Necrotic core thickness and positive arterial remodeling index: emergent biomechanical factors for evaluating the risk of plaque rupture

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The characteristics of vulnerable coronary plaque have now been well defined in numerous pathological studies (12, 24, 45). Typically, such plaques have a large extracellular necrotic core and a thin fibrous cap (<65 μm) infiltrated by macrophages. Vulnerable atherosclerotic plaque rupture is a recognized major cause of acute coronary syndrome (12, 18). Clinical and biomechanical studies have identified plaque composition and morphology as the key predictors of vulnerability and likelihood of rupture (22, 36). Such vulnerable plaques can be detected clinically by various techniques, including intravascular ultrasound (IVUS) (3, 33), optical coherence tomography (17, 20), computed tomography (9), and magnetic resonance imaging (2). Detecting lesions vulnerable to rupture is a major issue, since it could lead to the development of specific treatment strategies for the prevention of acute thrombotic events (30).

Predicting vulnerable coronary plaque rupture, on the other hand, is still imprecise, as the thickness of the fibrous cap (Cap thickness) alone is not a sufficient predictor of plaque stability (46). For example, Virmani et al. (46), in a series of 200 cases of sudden death, found that, while 60% of acute thrombi resulted from rupture of a thin fibrous atheromatous cap, in 70% of the same patients, there were similar vulnerable-appearing lesions that were found without rupture. Thus thin-cap fibroatheroma do not all have the same likelihood of rupture; other morphological characteristics must be involved, and Virmani et al. (46) emphasized the need for biomechanical studies to help define such relationships.

We hypothesize that our inability to predict plaque rupture based on morphological characteristics of vulnerable plaque may be due to the complexity of the biomechanical interactions. Surprisingly, although Cap thickness is often taken into consideration, geometrical features of the necrotic core remain largely unexplored as clinical morphological indexes of plaque stability or instability. To date, there is no clear indication of the relative necrotic core area (Core area) threshold above which a plaque becomes unstable. The data in the literature show a wide dispersion in the necrotic core areas, even as a percent of the wall area, that is associated with plaque rupture (11, 13, 19, 34). Moreover, this dispersion has not been reduced by the discordant results of the few computational studies analyzing the influence of Core area on coronary plaque stability (16, 22, 38). Although Varnava et al. (43) highlighted a direct correlation between Core area and arterial remodeling index (Remod index), an indicator of plaque growth, the above structural analyses did not take into consideration the positive arterial remodeling process (or expansive remodeling) described by Glagov and colleagues. Thus it still remains unclear how both the plaque growth process and necrotic core size affect thin-cap fibroatheroma peak stress (which is a predictor of rupture) (6, 10, 21, 22, 28).
To understand the evolution of plaque vulnerability during lesion development, we followed an original preclinical approach supported by a large-scale computational analysis based on idealized morphologies that would include the compensatory atherosclerotic arterial enlargement mechanism described by Glagov et al. (14). Such an approach enabled us to investigate the effects of anatomical necrotic core features on peak cap stress (Capstress) at each stage of plaque evolution. Coronary lesion geometries from 24 in vivo IVUS studies were used to test and validate the plaque growth model used in this extensive computational analysis.

**METHODS**

Various idealized cross-sectional plaque morphologies, mimicking different stages and variations in atherosclerotic lesion growth, were designed to investigate the combined effects of necrotic core size and shape, cap thickness, and remodeling index on the stress distribution inside the plaque. A series of patients underwent coronary IVUS, and the extracted plaque geometries were used to evaluate the accuracy of the modeling by comparing the Capstress value predicted by the idealized morphological models with the Capstress value computed using the actual plaque geometry.

**IVUS Study**

**Patient population.** Arteries were explored in a large population of patients (n = 130) referred for percutaneous coronary intervention at the Lyon Cardiology Hospital (Hôpital Cardiologique et Pneumologique de Lyon, Lyon, France) after a first acute coronary syndrome with troponin I elevation. One patient had a vulnerable plaque with two necrotic cores. This patient also had a follow-up IVUS study 10 mo later (34). Investigations were approved by the institutional board of the Hospital Cardiology Department, and the patients were studied only after giving informed consent.

**Intravascular ultrasound imaging.** A dataset of nonruptured plaques with a positive remodeling index was constructed from a systematic IVUS scan of the three principal coronary artery trunks, following the protocol described by Rioufol et al. (33). All patients were examined by IVUS after intracoronary administration of 200 μg of nitroglycerine, to avoid vasospasms. Each plaque was imaged using a manual pullback. For each selected nonruptured plaque, the cross section exhibiting the thinnest fibroatheromatous cap was considered in the succeeding analysis. The IVUS system was a commercially available ultrasound catheter (iLab system with Atlantis SR Pro 3.6F at 40 MHz; Boston Scientific, Watertown, MA).

**IVUS image analysis.** IVUS coronary lesion images were digitized (SAMBA PDB 5.01 software, Grenoble, France) and saved on a computer for image processing. Plaque components were characterized by their IVUS features: 1) highly hypoechogenic components (or anechogenic zones), suggestive of wwwulcerous tissue (lumen or cellular deposition) or 2) homogeneous reflective components (reflectivity lower than or similar to that of the tunica adventititia), suggestive of organized or disorganized fibrosis (7). The two external layers of the arterial wall, media and adventitia, were defined as an anechogenic and a hyperreflective layer, respectively. Manual segmentation using image-processing software (ImageJ; NIH, Bethesda, MD) was performed to extract the contours of each plaque component.

**IVUS measurements and definitions.** Each cross-sectional IVUS image of a lesion was quantitatively analyzed. Measurements were made of the external elastic membrane area (EEMarea, equal to plaque plus media plus lumen areas; EEMarea = Plaarea + Mearea + Luarea, mm²), necrotic Corearea (mm²), Capthick (mm), necrotic core and plaque thicknesses measured at the location of the thin cap (Corethick and Plathick respectively, mm), and necrotic core arc angle (Coreangle, degrees) (see Fig. 1). Relative necrotic core thickness (Corethick/Plathick) was calculated as 100 × Corethick/Plathick; relative intraplaque necrotic core area (Corearea) as 100 × Corearea/Plaarea; plaque burden (Plaburden) as 100 × (Plaarea + Mearea)/EEMarea; degree of stenosis (Stenosdeg) as 100 × (Plaarea + Mearea)/Luarea; and vessel remodeling index (Remodindex) as EEMarea at plaque/EEMarea at reference ("EEMarea at reference" was the total cross-sectional vessel area measured at a nearest segment judged to be free of plaque.)

**Plaque Growth Model and Plaque Morphology Designs**

Glagov et al. (14) found that coronary arteries enlarged in response to lesion growth; atherosclerotic lesion lumen area, on the other hand, remained almost constant until the percentage of stenosis exceeded 40%, which corresponds to a remodeling index of 1.23 (Fig. 1A), and then decreased, resulting in disturbed flow and cardiovascular complications. For the purpose of our structural analysis, we used the...
positive coronary plaque remodeling process reported by Glagov et al. (14). Glagov’s mathematical description of positive arterial remodeling was reformulated so as to model the time evolution of eccentric vulnerable plaques and plaque morphologies (see Appendix).

Thus the geometrical parameters used to define and design the idealized cross-sectional coronary plaque anatomy were as follows: Remodindex, Capthick, Core*thick and Coreangle. (Fig. 1). Realistic morphological diversity in clinical and postmortem data (12, 36, 46) was investigated by varying relative necrotic core thickness (5 ≤ Core*thick ≤ 95, in %), necrotic core arc angle (10 ≤ Coreangle ≤ 180, in degrees), fibroatheromatous cap thickness (0.03 ≤ Capthick ≤ 0.5, in mm), and arterial remodeling index (1.1 ≤ Remodindex ≤ 1.8) (Fig. 1). A total of 5,500 distinct idealized eccentric plaque topologies were used for the computational study.

Structural Analysis

The computational analysis was performed on the large set (5,500) of idealized plaque morphologies and on 24 atherosclerotic lesion geometries acquired by IVUS in vivo. Static finite-element computations were performed using ANSYS 11 software (Ansys, Canonsburg, PA). The various regions of the plaque components were meshed with ~1,300 triangular (six-node) and quadrangular (eight-node) elements. The finite element models were solved under the assumption of plane and finite strains and a systolic pressure of 18.7 kPa (or 140 mmHg).

Material properties. The arterial wall and fibrous plaque were modeled as anisotropic materials (22). The two tissue media were assumed to have the same mechanical properties in the circumferential (θ) and axial (z) directions and different ones in the radial (r) direction (10). Their Young’s modulus values Er, Ez, and Ez (in the r-, θ, and z directions, respectively), Poisson ratios vrv, and vrv, (in the r-θ and r-z planes, respectively), and shear modulus G0 (in the r-θ plane) were taken from the study by Williamson et al. (47) (Table 1). Necrotic medium was modeled as a virtually incompressible and very soft isotropic solid, with a Poisson ratio and Young’s modulus of 0.49 and 1 kPa, respectively (47). To evaluate the sensitivity of Capstress to the geometric properties of the arterial wall, additional computations were performed by varying the arterial Young’s moduli Er, Ez, and Ez.

Critical plaque rupture value. In vitro experiments have shown that human atherosclerotic materials generally fracture under a threshold stress close to 300 kPa (2,250 mmHg) (6, 15). Therefore, an ultimate tensile stress threshold of 300 kPa was used in this study for the transition from plaque stability to instability. The degree of plaque vulnerability was directly correlated to the Capstress value.

Statistical Analysis

The correlations between Capstress and all considered morphological plaque features were analyzed by multiple linear regression using a commercially available software package (SigmaStat 3.5; Systat Software, Point Richmond, CA). Regressions with probability values P < 0.005 were considered statistically significant.

Table 1. Material constants used in the structural analysis

<table>
<thead>
<tr>
<th>Material</th>
<th>Young’s Moduli, kPa</th>
<th>Poisson Ratios</th>
<th>G0, kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
<td>E_r = 100</td>
<td>v_r = 0.10</td>
<td>G0 = 52</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>E_r = 115.6, E_z = 2312</td>
<td>v_r = 0.07, v_z = 0.27</td>
<td>G0 = 1175</td>
</tr>
<tr>
<td>Necrotic core</td>
<td>Isotropic medium</td>
<td>v = 0.49</td>
<td></td>
</tr>
</tbody>
</table>

The subscripts r, θ, and z denote radial, circumferential, and axial directions, respectively; G, shear modulus.

RESULTS

IVUS Study

Twenty-four nonruptured plaques with positive remodeling indexes were found after the extensive IVUS scanning. Distinct and multiple ruptured vulnerable plaques were observed in each patient referred for percutaneous coronary intervention, but nonruptured plaques were found in only 24 of the studies. Thus each cross-sectional IVUS image selected for this study resulted from a different nonruptured plaque. Table 2 summarizes the geometrical features of the 24 plaques acquired by IVUS in vivo. All had similar Plaburden (mean = 72.06 ± 9.63%), Remodindex (mean = 1.34 ± 0.14%), and Core*thick (mean = 49.41 ± 15.50%) values.

Atherosclerotic Vessel-Growth Model Performance

Two distinct structural computations were performed for each patient. Capstress was assessed using both the real IVUS-determined geometry and the associated idealized geometry (Fig. 2A). Linear regression analysis and Bland-Altman plots revealed good agreement between the two values (Fig. 2B and C), indicating that the idealized model mimicked real plaque performance reasonably well. (For the purposes of this model validation, Capthick was arbitrarily assigned a value of ≈80 μm when found to be below the 90-μm IVUS resolution limit.)

Correlation Between Peak Cap Stress and Anatomical Necrotic Core Features

Statistical analyses were performed both to highlight the best linear correlations existing between Capstress value and morphological plaque features and to predict Capstress value accurately from the independent geometrical variables.

IVUS study. Approximately 70% of the IVUS population had similar Remodindex and Core*thick values (see Table 2) so that statistical analysis failed to disclose any influence on plaque stability by Remodindex values lower than ~1.2 or by extreme Core*thick values (i.e., < 0.3 or > 0.7). In this population, plaques were only effectively differentiated by Capthick measurements so that a single power law closely fit the full set of simulated Capstress-Capthick points for all patients (Fig. 3).

Model study. Idealization of plaque morphology during the growth process was the only simple way to create a significant dataset of characteristic plaque geometries on which a complete statistical analysis could be performed. We therefore took advantage of the extensive simulations performed on the idealized but morphologically varied plaque-growth geometries (n = 5,500) to investigate correlations between Capstress value and the geometrical variables Capthick, Core*thick, Corearea, and Coreangle. The best Capstress predictions were obtained by multiple linear regression on groups of constant Remodindex and Capthick for two independent variables Core*thick and Coreangle (mean r^2 = 0.92 ± 0.07 and P < 0.001). However, knowledge of Core*thick alone seemed sufficient to predict Capstress value reasonably well for such groups (P < 0.001 and mean r^2 = 0.81 ± 0.08).

Influence of Necrotic Core*thick on Plaque Vulnerability

Interestingly, Core*thick appears to be the emergent morphological parameter that is a key determinant of peak cap stress. Figure 4A clearly illustrates this finding in the group of plaques...
with Capthick = 0.085 mm and Remodindex = 1.30. Varying Corethick by a factor of three while keeping Coreangle constant significantly increased the Capstress value by 72% (Fig. 4B). On the other hand, Fig. 4C shows that keeping Corethick constant while tripling Coreangle had no significant effect (close to 3%) on Capstress. This figure also shows how peak cap stress, quantified for the group of plaques with the same remodeling index and cap thickness, depends on the relative necrotic core thickness.

**Nonuniqueness of Critical Capthick Value**

Critical Capthick was defined as the value of Capthick at which Capstress reached the critical tensile stress of 300 kPa, which may cause the thin cap to rupture. Below but near this critical Capthick, coronary plaque may be considered as biomechanically vulnerable and at high risk of rupture. Our computational results showed that the critical Capthick was nonunique but depended mainly on Corethick and Remodindex (Fig. 5). We found that the likelihood of plaque rupturing is higher for coronary plaques with small Remodindex and large Corethick. Indeed, such plaque morphologies have the highest critical cap thickness values. Hence, with regard to other plaque morphologies, such young lesions appear to be more vulnerable and likely to rupture because their peak cap stress was found to be significantly larger than the critical stress of 300 kPa even, with a cap thickness greater than the standard clinical rupture threshold of close to 65 μm. Thus, the results presented in Fig. 5 could also be interpreted with regard to the probability of plaque rupture relative to the cap thickness: plaques with a cap thickness substantially larger than 65 μm can have a high probability of rupturing if the remodeling index is low and the necrotic core thickness is high.

**Combined Effects of Remodeling and Necrotic Corethick on Plaque Vulnerability**

Coronary plaques with small Remodindex and Corethick greater than approximately one-half of the Plaithick (i.e., when Corethick > 50%) were found to be the most liable to rupture, since they had the highest critical Capthick thresholds (Fig. 5). In contrast, plaques with low Corethick and small Remodindex appeared to be the least prone to rupture (Fig. 5). The effects of Corethick on Capstress value also depended on the magnitude of Remodindex: an increase in Corethick during early stage coronary disease, when the remodeling index is smaller, dramatically increases the Capstress value (Fig. 6).

**Sensitivity of Peak Capstress to the Material Properties of the Arterial Wall**

The sensitivity of Capstress to changes in the radial (E_r), circumferential (E_θ), and axial (E_z) Young’s moduli of the arterial wall was investigated. These computations were performed by varying the initial values of the Young’s moduli (E_r = 10 kPa, E_θ = 100 kPa, and E_z = 100 kPa) from −50 to +100%. The maximal absolute relative Capstress variations were evaluated with regard to the control simulations performed with the initial mechanical properties. This sensitivity study was done on two series of vulnerable plaque morphologies (i.e., Remodindex = 1.10 and 1.45) with the same Corethick and Coreangle values of 50% and 120°, respectively. A nonsig-
significant Capstress variation (<5%) was found when material parameters were varied over the ranges considered, indicating that such variations do not affect the principal conclusions of this study.

Clinical Relevance

A follow-up study performed on the patient with a vulnerable lesion comprised of two necrotic cores (Fig. 7, A and B) exemplifies how such clinical morphological indexes may help to quantify the degree of coronary plaque stability. After the initial study (10 mo), IVUS examination of the same patient and the same lesion with a Remodindex = 1.40 revealed a fissured cap (Fig. 7, C and D). Interestingly, the Cap thick values of the two necrotic cores were similar (close to 0.090 mm), and the two necrotic core shapes differed only in Core thick and Core angle, which were 57° and 79° for the first and 24° and 31° for the second. The Capstress value at the fibrous cap of the thicker necrotic core was higher than in the thinner one, and peak stress location perfectly matched the actual site of rupture (Fig. 7).

DISCUSSION

Quantifying the mechanical stress in the wall of a pathological artery, and more specifically in the fibrous cap, is a crucial step in predicting the risk of plaque rupture based on biomechanical features. Necrotic core size and remodeling index have historically been viewed as among the factors that are determinants of plaque vulnerability (1, 2), but no study hitherto seemed able to explain clearly their impact on plaque stability/instability. The present study, based on a combined clinical and computational approach, investigated the biomechanical interaction between necrotic core size and shape, cap thickness, and remodeling index in coronary plaque. We included the positive coronary remodeling process described by Glagov et al. (14) in this biomechanical study on plaque vulnerability. To the best of our knowledge, this is the first study to take such an approach.

Two important questions are addressed by this investigation: 1) How do the geometrical features of the necrotic core affect Capstress value and concomitantly the degree of plaque stability? and 2) What are the key morphologic determinants of plaque instability that might be routinely measured?

Is There a Single Critical Necrotic Core Area Value?

The present study demonstrated that knowing Core area was not sufficient for predicting plaque rupture. Indeed it is possi-
ble to double Core area without significantly affecting the Capstress value. This could be done by simply modifying Core angle alone, keeping all other geometrical plaque parameters constant (Fig. 4C). Thus Core angle has a limited effect on Capstress. Interestingly, these results could explain the wide dispersion found in the literature for critical Core area values above which the atherosclerotic lesion becomes unstable, from 10–20% to >40% (11, 13, 19, 34). This illustrates why it is difficult to use Core area as a predictive parameter clinically.

Necrotic Core Thickness, an Emergent Factor for Predicting Plaque Vulnerability

Necrotic core thickness, rather than area or angle, has emerged from this study as a parameter that is critical to overall plaque stability. To date, few computational studies have been performed to investigate specifically the effect of necrotic core size on plaque stress distribution. Loree et al. (22) and Tang et al. (38) used a small number of distinct models (n = 6 and n = 3, respectively), to investigate the effect of Core thick on plaque stress distribution. However, the arterial remodeling process described by Glagov was not taken into consideration in their structural analyses. Additionally, with their design, decreasing Core thick was associated with an increase in Cap thick. They concluded that the smaller necrotic core model significantly lowered Cap stress, but it is difficult to distinguish whether this drop in Cap stress resulted from the increase in Cap thick or from the decrease in Core thick. More recently, in their elegant three-dimensional structural analysis of concentric lesions, Imoto et al. (16) found that the size of the necrotic core had no influence on the Cap stress value. Their model is relevant to concentric plaques, but their conclusions are not generalizable to eccentric human coronary lesions with necrotic cores, which are the focus of the present study. Our results clearly indicate that it is crucial to consider Core thick to estimate the vulnerability of eccentric coronary plaques. Subject to further studies, this result could explain why 70% of coronary lesions with thin caps were not observed to have ruptured in the investigative review by Virmani et al. (46).
It is now known that more than one-half of myocardial infarctions originate in vessels with relatively small stenosis (i.e., Stenosdeg < 50%) (12, 18, 43). Lee’s group (22), in their structural analysis, explored the influence of Stenosdeg. However, in their models, increasing Stenosdeg induced an increase in Capthick, which in turn reduced the stress in the fibrous cap. Moreover, their analyses were restricted to high values of arterial stenosis (i.e., 70% < Stenosdeg < 99%), which correspond to arterial remodeling indexes >1.6 in Fig. 5. In this range of stenosis, results have shown a limited influence of the necrotic core thickness (Fig. 5). Thus no conclusions about the plaque stability at the early stages of the arterial remodeling process could be inferred from their study. We therefore investigated the effect of Stenosdeg alone on plaque stability by considering the arterial remodeling process that occurs in response to plaque growth. Interestingly, among all plaque topologies with high Stenosdeg, those with a large relative Corethick and small Stenosdeg were found to be more liable to rupture. This finding may explain, on the one hand, the progression and growth of clinically silent lesions and, on the other, why plaques with relatively small stenoses have been observed to frequently rupture.

**Risk of Plaque Rupture and Plaque Growth**

It is now known that more than one-half of myocardial infarctions originate in vessels with relatively small stenosis (i.e., Stenosdeg < 50%) (12, 18, 43). Lee’s group (22), in their structural analysis, explored the influence of Stenosdeg. However, in their models, increasing Stenosdeg induced an increase in Capthick, which in turn reduced the stress in the fibrous cap. Moreover, their analyses were restricted to high values of arterial stenosis (i.e., 70% < Stenosdeg < 99%), which correspond to arterial remodeling indexes >1.6 in Fig. 5. In this range of stenosis, results have shown a limited influence of the necrotic core thickness (Fig. 5). Thus no conclusions about the plaque stability at the early stages of the arterial remodeling process could be inferred from their study. We therefore investigated the effect of Stenosdeg alone on plaque stability by considering the arterial remodeling process that occurs in response to plaque growth. Interestingly, among all plaque topologies with high Stenosdeg, those with a large relative Corethick and small Stenosdeg were found to be more liable to rupture. This finding may explain, on the one hand, the progression and growth of clinically silent lesions (24) and agrees with Varnava et al.’s findings (43) that plaque rupture often occurs at sites with relatively small luminal stenosis.

**Plane Strain Assumption and Peak Cap Stress Value**

To take full advantage of the arterial remodeling process described by Glagov et al. (14), the atheromatous plaque is considered as a three-dimensional structure, but under a plane strain condition. This assumption is reasonable insofar as 1) plaque length is large with regard to the radial dimension, and 2) neighboring cross-sectional morphologies remain similar (27). However, to overcome the limitations entailed by the plane strain assumption, two additional and more realistic three-dimensional plaque geometries were considered, slightly modifying the three-dimensional “plane strain” model (data not shown). In the first one, cap thickness varied while necrotic core thickness and plaque length remained constant. In the second case, cap thickness was kept constant while necrotic core thickness varied. Capstress values were then computed within the plaque cross section where the cap thickness was the thinnest (first case) or where the necrotic core thickness was the largest (second case). For these models, material properties were as in the plane strain simulations. Interestingly, we found that the variation in Capstress values computed with or without the plane strain assumption did not exceed 25%. Moreover, additional computations performed with these two models (data not shown) confirmed the results obtained with the present model: namely, the larger the necrotic core and the smaller the cap thickness, the greater the peak cap stress. Thus the change in stress values accompanying more accurate spatial modeling of cap and necrotic core thickness along the length of the plaque would not significantly affect the main conclusions of our study that are based on stress values at the thinnest cap site.

![Fig. 5. Three-dimensional plot highlighting the influences of remodeling index and relative necrotic core thickness on critical cap thickness. The critical cap thickness is defined as the value at which cap stress reaches the critical or rupture point tensile stress. This result shows that there is no single such threshold, which rather depends strongly on remodeling index and relative necrotic core thickness. More interestingly, plaques with low remodeling index and a large relative necrotic core thickness can be seen to be more prone to rupture, with a high critical cap thickness. This finding may explain, on the one hand, the progression and growth of clinically silent lesions and, on the other, why plaques with relatively small stenoses have been observed to frequently rupture.](http://ajpheart.physiology.org/)

![Fig. 6. Combined effects of remodeling index and relative necrotic core thickness on the relationship between cap thickness and peak cap stress. Results are given for remodeling index = 1.1 (A), 1.45 (B), and 1.8 (C). The most significant effects were observed for plaques with relatively small stenosis (i.e., for small remodeling index), where increasing the necrotic core thickness dramatically increases the peak cap stress. This seems to indicate that such young plaques may rapidly shift from stable to unstable domains and thus become more vulnerable and likely to rupture.](http://ajpheart.physiology.org/)
Structural Analysis and Accuracy of the IVUS Images

Measuring cap thickness is difficult. Sometimes this is impossible (such cases are specified in Table 2) when it is below the resolution of the IVUS technique, i.e., <90 μm for scans obtained with an ultrasound catheter of 40 MHz. However, it is precisely one of the added values of our conclusions that they do not depend on the accuracy of the IVUS measurements. Indeed, the nonruptured plaque geometries acquired by IVUS were used only to assess the accuracy of the Capstress value predicted by the associated idealized morphological models. This prerequisite being satisfied, the critical morphological factors identified from our computational analysis emerged from the significant correlations found between accurately tunable geometrical parameters, characterizing the idealized cross-section morphologies, and the corresponding computed Capstress. It is the combination of such modeling-based results with very high-resolution intravascular techniques, such as optical coherence tomography (OCT), which will be essential for identifying vulnerable plaque based on lesion detection and morphological features.

Study Limitations

Several limitations deserve to be pointed out, even if the results include findings that may help to increase our understanding of critical biomechanical factors leading to plaque rupture.

Limitation 1. We restricted our study to the risk of rupture in vulnerable plaques with positive remodeling indexes in light of the following arguments. First, the majority of clinical cases involve vulnerable plaques with expansive remodeling (4, 44). Second, plaques with constrictive remodeling appear to be more stable than those with expansive remodeling (4, 29). Finally, it remains unclear how a large data base, similar to the one considered here but dedicated to vulnerable plaques with constrictive remodeling, could be generated. Indeed, to the best of our knowledge, we still lack experimentally founded phenomenological laws similar to those proposed by Glagov and colleagues (14), which could be used to model constrictive arterial remodeling. However, plaques associated with constrictive remodeling clearly deserve to be investigated in future work.

Limitation 2. The clinical case presented in this study (Fig. 7) is relevant but not sufficient to broadly validate our computational findings in patients. This should, however, be seen in the light of our aim, which was to perform a large-scale computational analysis to extract the critical morphological parameters that indicate plaque vulnerability and the likelihood of rupture. However, our findings are already supported by some clinical observations showing that atherosclerotic lesions are more prone to rupture during the early stages of positive remodeling (43).

Limitation 3. At this stage, we model the arterial wall as a monolayer, and our growth model considers fixed material features without taking into account dynamic processes such as the modulation of cell dynamics and enzymatic activity by mechanical processes that may modify the elastic properties of the plaque. Several papers reported that such processes significantly contribute to the formation and stability of vulnerable plaque (25). However, to our knowledge, variation in material properties with increasing stenosis stage has not been reported.
Therefore, changes in atherosclerosis were only considered here in terms of variation in plaque morphology.

Limitation 4. This structural analysis fails to reproduce the pulsatile nature of physiological blood pressure. Thus the fluid-structure interaction effects resulting from such cyclic loading (4, 5, 38, 39) were not considered, nor were the nonlinear mechanical properties of the arterial wall, which have been well described in the elegant experimental and theoretical work by Holzapfel et al. (15). The choice of a linear constitutive law was mainly based on the absence of significant peak cap stress sensitivity to arterial wall material parameters. Regarding the first point, it is noteworthy that, in their remarkable fluid-structure interaction model, Tang et al. (39) found a quasilinear relationship between peak cap stress and blood pressure amplitude.

Limitation 5. The influence of residual stresses (23, 26, 31, 32, 42), generated by remodeling and plaque growth processes, has been ignored in this study. Residual stress patterns have been studied ex vivo in several human vulnerable coronary plaque samples (26). It was found that neglecting residual stress in structural analysis could overestimate the stress amplitude in the thin fibrous cap, while taking it into account would not shift peak stress location within the cap (26). However, residual stress may mainly cause the rupture-threshold stress to be overestimated. Additional simulations showed that a decrease in the critical stress value will make plaques more sensitive to rupture but will not affect the sensitivity of identified emergent factors to peak cap stress.

Clinical Implications

Although several additional processes are known to be involved in the plaque rupture mechanism, including plaque erosion (12), shear stress (4, 5, 24, 37), tissue degradation due to macrophages (12, 24), and biological processes involved in the inflammatory reaction (1, 12, 25, 35, 40, 41), the present biomechanical study suggests that 1) the use of additional high-resolution (<65 µm) techniques for lesion detection and plaque morphology definition remains crucial for a better diagnosis of plaque vulnerability, and 2) plaque rupture is to be viewed as a consequence not of cap thickness alone but rather a combination of arterial remodeling index, fibroatheromatous cap thickness, and necrotic core thickness effects. Thus, subject to further study, arterial remodeling index and necrotic core thickness may be new prognostic factors for assessing plaque rupture and, more generally, key elements in improving our understanding of how anatomical factors determine the biomechanical stability of eccentric coronary plaques with necrotic cores.

APPENDIX

Plaque-Growth Model and Idealized Plaque Morphology Designs

The cross-sectional vulnerable plaque geometries used for this computational study were based on anatomical observations (12, 36, 46). Therefore, a generic arterial cross section with an eccentric plaque, a circular lumen, and a blunt crescent-shaped necrotic core was chosen as the baseline anatomy. Next, the possible relevant anatomical diversity resulting from positive arterial remodeling was generated by continuously varying the size of the blunt crescent-shaped necrotic core and the cross-sectional sizes of the lumen and artery areas. In the plaque-growth model, the degree of arterial stenosis (Stenosisdeg) reflects the morphological evolution of the plaque over time as remodeling takes place. Fourteen successive stages (n = 14) of vulnerable plaque evolution were simulated in this structural analysis by increasing the Stenosisdeg value from 25 to 90% by increments of 5%. The equations used to model eccentric plaque growth were supported by the quantitative descriptions of the expansive arterial remodeling given by Glagov et al. (14). From their work, an original relationship was first derived, describing the change in lumen area (Luarea) according to Stenosisdeg (in %). To this first equation we then coupled the famous relationship proposed by Glagov and colleagues (14) to express the strong correlation between cross-sectional plaque area (Plaarea in mm²) and Luarea (in mm²). Our plaque-growth model equations then read:

\[
Lu_{area} = 13.125 \left( \frac{Stenos_{deg} - 100}{0.583 Stenos_{deg} - 100} \right)
\]

(1)

\[
Pla_{area} = -2.398 Lu_{area} + 31.475
\]

(2)

For each degree of increasing arterial stenosis considered during plaque growth, we first computed the Luarea value from Eq. 1 and then derived the Plaarea value using Eq. 2. As a geometrical constraint, we furthermore assumed that the luminal and external contours were circular, sharing one common tangential point in the region of contact with the healthy arc of the artery (Fig. 1A). Finally, the arterial wall was modeled as a circular 0.3-mm-thick tunica (Fig. 1A). Interestingly, this mathematical description of expansive plaque remodeling (Eqs. 1 and 2) may be reformulated so as to derive a direct relationship between Stenosisdeg and the remodeling index.

Another geometrical factor to deal with is the variability of the necrotic core size. The necrotic core shape was bounded by an internal circular contour; the external contour was designed to maintain a constant relative radial gap between arterial wall and necrotic core, the two contours being delineated with respect to the lumen center O. The two ends of the necrotic core were drawn assuming a parabolic shape. Because the size of the necrotic core may not be correlated to the degree of arterial stenosis, we decided to unfold the 14 idealized plaque/lumen cross sections, mimicking plaque evolution by inserting a rather large number of topologically admissible blunt crescent-shaped necrotic cores (mean no. of shapes n = 393) (Fig. 1B). Thus the data base of 5,500 distinct idealized eccentric plaque topologies generated for this study largely originates from the major observations and phenomenological laws proposed by Glagov et al. (14).

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