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Comparison of the vulnerability risk for positive versus negative atheroma plaque morphology

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ABSTRACT

As plaque develops in arteries two types of remodeling can occur; positive and negative remodeling. Positive remodeling is an outward compensatory remodeling in which the arterial wall grows outward in an attempt to maintain a constant lumen diameter, while negative remodeling is defined as a local shrinkage of vessel size. Sudden heart attacks remain one of the primary causes of premature death in the developed world. The role of positive remodeling in vulnerable plaque rupture mechanics, which could explain why many of these heart attacks occur without prior symptoms, is still debated. In this manuscript we present a numerical study of the role of vascular growth on plaque vulnerability. Plane strain finite element models of a coronary artery with positive and negative morphology have been compared by systematically varying the most influential values of the geometry of the vessel on plaque stresses: (i) the fibrous cap thickness, (ii) the stenosis ratio, (iii) the lipid core dimensions and (iv) the atheroma plaque distribution (eccentric or concentric). All models have been developed with the same average dimensions and material properties. Vessel wall stress concentrations were always predicted to be higher in the fibrous cap of atheroma plaques with positive morphology compared to those with negative morphology. Furthermore, our conclusions are independent of the fibrous cap and the degree of stenosis considered. These results may explain why plaque rupture is often apparent at sites with only modest luminal stenoses but marked positive remodeling. The results of this study support the hypothesis that coronary arteries with positive remodeling are more vulnerable to rupture than those arteries with negative remodeling for comparable geometrical conditions.

1. Introduction

Atherosclerotic cardiovascular disease results in millions of sudden deaths annually and coronary artery disease accounts for the majority of this toll. Plaque rupture plays a role in the majority of acute coronary syndromes (Naghavi et al., 2003). Moreover, despite major advances in the treatment of coronary heart disease, a large number of victims of the disease who are apparently healthy die suddenly without prior symptoms. Arteries adapt to changes in their environment such as modification in blood pressure or shear stress, both by vascular growth and remodeling (G&R). Remodeling may involve the composition of the tissue, i.e., the relative amounts of load bearing tissue components, such as elastin, collagen and smooth muscle cells. It may also involve the orientation of the collagen fibers. While it is generally recognized that mechanical load is a stimulus for G&R, the exact relationship between mechanical load and G&R is still unclear (Rodriguez et al., 1994; Humphrey, 2009). Glagov et al. (1987) demonstrated that in the early stages of atherosclerosis, coronary arteries enlarge in relation to plaque area to preserve lumen diameter until plaque area occupies approximately 40% of vessel area. This phenomenon, commonly referred to as arterial remodeling, describes the process by which the arterial wall adapts to physiological or pathological insults by a change in vessel size, or area, within the external elastic lamina. According to the analyses of Glagov et al. (1987), coronary arteries may respond to plaque growth by either outward expansion of the vessel wall (positive) or vessel shrinkage (negative). The compensatory remodeling process can maintain luminal dimensions during early atherosclerosis. These plaques grow further and the plaque does not generally begin to encroach on the lumen until it occupies 40% of the cross-sectional area. There is evidence to suggest that positive remodeling may be advantageous, providing benefit in terms of avoiding luminal stenosis, but also harmful in that such marked compensatory remodeling may make the plaque more

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vulnerable to rupture. In contrast, lesions with negative remodeling may be associated with higher grade stenoses but may appear more stable (Varnava et al., 2002). Positive remodeling could potentially explain why many heart attacks occur suddenly by potentially increasing the venerability of the plaque rupture. Available screening and diagnostic methods could be insufficient to identify the victims before the event occurs (Sipahi et al., 2006) since the plaques that rupture do not necessarily protrude very far into the blood channel and so, may not cause angina or appear on angiograms.

Plaque disruption tends to occur at points where the plaque surface is weakest and most vulnerable which coincide with points where stresses, which are affected mainly by tissue properties and plaque geometry, are concentrated (Falk et al., 1995; Van der Wal and Becker, 1999). The risk of plaque rupture depends on plaque type and size (Schroeder and Falk, 1995). Major determinants of a plaque's vulnerability to rupture are the size and consistency of the lipid core, the thickness of the fibrous cap covering the lipid core and ongoing inflammation and repair within the cap (Pasterkamp and Falk, 2000). Several studies have explored the mechanical risk factors associated with plaque vulnerability (Ohayon et al., 2005, 2008; Cheng et al., 1993; Finet et al., 2004; Lee, 2000; Cilla et al., 2012b; Cilla et al., 2012a), however the role of vessel remodeling on plaque stresses has not been adequately addressed. Ohayon et al. (2008) include in their element finite study a remodeling index, which takes into account positive and negative vascular remodeling, as a parameter effecting plaque stability. The aim of their study was to investigate the biomechanical interaction between vessel and plaque geometry and the risk of plaque rupture. Their study demonstrated that in the early stages of positive remodeling, lesions were more prone to rupture, motivating the need for further research into the influence of positive and negative remodeling on plaque stability.

The objective of this study is to demonstrate that coronary artery atheroma plaques with positive remodeling are more vulnerable to rupture than those with negative remodeling. Despite the fact that positive remodeling has been correlated with plaque rupture, to the best of the authors' knowledge, no finite element studies have attempted to test the hypothesis that positive remodeling increases plaque vulnerability from a structural perspective. We therefore investigated the effect of positive and negative remodeling on plaque stability by considering the arterial remodeling process that occurs in response to plaque growth. Various idealized cross-sectional plaque morphologies, mimicking different stages and variations in atherosclerotic lesion remodeling, were modeled. The relevant anatomical diversity was simulated by continuously varying the most influential values of the diseased vessel geometry: (i) the fibrous cap thickness, (ii) the stenosis ratio, (iii) the lipid core dimensions and (iv) the atheroma plaque distribution (eccentric or concentric).

2. Materials and methods

2.1. Idealized geometry

Three idealized geometries corresponding to a coronary vessel with atheroma plaque have been chosen: (i) a vessel with positive arterial morphology, (ii) a vessel with negative arterial morphology and an eccentric atheroma plaque and (iii) a vessel with negative arterial morphology and a concentric atheroma plaque. Atherosclerotic vessel morphology and average dimensions were obtained from Varnava and Davies (2001), Versluis et al. (2006) and Bluestein et al. (2008); a 2D cross-sectional vessel with external radius of 2 mm and vessel wall thickness of 0.5 mm was considered.

A generalized arterial cross-section with an atheroma plaque, a circular lumen and a blunt crescent-shaped lipid pool was chosen as the baseline anatomy. The model was extruded at a small length in order to introduce some purely 3D parameters such as the fiber orientation. The whole media layer has been considered as fibrotic, whereas the adventitia was modeled as the only healthy layer of the vessel.

Various idealized cross-sectional plaque morphologies, mimicking different stages and variations in atherosclerotic lesion development, were modeled to test the hypothesis that atheroma plaques with positive remodeling are more prone to rupture than atheroma plaques with negative remodeling. The relevant anatomical diversity was generated by continuously varying the size of the lipid core, the stenosis ratio, the fibrous cap thickness and the atheroma plaque distribution (eccentric or concentric), following previous works (Cheng et al., 1993; Williamson et al., 2003; Finet et al., 2004; Ohayon et al., 2008; Cilla et al., 2012b). The geometric parameters considered were the fibrous cap thickness (fc), the stenosis ratio (sr) - which is obtained by dividing the lumen radius (r) by the lumen radius of a normal artery ($R=1.5$ mm), $sr(\%)=(r(\text{mm})/R(\text{mm}))100$—and the lipid core size (lc) determined by the width (w) and the angle (α). The lipid core size (lc) was defined as the ratio between the area of the fibrotic plaque (a_p) and the area of lipid core (a_{lc}), $lc(\%)=(a_{lc}(\text{mm}^2)/a_p(\text{mm}^2))100$ (see Fig. 1).

A fine mesh was created with an adaptive mesh implemented for the fibrous cap region. Sensitive analyses were first performed on the mesh, and finally approximately 20,000 linear hexahedral elements and 25,000 nodes were used to mesh the geometry.

2.2. Material model and boundary conditions

All tissues were modeled as nonlinear (Roy, 1881; Patel and Fry, 1969; Cox, 1978) and incompressible materials (Carew et al., 1968; Chuong and Fung, 1984). Despite some authors consider the arterial as pseudoelastic (Fung et al., 1979; Fung, 1993), a hyperelastic (Holzapfel et al., 2005) model has been chosen to model the arterial tissue. The lipid core and the atherosclerotic plaque were modeled as isotropic materials, while the arterial wall was considered as an anisotropic material with two families of fibres, oriented at $\pm 61.8^\circ$ with respect to the circumferential direction. Both families of fibres were assumed to have the same mechanical properties (Holzapfel et al., 2005). The behavior of the tissue was modeled by using a strain energy function proposed by Gasser et al. (2006)

$$\Psi = \mu[I_1-3]+\frac{k_1}{2k_2}\sum_{i=4,6}\exp(k_2[\kappa[I_1-3]+[1-3\kappa][I_i-1]]^2)-1, \quad (1)$$

where $\mu>0$ and $k_1>0$ are stress-like parameters and $k_2>0$ and $0\le\kappa\le\frac{1}{3}$ are dimensionless parameters, I_1 is the first invariant of $\mathbf{C}=\mathbf{F}^T\mathbf{F}$ with $\mathbf{F}$ the deformation gradient tensor, $I_4=\mathbf{m}_0\cdot\mathbf{Cm}_0$ and $I_6=\mathbf{n}_0\cdot\mathbf{Cn}_0$ are invariants which depend on the direction of the family of fibres at a material point $\mathbf{X}$ that is defined by the unit vectors field $\mathbf{m}_0$ and $\mathbf{n}_0$ (Spencer, 1971).

To obtain the material parameters for this constitutive law, experimental data presented in previous studies for arterial tissue (the adventitia properties from

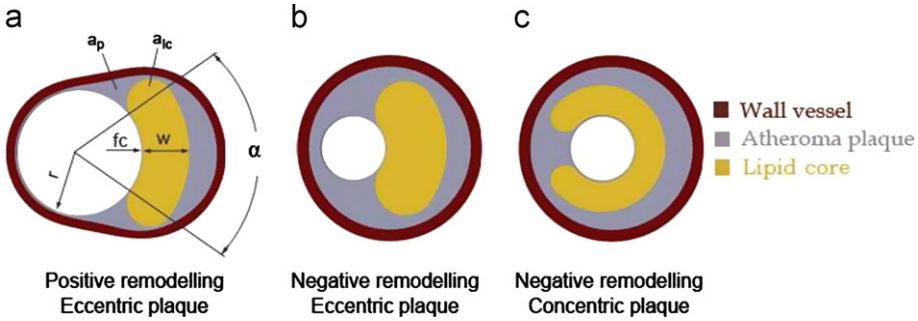

Fig. 1. Idealized cross-sectional models and geometrical parameters studied; fc—fibrous cap thickness, r—lumen radius, a_{lc}—lipid core area, w—lipid core width – α – lipid core angle and a_p—atheroma plaque area. (a) Positive arterial remodeling. (b) Negative arterial remodeling with an eccentric atheroma plaque. (c) Negative arterial remodeling with a concentric atheroma plaque.