-3]

Shear stress and atheromatosis

Flowing blood imposes on the wall of the arterial lumen (endothelial surface) a haemodynamic stress that has two components: a vertical component, pressure, and a tangential component, shear stress. Shear stress is equal to shear force (frictional force) per unit area and is due to the viscous nature of blood. The hypothesis relating shear stress with atherogenesis dates back a few decades and was used as the basis of two conflicting theories that were proposed towards the end of the 60s to explain the local distribution of atheromatous lesions. The first of these considered the cause of atheromatosis to be high shear stress and the direct endothelial injury and denudation in which this resulted. Furthermore, according to the same theory, high shear stress was correlated with an increase in the permeability of the vascular wall. These phenomena were confirmed experimentally in dog aortas only when they were exposed to shear stress of about 400 dyn/cm^2, [4,5] much higher than that observed in arteries under normal conditions (<100 dyn/cm^2).[6]

The second theory, which was proposed by Caro et al[7,8] and is the prevailing theory nowadays, related the atheromatic process with low shear stress and was based on the hypothesis that the accumulation of lipoproteins on the arterial intima is due to the pathological mass transfer between the blood and the arterial wall as a result of low shear stress. Caro et al compared the lesion localisation at human aortic bifurcations with the theoretical steady flow shear stress patterns at a bifurcation and concluded that the haemodynamic condition of low shear stress at the outer walls of bifurcations was consistent with plaque localisation.

Experimental models and methods of calculating haemodynamic parameters

Various experimental studies have been carried out in order to investigate the relationship between flow characteristics and atheromatosis. Since the 70s the visualisation of flow characteristics and the quantification of various haemodynamic parameters, such as velocity, pressure and shear stress, have been achieved through the use of either transparent glass tubes with side bran-ches and different degrees of curvature, or casts of actual vessels,[9,10] or models based on measurements from cadaver specimens, angiograms[11] or magnetic resonance images.[12] The qualitative flow characteristics in these models have been observed by means of dye injection[13] and particle tracking based on the photochromic method[14] or charge-coupled device technology,[15] while quantitative measurements of velocity profiles under conditions of both steady and pulsatile flow have been achieved using laser Doppler velocimetry[16,17] or Doppler ultrasound.[18] Also, *in vivo* studies have employed hot-film velocimetry,[19,20] Doppler ultrasound[21,22] and, more recently, phase contrast magnetic resonance imaging.[23,24] The direct and indirect correlation between the findings resulting from the above investigations and histological studies of atheromatous vascular prepara-tions[25,26] gave indications according to which fluid mechanical factors, such as shear stress at the vascular wall (wall shear stress), are implicated in the pathogenesis of atheromatosis. The forces, then, to which the endothelium is subjected by circulating blood, and more specifically their magnitude, their rise and fall during the cardiac cycle and their alterations in direction, appear to play an important role in phenomena such as endothelial injury, platelet accumulation, secretion of chemotactic and growth factors, and lipoprotein deposition on the vascular wall.[27-29] Moreover, according to these studies, arterial intimal thickening due to lipid deposition occurs selectively in regions where the shear stress has a low value or is retrograde for at least part of the cardiac cycle (oscillating shear stress).

Numerical analysis and calculation of haemodynamic parameters

Even though detailed experimental investigations into the fluid mechanics of blood flow in the vascular system, such as those mentioned above, have contributed a great deal to our understanding of the relationship between shear stress and atheromatous disease, they have certain limitations. To begin with, the construction of the models used in the experiments and the derivation of quantitative flow measurements often constitute a time-consuming and expensive process. In addition, it is not feasible to use fluids with the same rheological characteristics as blood or to construct models with the same geometrical features and mechanical properties as arteries. Finally, the quantitative information that can be derived from experimental flow studies lacks precision and is limited to specific locations within the flow field. It is not feasible to measure all the alterations in scalar and vector variables, such as pressure, velocity and shear stress throughout the flow field, while most *in vitro* studies employ an indirect approach for measuring shear rate, which is based on the detection of flow velocities in the vicinity of the vessel wall.

Therefore, the theoretical calculation of haemodynamic parameters becomes essential, but it cannot be based on the Hagen-Poiseuille equations since these may only be used in idealised cases of steady (time unvarying), fully-developed flow of a Newtonian fluid through a straight tube of constant circular cross-section. The nature of the problem consequently necessitates the use of the differential continuity equation and the differential equation of fluid motion, which, in the case of incompressible flow of a constant viscosity Newtonian fluid, are given by the following mathematical formulations, respectively:

$$\nabla \cdot \mathbf{u} = 0, \qquad \rho \frac{\partial \mathbf{u}}{\partial t} + \rho \mathbf{u} \cdot \nabla \mathbf{u} = \rho \mathbf{g} - \nabla p + \mu \nabla^2 \mathbf{u}$$

where **u** is the velocity vector, p the pressure, ρ the density, μ the dynamic coefficient of viscosity and **g** the acceleration vector due to gravity. Since such equations cannot be solved analytically for complex flow fields like those in arteries, a new scientific field has emerged: computational fluid dynamics (CFD), which is concerned with the numerical solution of these equations. Briefly, in CFD modelling, a complex geometry is separated into a large number of smaller finite elements, creating a grid on which the equations describing the phenomenon are discretised. By assuming the velocity field within them, it is possible to solve the equations of motion at the nodes connecting these elements, provided that certain boundary conditions for velocity and pressure are imposed. From this solution arise the measurements of wall shear stress and other haemodynamic parameters. The advantage of CFD compared to the other *in vitro* and *in vivo* techniques, as well as to simple theoretical models based on Poiseuille flow, is that it provides invaluable knowledge of the detailed spatiotemporal variations that shear stress may exhibit,

while the parameters that determine each set of haemodynamic conditions are completely controlled. The application of computational techniques to models corresponding to those used in *in vitro* experiments proved the accuracy of their results and also confirmed the existing findings supporting an inverse correlation between the thickness of atheromatous lesions and the magnitude of shear stress.

Applications in human coronary circulation

Since flow and the resulting shear stress depend particularly on the specific geometry of every human artery, CFD has been used in realistic human artery models based on three-dimensional reconstruction of the vessels. Three-dimensional reconstruction of large arteries (e.g. aorta, carotids) is relatively easy and can be carried out using computerised or magnetic tomography, whereas coronary arteries present special difficulties.

Recently, three-dimensional reconstruction of the coronary arteries has been based on a fusion of data provided by intracoronary ultrasound and coronary angiography.[30,31] Such models have been used lately for studying the effect of haemodynamic factors on the atheromatous process in coronary vessels using CFD (Figure 1). In a pioneering study, Krams et al[32] estimated the shear stress imposed on the endothelium using the three-dimensional model of the right coronary artery of a patient and compared its magnitude with the thickness of existing atheromatous plaque; they found an inverse proportional relationship. Other more recent studies investigated the effect of haemodynamic parameters on arterial remodelling and particularly on "positive arterial remodelling," according to which the total area of the vessel (media-adventitia boundary) is dilated in regions where the atheromatic process progresses, up to the point that the plaque area has taken over around 40% of the total vascular area.[33] It appears that as long as the "positive remodelling" is in progress, and the size of the lumen therefore remains constant, the generally accepted inverse proportional relationship between shear stress magnitude and plaque thickness is valid, whereas once the atheromatous process exceeds the boundaries of positive remodelling and the lumen inevitably shrinks, any further increase in plaque is independent of shear stress.[34]

"Negative arterial remodelling", which is the main cause of restenosis after balloon angioplasty, has also been studied in association with shear stress in three-dimensional models of porcine external iliac arteries after angioplasty. In this study, the investigators observed a correlation between shear stress and the restenotic process that could not be eliminated by the use of metalloproteinase inhibitors.[35]

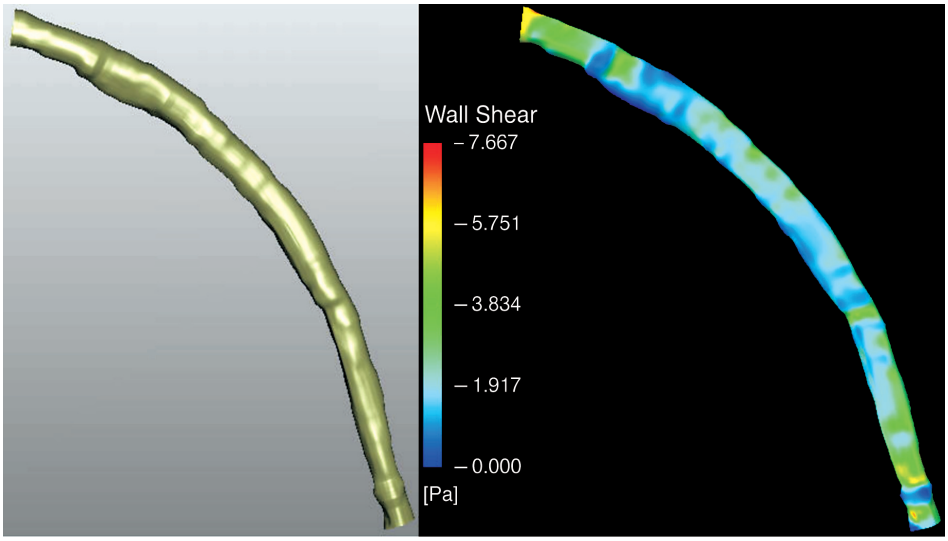

Figure 1. Three-dimensional image of the lumen of the left anterior descending coronary artery of a patient and colour-coded representation of the magnitude of shear stress within that artery (unpublished data from research in progress at the Michaelideion Cardiac Centre).

Future directions

Since the use of stents has now become widespread, investigators have begun to study the relationship between the haemodynamic alterations following stent implantation and in-stent restenosis. The local changes in three-dimensional geometry and the subsequent changes in the distribution of shear stress following stent implantation were studied by Wentzel et al[36] in porcine coronary arteries, which were reconstructed in three dimensions from a fusion of angiographic and intracoronary ultrasound images. Stent implantation was found to change the geometry of vessels with significant curvature in such a way that regions with increased or reduced shear stress appeared near the stent margins, where restenosis after stenting seems mainly to develop. Although there is a general consensus among researchers concerning *de novo* atherosclerotic lesions and restenosis after plain angioplasty, the results of investigations into the association of shear stress with instent restenosis are not clear or are sometimes contradictory.[37-39] In any case, there is certainly a need for ongoing research, so that the role of haemodynamic conditions in restenosis after stenting is clearly demonstrated. The knowledge thus obtained might lead to the construction of a new generation of stents that will regulate the flow conditions in such a way that the incidence of restenosis is reduced.[40]

Conclusions

Modern imaging methods allow the sequential *in vivo* monitoring of the natural history of coronary artery disease, as well as that of the restenotic process following intracoronary procedures. Both older and recent studies highlight the rapidly changing "atheromatic behaviour" of various regions within an artery as a result of different haemodynamic conditions. A detailed evaluation of shear stress can provide deeper knowledge concerning the onset and subsequent progression of atheromatosis as well as the vascular response to stenting. Improvements in the acquisition and analysis of imaging and haemodynamic data may enable us in the future to recognise lesions that are not angiographically significant but carry a high risk of rupture and may help us to construct stents that carry a small risk of restenosis.

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