Haemodynamics, wall mechanics and atheroma: a clinician's perspective

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Abstract: Atherosclerosis, leading to myocardial infarction and stroke, is the major cause of death and morbidity in Western societies. Atheromatous lesions characteristically occur in regions of branching and marked curvature. Low shear stress and increased mural tensile stress may be major determinants underlying atheroma formation at these sites. Furthermore, the distribution of circumferential tensile stresses may play a critical role in where, why and when advanced atheromatous plaques rupture, leading to catastrophic ischaemic events. Recent advances in the application of computational modelling to *in vivo* vascular ultrasound and magnetic resonance imaging data should further elucidate the roles of haemodynamic factors and vessel wall mechanics in atherosclerosis. In future this is likely to lead to better use of currently available anti-atherosclerosis strategies. It may also facilitate the discovery, evaluation and development of novel treatments.

Keywords: Atherosclerosis, blood vessels, haemodynamics, shear, mechanics, tensile stress

1 BACKGROUND

There is considerable evidence that mechanical factors may play key roles both in the early development of atherosclerosis [**1–4**] and in plaque rupture [**5–7**], resulting in myocardial infarction and cerebrovascular accidents. Atherosclerosis, by causing heart attacks and strokes, is the major cause of death and morbidity in Western societies. A recent comprehensive survey of the global patterns of disease has projected that, by the year 2020, ischaemic heart disease (currently the fifth leading cause of global disease burden) will become the leading cause of disability in the world, and cerebrovascular disease will move from sixth to fourth position [**8**].

Atherosclerosis is a disease of large conduit arteries. The main role of such arteries is fluid transport and distribution. Consequent to performing this role, these large arteries are exposed to many mechanical factors [**9**]. They experience circumferential, radial and longitudinal deformations and stresses, and pulsatile deformation and stress. Additionally, pulsatile blood flow within the vessel leads to generation of time-varying shear stress at the blood–vessel wall interface. The usual response to changes in deformation and tensile stress is a change in wall thickness and composition, an attempt to normalize wall tension [**10**]. Altered flow results in changes in vessel diameter, which tend to restore the wall shear stress to baseline values of 15–20 dyn/cm^2 [**10**].

The normal arterial wall is composed of three layers: the inner intima, lined on its luminal surface by endothelium; the media, mainly composed of smooth muscle cells; the outer adventia, a connective tissue layer which contains the vasa vasorum, the vascular supply to the vessel wall. Atherosclerosis is a disease of the intimal and medial layers of the arterial wall. Atheromatous lesions are thought to result from an excessive inflammatory-fibroproliferative response to various forms of insult [**11**]. Many cells, endothelial cells, platelets, monocytes, lymphocytes, macrophages and vascular smooth muscle cells, and a large number of lipoproteins, clotting factors, mitogens, growth factors, cytokines and vasoregulatory molecules participate in the process [**11, 12**]. Lipid accumulation, blood monocyte and T lymphocyte adherence and migration through the endothelium are early events in the natural history of an atheromatous lesion. Monocyte transformation to activated macrophages signals progression of the lesion to a fatty streak. Fibrofatty lesions involve platelet adherence to the endothelium, and smooth muscle migration from the media to the subendothelial area. With persistence of the initial insult, progression of lesions will occur; a fibrous cap

The MS was received on 29 October 1998 and was accepted after revision for publication on 15 June 1999.
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will form and overlie the more fluid plaque core. The core of an advanced plaque contains intracellular and extracellular lipid, necrotic cell debris, smooth muscle cells and macrophages. Later the fibrous cap may tear or rupture, leading to intraplaque thrombosis. In a significant proportion of cases this is followed by luminal thrombosis. Blockage of coronary, carotid, femoral and renal arteries by thrombosis results in myocardial infarcts (heart attacks), cerebrovascular events (strokes), peripheral vascular disease (gangrene) and kidney infarcts respectively.

2 MECHANICAL FACTORS AND EARLY DEVELOPMENT OF ATHEROSCLEROSIS

Previous studies have indicated that several global factors contribute to accelerated large vessel atheroma, including hypertension, ageing, smoking, hypercholesterolaemia and diabetes mellitus [**13–18**]. Correction of some of these risk factors has been shown to reduce the rate of progression of plaque, and to reduce wall thickening [**19–22**]. However, despite the importance of global risk factors, atheroma is essentially a focal disease. A large number of human autopsy and *in vivo* studies have shown that atheromatous lesions characteristically occur at arterial branch ostia, bifurcations and bends [**23–29**]. These are regions of low shear and high tensile stress. The typical locations of wall thickenings and plaque suggest that modifications of flow dynamics and/or mural tensile stresses may induce or potentiate the formation of intimal plaques, and that mechanical forces may be major determinants underlying atheroma formation at specific sites [**1–4**, **29**].

During flow visualization studies, using hydrogen bubbles and glass models of human arterial bifurcations [**3**], under conditions of pulsatile flow, complex vortices may be seen along the lateral walls of bifurcations in the low-shear regions with flow separation. The hydrogen bubbles are more slowly cleared from these lateral regions than from all other regions, while passage of bubbles is not retarded at the relatively spared flow divider, where the shear stress is high and flow remains unidirectional. The implication of these observations is that delays in particle clearing or increased residence times prolong the duration of exposure of the endothelium to circulating atherogenic particles.

Altered flow dynamics, such as reduced shear stress, departures from unidirectional laminar flow and flow separation on the outer walls of bifurcations and on the inner walls of curvatures, may also promote atherosclerosis through influences on leukocytes, platelets and endothelial cell function. Activated leukocytes show pseudopodium extensions and express surface adhesion molecules. These features facilitate adherence to and migration through the endothelium. It has recently been shown that application of a mild fluid shear stress leads to instant retraction of pseudopodia and inactivation of leukocytes [**30**]. *In vitro* studies have shown that, in the presence of flow, endothelial cells align themselves with their longitudinal axes parallel to the direction of flow while, in regions of low and oscillating shear, cells are not as prominently aligned [**31**]. High levels of wall shear may elicit formation of tighter intercellular attachments, thereby reducing transjunctional permeability, while low and/or changing shear rate directions could be associated with reduction in junctional tenacity. Increased passage of protein into the intima in atherosclerosis-susceptible locations has been demonstrated in animal models by means of albumin-bound dyes. Leukocyte adhesion molecules facilitate monocyte and T lymphocyte adherence and migration through the endothelium. Shear inhibits expression of leukocyte adhesion molecules on endothelial cells [**32**]. Shear selectively upregulates the expression of certain other genes, cyclooxygenase-2, manganese-dependent superoxide dismutase and endothelial cell nitric oxide synthetase [**33–35**]. These endothelial genes encode enzymes that exert potent anti-thrombotic, anti-adhesive, anti-proliferative, anti-inflammatory and anti-oxidant effects. The biological consequences of these upregulated genes would be predicted to be vasoprotective or anti-atherogenic.

Mural tensile stresses are thought to promote atherosclerosis, principally through effects on wall thickening and alterations in composition [**10**]. The vessel wall thickness and density affect the transmural permeability and sieving [**36**] and would therefore influence the particle efflux rates. Reduced particle efflux rates favour intimal accumulation of atherogenic cholesterol and leukocytes. In support of an important role for transmural pressure gradients in atherogenesis are the following observations:

1. Atheroma formation in humans is in large part confined to the larger proximal arteries with relatively thick and fibrous walls, but sites where transmural pressure gradients are reduced, such as in the intraosseous segment of the internal carotid artery and in intramyocardial deviations of segments of the epicardial coronary arteries, are typically spared of plaques.
2. Atheromatous plaques do not usually form in veins. This is despite the facts that veins are exposed to precisely similar concentrations of atherogenic particles (LDL-cholesterol and activated leukocytes) and venous wall permeability for LDL-cholesterol is greater than arterial wall permeability. However, where veins are exposed to arterial pressures, as in venous grafts (venous tissue used to bypass high-grade arterial stenoses or blockages), plaques do readily occur.

With age, the progressive accumulation of connective tissue fibres tends to make these vessels more dense, less compliant and increasingly resistant to clearance across

the wall from the intima. Arteries subjected to hypertension also elaborate more connective tissue, with increased wall thickness and cross-sectional area, rendering the wall increasingly dense and thereby tending to retard transmural transport. Smooth muscle contraction in the media would also be expected to increase the wall density, and this may be one mechanism whereby the vasoactive nicotine of cigarette smoking promotes atherosclerosis.

The magnitude of mural tension can be approximated by applying the law of Laplace, which relates the wall tension to the pressure and radius. If the thickness of the wall is small compared with the radius, the expression may be simplified to $T = Pr$, where T is the tension, P is the pressure and r is the radius of the vessel. The effective radius is increased on the inner or concave side of arterial bends and along the outer walls of bifurcations, with corresponding increases in circumferential mural tensile stresses.

Hence modifications of flow dynamics and/or mural tensile stresses is likely to contribute to the preferential location of plaques at bifurcations and bends in older subjects, in smokers and in patients with hypertension and dyslipidaemia.

3 MECHANICAL FACTORS AND CONSEQUENCES OF ATHEROMA

Figure 1 shows a post-mortem specimen of a carotid bifurcation plaque that ruptured. Distal embolism of the lipid-rich core, intraplaque haemorrhage and internal carotid artery thrombosis all contributed to extensive cerebral infarction (stroke) and death. It is now accepted that almost all acute coronary and many cerebral events are precipitated by sudden plaque rupture followed by thrombosis [**37**]. From comparisons of plaques that have ruptured and plaques that have remained quiescent, many features of unstable plaques have been elucidated. Plaque rupture typically occurs in eccentric plaques with large necrotic cores and pools of extracellular lipid and thin fibrous caps [**5**, **38**]. Many unstable plaques also demonstrate juxtaposed regions of contrasting composition, lumen irregularity and asymmetry [**5**]. Computer modelling of the distribution of mechanical stress in arteries with plaque [**6**, **7**] has shown that circumferential stress is highest near the plaque cap edge, this is the typical site of plaque rupture. The maximum stress at plaque edge is significantly increased when there is a large lipid pool, when the fibrous cap is thin and somewhat surprisingly when stenosis is of a lower grade.

It is likely that cap weakening also plays a role in plaque disintegration [**6**]. Plaques that have ruptured by comparison with unruptured plaques demonstrate decreased resistance to mechanical deformation and decreased maximum stress at fracture [**39**]. At the cap shoulder, the fibrous layer is typically thinner, and there

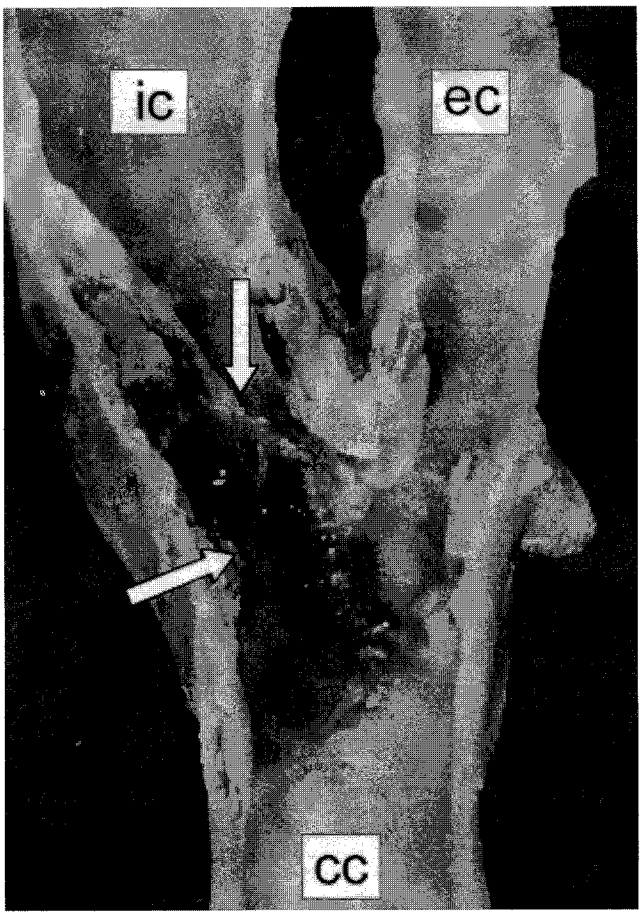

Fig. 1 A post-mortem specimen showing the right common carotid (cc) artery and its two branches, the internal carotid (ic) artery and the external carotid artery (ec). There is a large plaque in the proximal internal carotid artery that has ruptured at its proximal edge (site indicated by white arrows) allowing release of the necrotic core. Intraplaque haemorrhage (indicated by the dark discoloration) was followed by internal carotid thrombosis. The patient died of extensive cerebral infarction (stroke)

are increased numbers of foam cells and reduced numbers of smooth muscle cells [**39**]. Collagen is a major determinant of cap strength. Recently Lee *et al.* [**40**] have shown increased expression of collagenase, the enzyme that breaks down collagen, in plaques at the junction of the fibrous cap with normal intima.

4 MEASUREMENT OF HAEMODYNAMICS AND WALL MECHANICS *IN VIVO* IN MAN: COMPUTATIONAL MODELLING APPLIED TO ULTRASOUND OR MAGNETIC RESONANCE DATA

In vitro studies of the possible impact of mechanical forces on plaque formation and localization have used casts of actual vessels or glass or plastic models

constructed to scale from measurements on angiograms [41, 42]. Quantitative determinants of flow-field velocity profiles in such models have been achieved by means of Doppler laser anemometry and by particle tracking, under conditions of both steady and pulsatile flow. The effects of compliant walls on near-wall flow profiles are also under investigation.

Currently *in vivo* measurements of time-dependent vessel geometry and blood flow are achieved by ultrasound and magnetic resonance imaging (MRI) techniques. Ultrasound is well tolerated, widely available and relatively cheap. By contrast, MRI is associated with high costs and a significant number of patients do not tolerate the assessment due to claustrophobia.

High-resolution B-mode ultrasonography may be used to delineate vascular geometry, and M-mode ultrasonography to characterize wall movement. Rapid progress is being made in the development of three- and four-dimensional ultrasound. Three-dimensional vascular geometry may be reconstructed from a series of two-dimensional B-mode cross-sectional images, in combination with an electromagnetic locating device that tracks the position and orientation of the scanhead throughout scanning. Electrocardiographic monitoring may be integrated into the system so that acquired images may be related to temporal as well as spatial information to give four-dimensional ultrasonography, where time is the fourth dimension. Doppler ultrasonography allows estimation of blood flow velocities throughout the cardiac cycle. However, caution is necessary because flow velocities measured by Doppler are subject to considerable errors, where flow is complex, such as in the regions of plaques, bifurcations and curvatures [43].

Magnetic resonance angiography (MRA), using two-dimensional 'time-of-flight' sequences, may also be used to acquire vascular geometrical information. Indeed, by comparison with ultrasonography, it probably provides superior three-dimensional information regarding overall geometry. Phase contrast MRI allows acquisition of the distribution of blood flow velocities across vessel cross-sections throughout the cardiac cycle. MRI resolution of flow is currently somewhat limited, and it is doubtful that the key flow fields in the region of the lumen wall interface can be imaged with sufficient accuracy. In addition, similar to ultrasonography, there are unsolved technical difficulties associated with the handling of complex flow; blood flow estimations from bifurcations and in vessel regions with large plaques are unreliable.

Despite the above-described recent advances in clinical imaging techniques, accurate direct determination of temporally and spatially varying shear stress patterns and knowledge of human *in vivo* arterial wall mechanical behaviour are still precluded. These parameters, however, are quantifiable by the application of numerical models to ultrasound or MRI data. The geometric, flow and wall movement data acquired from clinical ultrasound and MRI measurements provide the boundary and entry conditions necessary for computational models of arterial blood flow and wall behaviour. An additional boundary condition, namely the vascular pressure throughout the cardiac cycle, can be measured non-invasively *in vivo* in humans by applanation tonometry.

Historically, the development of computational techniques for fluid (blood flow) and solid (vessel wall behaviour) mechanics has been carried out separately, and in parallel. Computational fluid dynamics (CFD) codes normally use what is termed a finite volume method (FVM), while solid mechanics uses in contrast the finite element method (FEM). A novel hybrid model is currently being developed and validated by a clinical and engineering collaboration [44]. The model combines the FVM-based fluid dynamics code CFX with the FEM-based structural analysis code ABAQUS. An iterative approach then allows the fluid and solid equations to be solved separately and coupled externally. The model appears to be able to treat all the important complexities of the human circulation: the asymmetric geometry, fluid viscosity, flow pulsatility, and the vessel wall behaving as non-linear viscoelastic material undergoing large deformations. From simple ultrasound or MRI data and tonometric pressure data the hybrid model will allow simulation of three-dimensional fluid flow, and the mechanics of the wall which is in contact with the fluid. Post-processing will allow calculation of many potential pathophysiologically relevant end points including the extent of flow separation, the magnitude of shear oscillation, the particle residence times and the average and peak tensile stresses. Once validated, it should provide a powerful, readily applicable non-invasive tool for the exploration of the role of local mechanical factors in atheroma formation and regression.

5 THE FUTURE

Further studies using improved non-invasive three-dimensional real-time imaging assessments of vessels with and without plaque, in combination with advanced computational models, should further elucidate the roles of haemodynamics and mechanics in early atherosclerosis and in plaque rupture. This is likely to lead to better use of currently available anti-atherosclerosis strategies, such as bypass surgery, angioplasty, antihypertensives, lipid lowering therapy and anti-platelet drugs. Improved technologies should also facilitate discovery, evaluation and development of novel treatments. Early development of atherosclerosis might be impeded through inhibition of endothelial permeability, promotion of LDL-cholesterol efflux from the arterial wall and inhibition of monocyte activation and migration. At a later stage in the natural history of atherosclerosis, protection against

plaque rupture might be achieved through specific inhibitors of collagenases or by anti-inflammatory agents.

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