

Biomechanical interaction between cap thickness, lipid core composition and blood pressure in vulnerable coronary plaque: impact on stability or instability

G rard Finet^a, Jacques Ohayon^b and Gilles Rioufol^a

Background A ‘thin’ fibrous cap atheroma is the typical morphological characteristic of vulnerable plaque. Yet the very pathological studies that have provided these descriptions have also shown the actual prediction of plaque rupture to be rather less exact. Other relevant characteristics must be involved in the mechanisms of plaque rupture—blood pressure loading (*P*) and the material properties of the soft atheromatous core—as predictors of the distribution of the peak circumferential stress (PCS) locations.

Methods and Results We used a computational structural analysis based on three typical *in-vivo* intravascular ultrasound images of fibrous cap atheroma in which we decreased the cap thickness (CTh). With different soft atheromatous core Young’s moduli (E_{core}), 414 simulations were performed under eight different physiological loading blood pressures. The transition from plaque stability to plaque instability was defined by a threshold of 300 kPa and is a feature of vulnerability. It was found that (1) irrespective of plaque geometry and composition, CTh < 60 μm exposed the plaque to PCSs in excess of 300 kPa; (2) the exponential variations in PCS with change in CTh and E_{core} values show that very slight structural changes are enough to tilt a vulnerable plaque from stability to

instability or vice versa; and (3) the relationship between *P* and PCS is proportional with *P* acting as trigger or as protector.

Conclusion The present study shows why, in clinical practice, mere morphological detection by imaging techniques of thin-cap fibro-atheroma is not in itself enough for the prediction of future rupture. *Coron Artery Dis* 15:13–20   2004 Lippincott Williams & Wilkins.

Coronary Artery Disease 2004, 15:13–20

Keywords: atherosclerosis, plaque, computers, mechanics, coronary imaging

^aDepartment of Hemodynamics and Interventional Cardiology, Hospices Civils de Lyon and Claude Bernard University and CREATIS, Research Unit associated to CNRS (UMR 5515) and affiliated to INSERM, Lyon and ^bLaboratory TIMC-IMAG, Institut A. Bonniot, Grenoble, France.

Sponsorship: This study was supported in part by a TERUMO France grant.

Correspondence and requests for reprints to Professor G. Finet, Service d’H modynamique et de Cardiologie Interventionnelle, H pital Cardiologique, BP Lyon-Montchat, 69394 Lyon Cedex 03, France.
Tel: +33 04 72 35 74 18; fax +33 04 72 68 49 27;
e-mail: gerard.finet@creatis.univ-lyon1.fr

Received 26 August 2003 Revised 30 October 2003
Accepted 31 October 2003

Introduction

The characteristics of vulnerable plaque are now well defined thanks to numerous pathological studies [1,2] and Virmani’s team [3] has recently added even greater exactness, describing ‘thin’ fibrous cap atheroma as a specific type of plaque with a cap thickness less than 65 μm —a morphological characteristic specifically associated with rupture. Clinical detection tools are available: intravascular ultrasound (IVUS), optical coherence tomography, computed tomography and magnetic resonance imaging [4–6]. Detecting such so-called vulnerable plaque is a major issue, as it could lead to the development of specific treatment strategies for the prevention of acute thrombotic accidents [7].

Prediction of plaque rupture, on the other hand, would seem to be less precise [3]. In a series of 200 cases of sudden death, 60% of acute thrombi resulted from rupture of thin fibrous cap atheroma; in these patients,

thin-cap fibro-atheroma without rupture was found in 70% of cases. Moreover, such plaques were present in 30% of deaths due to fibro-calcific lesions [8]. Thin fibrous cap atheroma thus does not necessarily develop into rupture.

Morphological description of a vulnerable coronary plaque seems not in itself to be quite enough for the prediction of future rupture. Relevant characteristics other than cap thickness must be involved in the rupture mechanism and Virmani *et al.* emphasized the interest of mechanical studies in this regard [3].

Coronary plaques are constantly subjected to stress that may exceed the rupture thresholds of the materials that make them up. Due to the complex geometry of the atherosclerotic plaque, the Laplace law cannot be used to obtain the distribution of the peak circumferential stresses (PCSs) on the wall under physiological loading.

In the case of a pressurized thin-walled cylinder, the circumferential wall stress σ_c may be estimated by using Laplace's law: $\sigma_c = Pr/h$, where P is the blood pressure, r the radius of the vessel and h the thickness of the wall. In spite of the fact that such a law is not valid for complex geometries, it still helps to explain why very high circumferential stress can develop in thin fibrous caps, causing the plaque rupture. A biomechanical study using the finite element (FE) method is therefore necessary. PCS may be considered as a determining factor in the mechanisms leading to rupture of the atherosclerotic plaque [9,10] and as an *in vivo* predictor of atherosclerotic plaque rupture location [11].

Our hypothesis is that the paradox found between precise knowledge of the morphological characteristics of vulnerable plaque and their poor predictive value with respect to rupture is largely due to the complexity of the biomechanical interactions. Two unresolved questions arise. (1) While it seems clear that arterial blood pressure triggers PCS, what kind of relationship holds between blood pressure and PCS? (2) It has been established that an increase in lipid core Young's modulus (E_{core}) reduces PCS [9], but exactly what kind of relationship holds between E_{core} and PCS and what degree of variation in E_{core} will affect PCS significantly? (The stiffness of a material is characterized by the elastic Young's modulus (E), which is the ratio between the applied stress σ and the observed strain ϵ (that is, $E = \sigma/\epsilon$). Using three fibrous cap atheromatous plaques of differing geometries, acquired by IVUS *in vivo*, for which we varied cap thickness, the present study was designed to understand the complex interactions between two mechanical factors—luminal pressure loading (P) and the material properties of the soft atheromatous core—as predictors of the distribution of the PCS locations.

Methods

Model design and image analysis

The study was performed using computational structural analysis based on three typical *in-vivo* IVUS images of fibrous cap atheroma with lipid core. The lumen cross-sectional areas (LAs) were 8.4, 6 and 6.8 mm², the external elastic membrane cross-sectional areas (EEMAs) were 24.4, 13.4 and 19.3 mm² and the plaque + media cross-sectional areas ($P + MA = EEMA - LA$) were 15, 7.4 and 12.5 mm², respectively.

Computerized simulations

The FE method is a computerized technique dividing a complex structure into small sections (elements) so that simpler functions may be used to derive the strain and stress distributions in each individual element. For each computerized simulation, parietal circumferential stress distribution was visualized as a stress map and the PCS thus determined and located with precision. The

unloaded physiological configuration of the artery was taken account of by the previously described method [11]. All contours were manually traced. These contours are those of the lumen border, media, adventitia and plaque components (dense fibrosis, cellular fibrosis and lipid core). The adventitia contour was added and given a mean 450 μm thickness [12] so as to account for its protective role against any radial overstretching of the artery [13]. The various contours were digitized using Un-Scan-It software (Silk Scientific, Inc., Orem, Utah, USA). From each real geometry, six idealized models with decreasing fibrous cap thickness values (230, 205, 118, 70 32 and 15 μm) were traced by increasing the initial lipid core size value (Fig. 1). Cap thickness was defined as the shortest distance between lumen and core.

Material properties

The adventitia, media, dense fibrosis and cellular fibrosis were modeled as transverse isotropic materials (so as to take the spatial orientation of fibers and cells into account for the purposes of estimating linear elastic properties [14]). The materials were assumed to have the same mechanical properties in the circumferential (θ) and axial (z) directions and different ones in the radial (r) direction [9]. The adventitia E_r and E_θ Young's modulus values were derived from those for normal coronary artery [11], on the assumption that plaque growth induces arterial wall dilation, stretching the wall layers by about 20%. The Poisson ratios $\nu_{r\theta}$ and $\nu_{\theta z}$ and other orthotropic material parameters (Young's and shear moduli E_r , E_θ and $G_{r\theta}$, respectively) for arterial wall and plaque components were close to those used by Cheng *et al.* [9] (Table 1). Lipids were modeled as quasi-incompressible (Poisson ratio $\nu = 0.49$) and very soft (Young's modulus $E_{\text{core}} = 1 \text{ kPa}$) isotropic solids [15]. Material properties of the different types of fibrosis were in accordance with those experimentally determined by Lee *et al.* [16]. Different soft atheromatous core properties were modeled as isotropic solids by different Young's moduli in a range from $E_{\text{core}} = 5$ to 400 kPa.

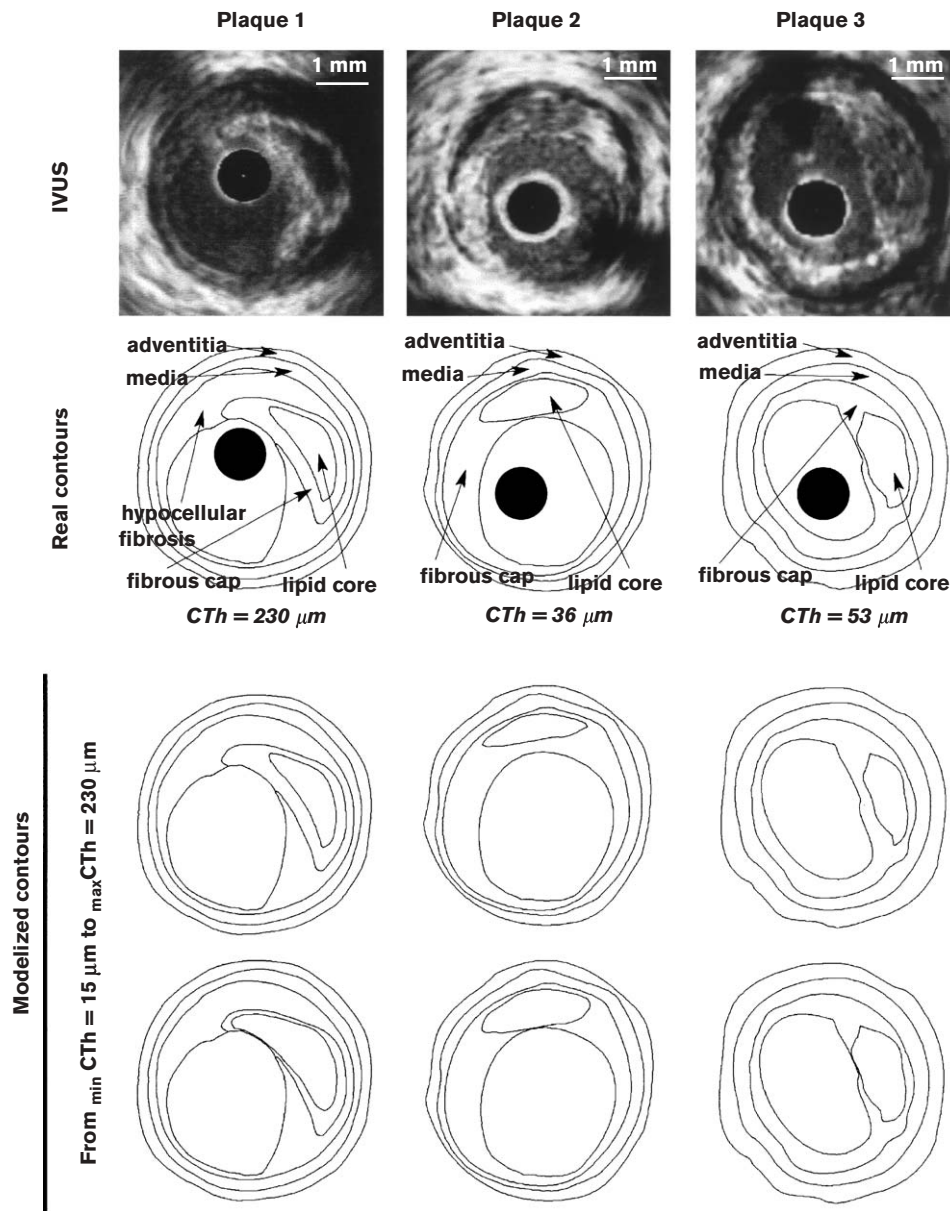
Structural analysis

FE computations were performed using the ANSYS 5.7 software (Ansys, Inc., Cannonsburg, Pennsylvania, USA). Static simulations of coronary plaque under different physiological loading blood pressures (6, 8, 10, 12, 14, 16, 18 and 20 kPa; 1 kPa = 7.5 mm Hg) were performed on the geometrical models previously described (Fig. 1). The various regions of the plaque components were meshed with approximately 1000 triangular (six-node) and quadrangular (eight-node) elements. The FE models were solved under the assumption of plane and of finite strains.

Critical plaque rupture values

In-vitro testing has shown that human atherosclerotic materials generally fracture under stresses in excess of

Fig. 1



Typical *in-vivo* intravascular ultrasound images of one fibrous-cap fibro-atheromatous plaque (plaque 1, cap thickness = 230 μm) and two thin-cap fibro-atheromatous plaques (plaques 2 and 3, cap thicknesses = 36 and 53 μm , respectively). Six idealized models in which the fibrous cap thickness decreases from 230 to 15 μm were manually traced by increasing the initial lipid core size for each plaque.

300 kPa (2250 mm Hg) [17]. These findings were confirmed by Cheng *et al.* [9] by structural analysis, using, as in the present study, finite elements with histopathological correlations from specimens of ruptured plaque, with $P = 14.6 \text{ kPa}$ (= 110 mm Hg): PCS in these ruptured plaques averaged $545 \pm 160 \text{ kPa}$ (= $4091 \pm 1199 \text{ mm Hg}$). In the study of Cheng *et al.* study, rupture was consistently associated with PCS values $> 2250 \text{ mm Hg}$. These rupture thresholds were much the same as those found by Huang *et al.* [18],

again using structural analysis: median and interquartile ranges (25th/75th) were 458 (378/605) kPa. In the present study, the transition from plaque stability to plaque instability was defined by a threshold of 300 kPa.

Statistics and graphs

Statistical analysis was performed using StatView 4.5 statistical software (Abacus Concept, Inc., Berkeley, California, USA). Data are presented as mean \pm SD.

Table 1 Rheological parameters used in the FE analysis

	E_r (kPa)	E_θ (kPa)	V_θ	$V_{\theta z}$	$G_{r\theta}$ (kPa)
Adventitia	80	800	0.01	0.27	400
Media	10	100	0.01	0.27	50
Cellular fibrosis	20	200	0.01	0.27	100
Dense fibrosis	100	1000	0.01	0.27	500
Lipid core	Isotropic medium with $E = 1$ kPa and $\lambda = 0.49$				

Table 2 Effect of blood pressure on normalized cap peak circumferential stress for different values of fibrous

		Cap thickness (μm)					
PCS/ P		15	32	70	118	205	230
Plaque 1	Mean \pm SD	42.29	30.07	19.11	14.55	10.60	10.15
		1.22	0.24	0.41	0.56	0.45	0.48
Plaque 2	Mean \pm SD	69.45	35.24	18.00	12.04	6.89	6.01
		^a	1.18	0.22	0.46	0.28	0.26
Plaque 3	Mean \pm SD	46.76	27.21	16.51	13.45	11.3	11.00
		^a	0.94	0.27	0.18	0.76	0.27

1 kPa=7.5 mm Hg. Core Young's modulus=1 kPa. P , blood pressure; PCS/ P , normalized cap peak circumferential stress.
^aThese entries correspond to non-convergence of some numerical finite element solutions.

TableCurve 3D software (SPSS Inc., Chicago, Illinois, USA) was used for the three-dimensional surface fitting.

Results

The interactions between the various fibrous cap thicknesses, core Young's moduli and blood pressures led us to perform 138 simulations for each of the three plaques studied, that is, 414 simulations in all.

Effect of blood pressure

For a given fibrous cap thickness, the normalized cap PCS stayed almost constant for P values in the physiological range 6–20 kPa. Above this range, the results showed that geometric non-linearity (the geometric complexity of the structure) was of negligible impact (Table 2). This means that there is an almost linear relationship between cap PCS and P : if blood pressure doubles, cap PCS more or less doubles. Thus, for any given blood pressure under constant plaque geometry, cap PCS can be determined with precision.

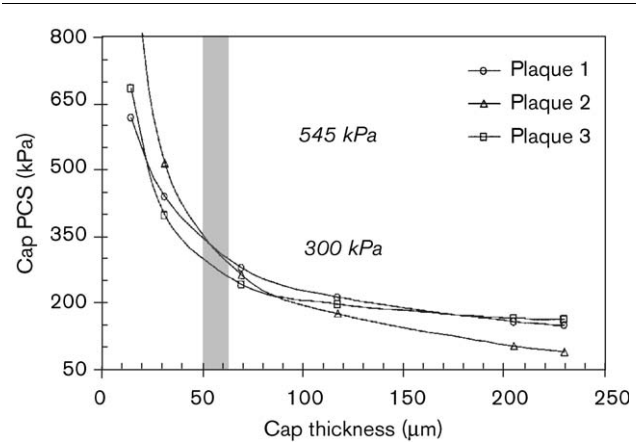
Effect of fibrous cap thickness

For a given pressure ($P = 14.6$ kPa) and material properties (Table 1), Figure 2 presents the findings concerning the biomechanical effect of fibrous cap thickness: reducing fibrous cap thickness increases cap PCS exponentially. PCSs lie mainly in the juxta-luminal part of the cap in all three caps, when cap thickness < 120 microns.

Effect of core material properties

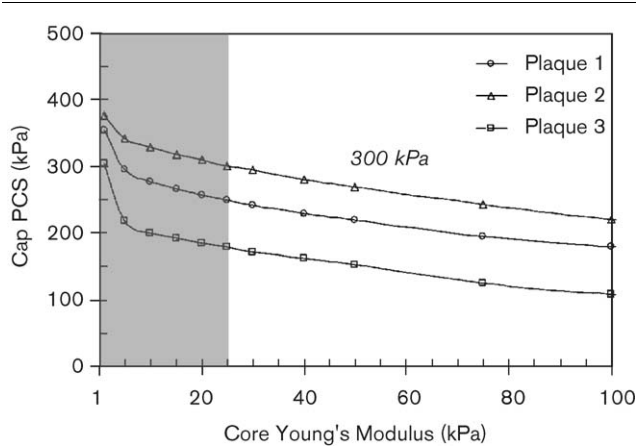
For the three plaques under study, Figure 3 shows the change in cap PCS with change in the Young's modulus of

Fig. 2



Biomechanical effect of fibrous cap thickness in the three plaques studied. Changes in cap peak circumferential stress (PCS) with cap thickness (CTh) at blood pressure ($P = 14.6$ kPa (= 110 mm Hg)). The mean curve interpolation of the three curves is given: $\text{PCS}/P = 291.2\text{CTh}^{-0.644}$ ($r^2 = 0.998$). The CTh threshold (transition from stability to instability, defined in the 'Methods' section) lay between 50 and 62 μm . The intersection of the PCS curves with the mean ruptured plaque PCS (545 kPa) calculated by Cheng *et al.* [9] would correspond to CTh values lying between 22 and 32 μm . (1 kPa=7.5 mm Hg.)

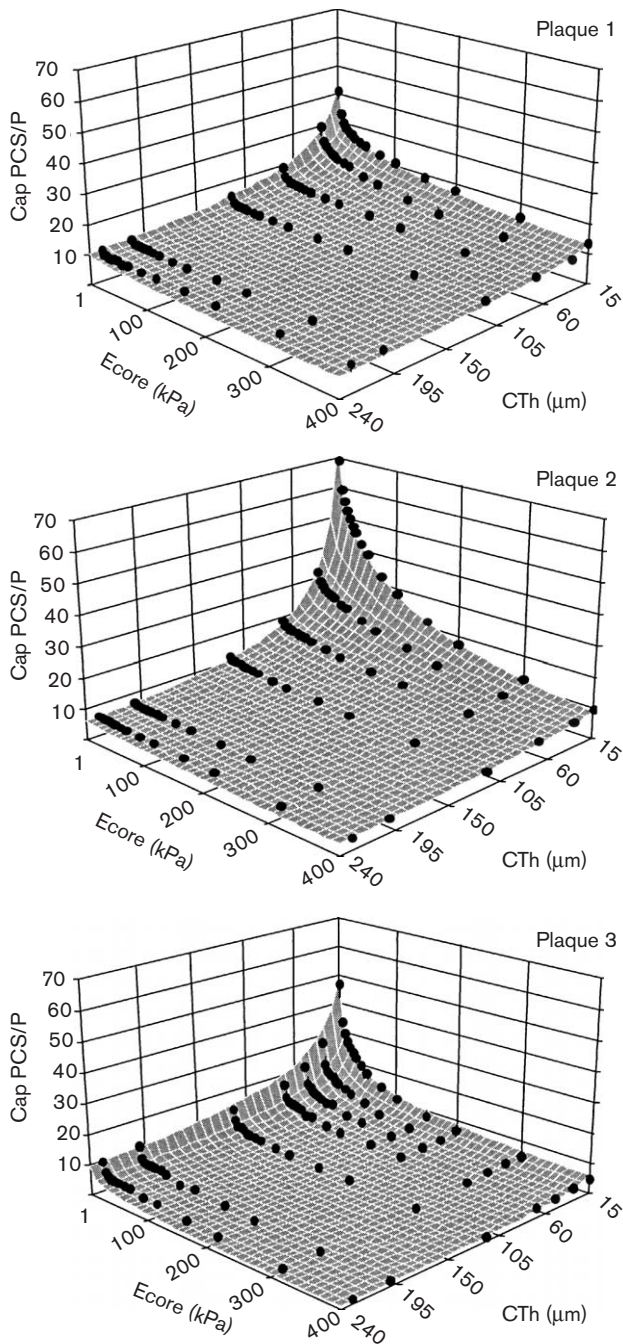
Fig. 3



Biomechanical effect of the core's material properties in the three plaques studied, for a constant fibrous cap thickness (CTh=50 μm) and blood pressure ($P = 14.6$ kPa (= 110 mm Hg)). Changes in cap peak circumferential stress (PCS) when the core Young's modulus varies ($E_{\text{core}} = 1$ –100 kPa): very slight changes in E_{core} (from 1 kPa (lipid core) to around 25 kPa (soft atheromatous core) (gray zone)) were enough to stabilize the three plaques and to bring PCS down below a critical PCS value of 300 kPa (defined in the 'Methods' section). (1 kPa=7.5 mm Hg.)

the core, all other material properties being held constant (see Table 1). For any given geometry, maximum PCS values occurred for $E_{\text{core}} = 1$ kPa. A change in the core's material properties from lipid to soft atheromatous exponentially reduced cap PCS, by increasing the core Young's modulus (E_{core} from 1 to 400 kPa).

Fig. 4

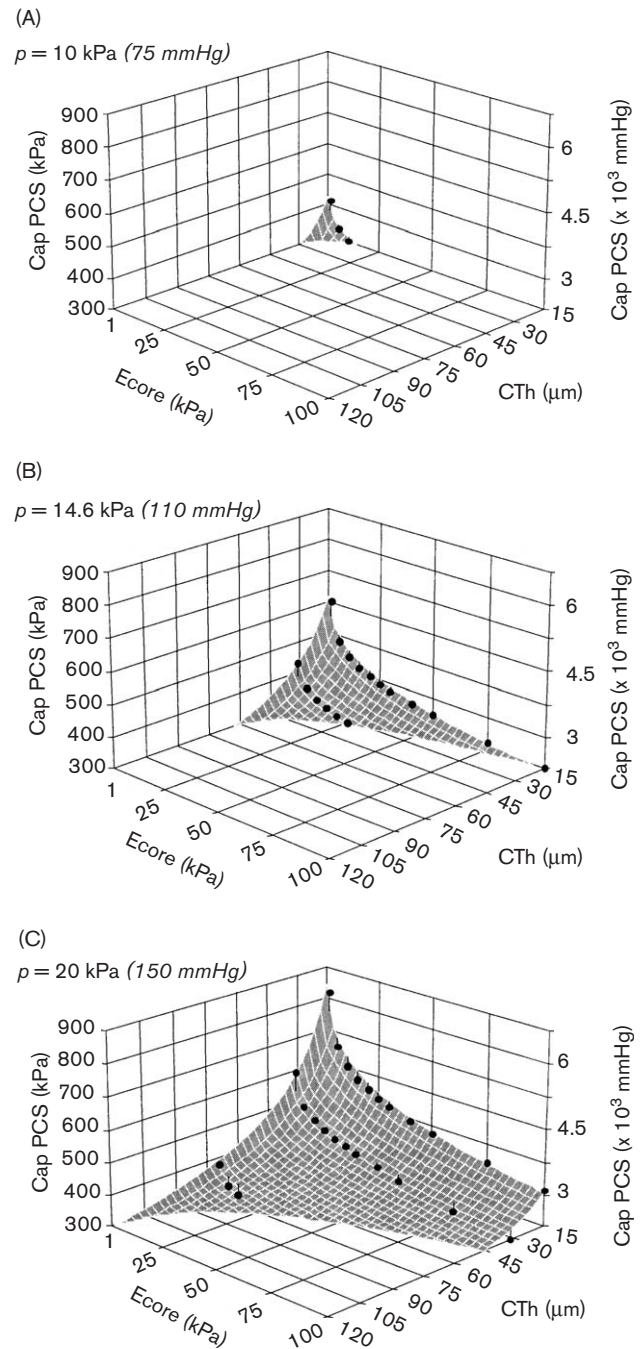


These three-dimensional representations quantify the interactions of blood pressure (P), cap thickness (CTh) and lipid or soft atheromatous core Young's modulus (E_{core}) on cap peak circumferential stress (PCS) for the three plaques studied. (1 kPa=7.5 mm Hg.)

Synthesis of biomechanical interactions

Figure 4 sums up the results of the various simulations, quantifying the interactions between the three mechanical factors (P , CTh and E_{core}) on cap PCS. Core rheology and thus its geometric singularity more or less cease to affect plaque PCS from $E_{core} > 200$ kPa. Figure 5 shows

Fig. 5



Trigger effect of blood pressure as seen in plaque 1. Three static blood pressure values were tested: 10 kPa (75 mm Hg), 14.6 kPa (110 mm Hg) and 20 kPa (150 mm Hg), respectively. Three-dimensional surface quantifying interaction between cap thickness (CTh) and the lipid or soft atheromatous core Young's modulus (E_{core}) and their impact on cap peak circumferential stress (PCS), based on the set of simulations. The lower plane corresponds to a 300 kPa PCS, the plaque instability threshold (see 'Methods' section). From blood pressure (P)=75 mm Hg to 150 mm Hg, the instability range widens as blood pressure rises. Moreover, the intersection of the three-dimensional surface with the 300 kPa plane gives the pair of critical E_{core} - CTh values corresponding to the transition from stability to instability: for example, for 150 mm Hg, E_{core} needs to be 30 kPa to stabilize a plaque with a 75 μ m thick cap. (1 kPa=7.5 mm Hg.)

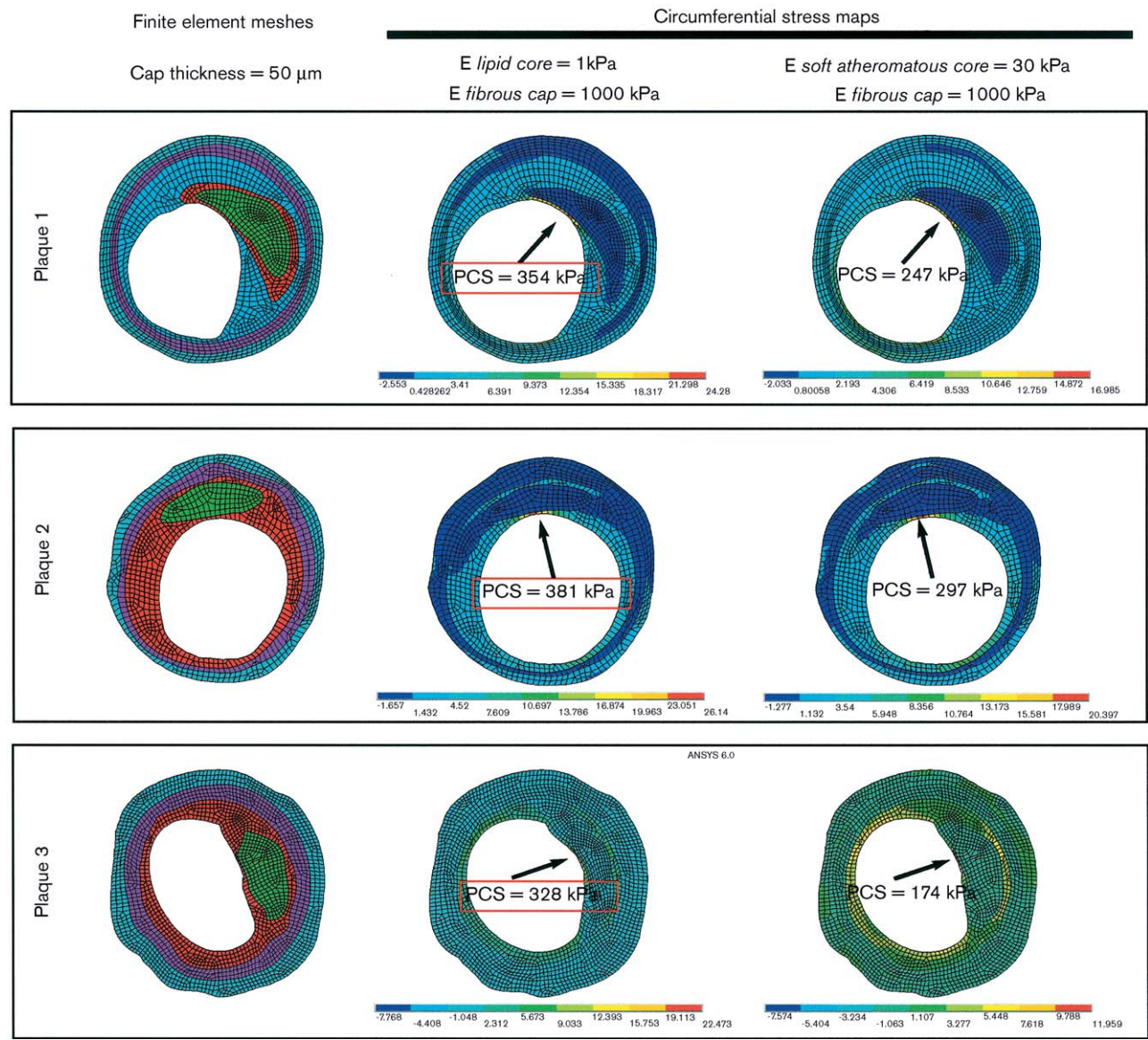
the effect of change in blood pressure on PCS according to CTh and E_{core} . A blood pressure rise from 110 to 150 mm Hg launches the PCS for a vulnerable plaque into a range of instability and rupture defined by a threshold $PCS > 300$ kPa (trigger effect). Conversely, a fall in blood pressure from 110 to 75 mm Hg swings PCS under the instability range (protector effect). Figure 6 recapitulates the impact of increasing the core Young's modulus and reducing the cap Young's modulus on the

circumferential wall stress maps of the three plaques at the same vulnerable CTh of 50 μ m.

Discussion

Simple morphological detection of a thin-cap fibro-atheromatous plaque does not seem to be enough for the prediction of possible future rupture [3,19,20]. In the present study, we looked at three morphologically

Fig. 6



Finite element meshes of the three cap fibro-atheromatous plaques studied, with fibrous cap thickness modeled at 50 μ m, the morphologically critical value characterizing a so-called 'vulnerable' thin-cap fibro-atheromatous plaque. Circumferential stress maps show how increasing the soft atheromatous core Young's modulus (E_{core}) affects peak circumferential stress (PCS). The colorimetric scales give the normalized cap PCS. Arrows show PCSs for blood pressure levels of 14.6 kPa (110 mm Hg). The PCS values framed in red are those above the critical PCS threshold for plaque instability at 300 kPa (see 'Methods' section). Turquoise, adventitia; purple, media; sky blue, cellular fibrosis; red, fibrous cap (dense fibrosis); green, lipid or soft atheromatous core. (1 kPa = 7.5 mm Hg.)

characteristic fibro-lipid plaques [3], for which we varied fibrous cap thickness.

The impact of fibrous cap thickness on PCS is now well known: reducing cap thickness concentrates and increases PCS dramatically in the subintimal structures at the junction of the cap and normal arterial wall [15,21]. We supplemented the previously acquired data by varying fibrous cap thickness from 15 to 230 μm with six experimental points, where Loree *et al.* had varied it from 50 to 500 μm with four experimental points. This gave a curvilinear relationship between CTh and PCS/ P , which our experimental points revealed to be exponential. Equations have been determined. For each of the three fibro-atheromatous plaque geometries studied, there was a threshold fibrous cap thickness zone of between 50 and 62 μm , below which stress values exceeded the stability ranges of the component materials. This 50–62 μm threshold value is in broad agreement with the 65 μm threshold ($\approx \text{mean} + 2\text{SD}$ from $\approx \text{mean} \pm \text{SD} = 23 \pm 19 \mu\text{m}$) or the 66 μm threshold ($\approx \text{mean} + 2\text{SD}$ from $\text{mean} \pm \text{SD} = 34 \pm 16 \mu\text{m}$, on aortic plaques) below which 95% of plaques were found to be ruptured in the pathological studies of Virmani *et al.* [3] and Moreno *et al.* [22] on coronary plaques and aortic plaques, respectively.

Many pathological studies have shown this morphological criterion to be sensitive, but its specificity in contrast is much poorer and it fails to predict rupture correctly [3]. Hangartner *et al.* [19], examining 448 plaques in 54 men presenting stable angina, found that 40% of the plaques showed morphological signs of instability, that is, fibro-atheroma with lipid core and cap. These morphological features may be easily detectable in clinical practice thanks to imaging techniques, but do not seem to be sole determinants of plaque instability [20]. Structural components, such as variation in fibrous cap thickness, variation in core size and composition and variation in inflammatory cell count [23] have been less well quantified.

The present work shows that a change in the composition of the soft atheromatous core significantly affects PCS levels, irrespective of plaque geometry. Furthermore, for a given plaque geometry, PCS varies proportionally with blood pressure. Thus, in the case of a morphologically vulnerable plaque, simple changes in blood pressure can send the plaque from a stable to an unstable range (trigger effect) or vice versa (protector effect) [24,25].

Cheng *et al.* [9] suggested a relative effect of E_{core} variation on PCS, such that a variation in E_{core} of $< 90\%$, that is, from 1 to 0.1 kPa, entails an increase in PCS of more than 26% and a variation in E_{core} of $> 900\%$, that is, from 1 to 9 kPa, entails a decrease in PCS of $> 46\%$. We

quantified these effects precisely and found that the relationship between E_{core} and PCS was exponential. Thus, a change in E_{core} caused large-scale changes in PCS, so that an increase in E_{core} from 1 to 25 kPa brings PCS down below the parietal stress values associated with rupture (significant as of $E_{\text{core}} = 5 \text{ kPa}$).

Coronary plaque instability or stability: a ‘vulnerable’ balance

There have been many studies of structural variation in the fibrous cap and lipid core, both negative (inflammatory processes aggravating plaque vulnerability) and positive (statin treatment enhancing plaque stability) [26]. The exponential variations in PCS with CTh and E_{core} show how very slight structural changes can tilt a vulnerable plaque from stability to instability or vice versa, when triggered by pressure change. Such small changes may either ‘precipitate’ rupture or, conversely, ‘stabilize’ a vulnerable plaque. Swings of this sort are to be observed in the clinical setting, with multiple coronary plaque rupture following acute coronary syndrome [27] or, conversely, a rapid fall-off in the incidence of acute coronary events with statin treatment (during the first few weeks to months of therapy) [28–30].

Potential limitations of the study

The arterial wall and almost all the plaque components (except the lipid core, which has a semi-fluid nature) turn out to have very non-linear elastic behavior, which can be modeled by hyperelastic laws [31]. The use of linear material laws leads to under-estimating rigidity. This may explain the non-convergence of the numerical finite element solution observed in some cases. The use of linear elastic material laws under large strain analysis is acceptable for the simulation of arteries under physiological pressure [9,15,16]. Uncertainty as to the reliability of the rheological parameters used will remain until experimental studies have characterized the tissue of the various coronary plaque components.

In all the FE simulations, static loading conditions were applied. These conditions fail to reproduce the pulsatile nature of physiological blood pressure. Fatigue due to the cyclic loading imposed by blood flow in the arteries was also not taken into account, nor was the time-dependent viscoelastic component of the plaque’s mechanical behavior [16]. By neglecting the viscoelastic properties of the plaque constituents, as well as the dynamic pressure loading imposed by the pulsatile blood flow, we have probably overestimated the local wall strain amplitudes.

Conclusions

The present study reinforces the discriminatory role of vulnerable plaque fibrous cap thickness, providing a mechanical demonstration that, whatever the geometry

and composition of the plaque, CTh $< 60\mu\text{m}$ entails vulnerability. More precisely, (1) the relationship between CTh $-E_{\text{core}}$ and PCS were found to be exponential and (2) the relationship between P and PCS was found to be proportional. These relationships explain why very slight variations in composition or loading are enough to cause large-scale changes in PCS; they also explain why a simple morphological description of thin-cap fibro-atheroma by imaging techniques in clinical practice is not enough in itself to predict probable future rupture and thus guide targeted treatment strategy. On top of any such morphological description, exact knowledge of plaque composition would seem to be essential, underscoring the need for IVUS, magnetic resonance and computed tomography plaque characterization.

References

- Davies MJ. Stability and instability: two faces of coronary atherosclerosis. *Circulation* 1996; **94**:2013–2020.
- Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; **92**:657–671.
- Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lesions from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000; **20**:1262–1275.
- Yamagishi M, Terashima M, Awano K, Kijima M, Nakatani S, Daikoku S, *et al.* Morphology of vulnerable plaque: insights from follow-up patients examined by intravascular ultrasound before and after acute coronary syndrome. *J Am Coll Cardiol* 2000; **35**:106–111.
- Jang IK, Bouma BE, Kang DH, Park SJ, Park SW, Seung KB, *et al.* Visualisation of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. *J Am Coll Cardiol* 2002; **39**:604–609.
- Fayad ZA, Fuster V, Nikolaou K, Becker C. Computed tomography and magnetic resonance imaging for noninvasive coronary angiography and plaque imaging. Current and potential future concepts. *Circulation* 2002; **106**:2026–2034.
- Rabbani R, Topol EJ. Strategies to achieve coronary arterial plaque stabilization. *Cardiovasc Res* 1999; **41**:402–417.
- Farb A, Burke AP, Tang AL, Liang Y, Mannan P, Smialek J, *et al.* Coronary plaque erosion without rupture in lipid core: a frequent cause of coronary thrombosis in sudden coronary death. *Circulation* 1996; **93**:1354–1363.
- Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT. Distribution of circumferential stress in ruptured and stable atherosclerotic lesions: a structural analysis with histopathological correlation. *Circulation* 1993; **87**:1179–1187.
- Lee RT, Loree HM, Cheng GC, Lieberman EH, Jaramillo N, Schoen FJ. Computational structural analysis based on intravascular ultrasound imaging before in vitro angioplasty: prediction of plaque fracture locations. *J Am Coll Cardiol* 1993; **21**:777–782.
- Ohayon J, Teppaz P, Rioufol G, Finet G. In vivo prediction of human coronary plaque rupture location using intravascular ultrasound and finite element method. *Coron Artery Dis* 2001; **12**:655–663.
- Gradius I, Bigelow B, Mahomed Y, Sawada SG, Rieger K, Feigenbaum H. Left anterior descending coronary artery wall thickness measured by high-frequency transthoracic and epicardial echocardiography includes adventitia. *Am J Cardiol* 2003; **91**:27–32.
- Rachev A. Theoretical study of the stress-dependent remodeling on arterial geometry under hypertensive conditions. *J Biomech* 1997; **30**: 819–827.
- Clark JM, Glagov S. Transmural organisation of the arterial media: the lamellar unit revisited. *Arteriosclerosis* 1985; **5**:19–34.
- Loree HM, Kamm RD, Stringfellow RG, Lee RT. Effects of fibrous cap thickness on peak circumferential stress in model atherosclerotic vessels. *Circ Res* 1992; **71**:850–858.
- Lee RT, Grodzinsky AJ, Frank EH, Kamm RD, Schoen FJ. Structure-dependent dynamic mechanical behavior of fibrous caps from human atherosclerotic plaques. *Circulation* 1991; **83**:1764–1770.
- Lendon CL, Davies MJ, Born GV, Richardson PD. Atherosclerotic plaque caps are locally weakened when macrophages density is increased. *Atherosclerosis* 1991; **87**:87–90.
- Huang H, Virmani R, Younis H, Burke AP, Kamm RD, Lee RT. The impact of calcification on the biomechanical stability of atherosclerotic plaques. *Circulation* 2001; **103**:1051–1056.
- Hangartner JRW, Charlston AJ, Davies MJ. Morphological characteristics of clinically significant coronary artery stenosis in stable angina. *Br Heart J* 1986; **56**:501–508.
- Van der Wal AC, Becker AE. Atherosclerotic plaque rupture: pathologic basis of plaque stability and instability. *Cardiovasc Res* 1999; **41**:334–344.
- Richardson PD, Davies MJ, Born GVR. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet* 1989; **2**:941–944.
- Moreno PR, Purushothaman R, Fuster V, O'Connor WN. Intimomedial interface damage and adventitial inflammation is increased beneath disrupted atherosclerosis in the aorta: implications for plaque vulnerability. *Circulation* 2002; **105**:2504–2511.
- Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001; **104**:365–372.
- Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: the lexicon of the new frontier. *J Am Coll Cardiol* 1994; **23**:809–813.
- Burke AP, Farb A, Malcom GT, Liang Y, Smialek JE, Virmani R. Plaque rupture and sudden death related to exertion in men with coronary artery disease. *JAMA* 1999; **281**:921–926.
- Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001; **104**:365–372.
- Rioufol G, Finet G, Ginon I, André-Fouët X, Rossi R, Vialle E, *et al.* Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three vessel IVUS study. *Circulation* 2002; **106**:804–808.
- Aronow HD, Topol EJ, Roe MT, Houghtaling PL, Wolski KE, Lincoff AM, *et al.* Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: an observational study. *Lancet* 2001; **357**:1063–1068.
- Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels. The pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; **286**:64–70.
- Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, *et al.* Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled study. *JAMA* 2001; **285**:1711–1718.
- Vorp DA, Rajagopal KR, Smolinski PJ, Borovetz HS. Identification of elastic properties of homogeneous, orthotropic vascular segments in distension. *J Biomech* 1994; **28**:501–512.