Morphological and biomechanical aspects of vulnerable coronary plaque

Summary

Vulnerable plaque morphology has been described by gross pathology and intravascular ultrasound, but morphological criteria cannot fully explain vulnerability, which involves four distinct factors: 1) inflammatory and biological processes; 2) geometry; 3) composition; and 4) hemodynamic stress. These last three aspects underlie the biomechanical study of vulnerable plaque.

By virtue of the nature of their evolution, atherosclerotic plaques tend to be excentric, and this is a crucial morphological feature, causing circumferential stress to peak in very specific juxta-luminal locations, where it can exceed the rupture threshold of collagen, the basic constituent of arterial architecture.

The lipido-necrotic core covered by a fibrous cap, formed in young plaques, is another morphological feature, which, can also increase and concentrate circumferential stress in the juxta-luminal fibrous cap. The larger the lipid core, the thinner the fibrous cap and the greater is the stress. There are also inflammatory processes in such areas, which tend to reduce cap thickness. Ruptures occur when this thickness falls below 65 microns. Heart rate, blood pressure and pulse pressure are all biomechanical factors affecting vulnerable arterial walls, increasing circumferential stress and material fatigue.

Vulnerable plaques are almost always associated with positive arterial remodeling. Numerical simulation has shown such so-called compensatory remodeling to be exclusively due to the healthy arc stretching in vulnerable plaques. Positive remodeling is optimal when the healthy arc is around 170°, which keeps the lumen area relatively stable as long as the plaque does not exceed 40% to 50%. This mechanism does not apply to concentric plaques.

In conclusion, the mechanism of vulnerable plaque rupture is highly complex and multifactorial. This complexity more or less precludes prediction in individual cases: we are in the realms of chaos theory and acute sensitivity to initial conditions. The greatest caution is therefore required in any attempt to predict rupture from diagnostic imagery, which provides only morphological data on plaque’s nature.

Résumé

Aspects morphologiques et biomécaniques de la plaque coronaire vulnérable

La morphologie de la plaque vulnérable a été décrite par l’anatomopathologie et l’échographie intra-vasculaire, mais les critères morphologiques ne peuvent à eux seuls expliquer la vulnérabilité qui implique en fait quatre 4 facteurs distincts: 1) les processus inflammatoires et biologiques ; 2) la géométrie ; 3) la composition de la plaque ; et 4) les contraintes hémodynamiques. Ces trois derniers aspects sous-tendent à l’étude biomécanique de la plaque vulnérable.

Comptez tenu de la nature de leur évolution, les plaques athéromateuses tendent à être excentriques, ce qui est un trait morphologique crucial, responsable de contraintes circonférentielles aux localisations spécifiques juxta-luminales, pouvant dépasser le seuil de rupture du collagène, un constituant élémentaire de l’architecture vasculaire.

Le noyau lipido-nécrétique couvert par la chape fibreuse formée dans la plaque jeune est un autre trait morphologique qui peut aussi augmenter et concentrer les contraintes circonférentielles de la chape fibreuse justa-luminaire. Le noyau lipide est volumineux, plus la chape fibreuse est fine, et plus la contrainte est importante. Il faut aussi ajouter les processus inflammatoires de ces zones qui tendent à réduire l’épaisseur de la chape. La rupture survient lorsque cette épaisseur passe au-dessous des 65 microns. La fréquence cardiaque, la tension artérielle et la pression pulsée sont toutes des facteurs biomécaniques affectant la vulnérabilité des parois artérielles, en augmentant les contraintes circonférentielles et l’usure des matériaux.
A 'vulnerable' atherosclerotic coronary plaque refers to the risk of sudden structural alteration, drawing special attention. Such an event takes either the form of a rupture of the fibrous cap (about 70% of cases) or of the endothelial erosion (about 30% of cases) [1]. These changes in plaque structure may lead to thrombotic processes of diverse clinical expression [2]. The subsequent clinical atherothrombotic events correspond to acute coronary syndrome.

How do such events occur in the evolution of an atheromatous plaque?

This is where combining morphological, biomechanical and biological analyses are necessary. The morphological and biomechanical aspects of vulnerable plaques join in complex interactions requiring to be spelled out in details prior to any scientific development.

Four factors act in concert: inflammatory and biological processes within the plaque, plaque geometry, plaque composition, and hemodynamic stress. Geometry, composition and hemodynamic stress triangulate the biomechanical analysis of vulnerable plaque, although geometry and composition are obviously closely related to the inflammatory processes within the atheromatous plaque (fig. 1).

The principles of biomechanical analysis of a vulnerable plaque

Parietal stress is defined as force acting upon arterial tissue. Deformation is defined as tissue displacement under such stress. Arterial wall properties are defined by the relations between stress and strain, described by the elasticity (or Young's) modulus and the compressibility (or Poisson's) modulus. The structure and geometry of a plaque are complex, and its mechanical behavior cannot be reduced to any simple mechanical law such as that of Laplace. Laplace's law applies schematically only to perfect axi-symmetric thin-walled cylinders – and an atheromatous coronary plaque is quite the opposite of that. Much more sophisticated methods of analysis are therefore needed: a biomechanical approach must enlist the finite elements method, which enables sophisticated and relevant numerical simulation [3, 4].

The spatial organization of the plaque components (collagen, elastin, cells, cholesterol crystals, calcification, lipids, etc.) will significantly impact the biomechanical behavior.

Underlying arterial biomechanics

Understanding the biomechanical behavior of a normal or a pathological artery means understanding its three physical states (fig. 2).

a) The loaded physiological state. This is the physiological state classically observed in vivo, with the artery subject to systolic and diastolic pressures.

b) The unloaded physiological state. This is the state, with the artery under zero endoluminal pressure, observed by pathologists. Mechanical models are drawn up on the basis of the geometry and composition of the arterial wall in this state. The artery is then put under physiological pressure to reveal the presence and pattern of parietal stress. We have developed an approach, which is more or less equivalent in all points except resolution, using 40 MHz high-resolution intravascular ultrasound scanning (IVUS) (90 mm axial resolution).

c) The zero-stress state. Even in absence of arterial pressure, stress is still at work within the arterial wall. This is known as residual stress, and results from
Biomechanical arterial wall analysis criteria (fig. 3)

Biomechanical analysis maps radial and circumferential stress and shearing [5]. The more or less circular arrangement of the cell structures and collagen matrix means that circumferential stress sheds the best light on the stress endured by the components. Shearing patterns are also indicative of how tissues are interacting. Alongside stress maps, deformation maps show the patterns of strain acting on the artery [6].

Impact of plaque geometry

Atherosclerotic plaques mainly occur and grow around bifurcations, where turbulence arises opposite the carina. Plaques thus tend to have an excentric development. This geometrical pattern of a crescent-shaped excentric plaque with a healthy arc is one of the main anatomic features of plaques, and has significant mechanical implications, concentrating circumferential stress and shearing in locations on the border between the plaque and the healthy arc (fig. 3) [7].

Impact of the lipid core and fibrous cap (fig. 4 and 5)

Fibrous cap thickness is a crucial biomechanical vulnerability factor [8] irrespective of the severity of stenosis [9]. The cap thickness value of around 60 μm, which the present study found to be critical for transition from stability to instability, is in broad agreement with the 65 μm threshold (≈ mean + 2SD from mean...
FIG. 4: Curvilinear relation between vulnerable plaque cap thickness and peak circumferential stress. Cap thickness below a critical value of 60 μm causes stress levels exceeding 300 kPa, the rupture threshold for collagen fibers. FIG. 4: Relation curvilinéaire entre l’épaisseur de la chape de la plaque vulnérable et la contrainte circonférentielle maximale. Une épaisseur de chape au-dessous du seuil critique de 60 μm est responsable d’un niveau de contraintes dépassant les 300 kPa, correspondant au seuil de rupture des fibres de collagène.

Fig. 5 – Curvilinear relation between the Young’s (elasticity) modulus of the lipid-necrotic core and peak circumferential stress in three vulnerable plaques. With a purely lipid core (Young’s modulus = 1 kPa), the three plaques show peak stress levels in excess of 300 kPa. Very slight reductions in elasticity, corresponding to slight changes in lipid-necrotic core composition, quickly and significantly reduce peak stress below the 300 kPa collagen rupture threshold. I.e., slight changes in lipid-necrotic core composition are enough to stabilize an initially vulnerable plaque by dramatically reducing peak stress. FIG. 5 – Relation curvilinéaire entre le module d’élasticité de Young du noyau lipid-noécrotique et la contrainte circonférentielle maximale de 3 plaques vulnérables. Avec un noyau purement lipidique (module de Young = 1 kPa), les 3 plaques montrent des contraintes maximales dépassant les 300 kPa. De légères réductions de l’élasticité, correspondant à de légères modifications de la composition du noyau lipid-noécrotique réduisent rapidement et significativement la contrainte maximale au-dessous du seuil des 300 kPa correspondant à celui de la rupture du collagène. Ainsi, de légères modifications de la composition du noyau lipid-noécrotique stabilisent une plaque initialement vulnérable, en réduisant de manière importante la contrainte maximale.

± SD = 23 ± 19 μm) below which 95% of plaques were found ruptured on pathology analysis in Virmani, et al.'s [10] study. Our present biomechanical data bear out these characteristic values.

The consistency of the gruel composing the core depends on its lipid composition [11]. Lipids in the form of cholesterol esters (liquid and mobile) soften plaques whereas crystalline cholesterol (solid and inert) has the opposite effect [12]. In numerical models [13, 9], the lipid core is assimilated to a very soft incompressible solid with a 1 kPa Young's modulus, offering no resistance to stretching. It is under this homogeneous and simplified core condition that peak circumferential stress (PCS) is maximal for a given geometry and loading. In other terms, the data relating to critical cap thickness are utterly dependent on highly heterogeneous cores rheology. This is probably how pathologists come to observe a wide range of cap thickness and lipid or soft atheroma core sizes without associated plaque rupture [14].

Impact of residual stress (fig. 6)

Vulnerable plaque instability is considered as the result of a subtle balance between intraplaque residual stress and external loading. In the diseased arteries studied here, the thin cap showed an attenuation mechanism similar to that found in normal arteries. Loading always tends to reduce internal stress/strain. Unlike in normal arteries, however, this attenuation was sub-optimal, intraplaque stress/strain remaining high even under physiological loading.

Thus, a subtle balance exists between residual stress/strain (RS/S) and the stress induced by blood pressure. Closing the artery compresses the lipid core, which reacts and generates high RS/S by pushing against the more compliant regions of the thin fibrous cap. In contrast, blood pressure tends to extend the luminal layers and induce an opposing stress, decreasing the ultimate stress within the thin cap. Thus, this study shows that plaque rupture must not be viewed as a consequence of endoluminal pressure alone, but rather as the result of a subtle combination of endoluminal loading and intraplaque RS/S. Moreover, the intraplaque RS/S may also affect the morphogenesis of the microvascular network within the plaque and, thus, plaque stability [15, 16].

Residual stress/strain present in a vulnerable coronary plaque influences dramatically the stress pattern and spotlights some new sites of stress concentration. RS/S may play a major role in the biomechanical stability of vulnerable coronary plaque and in the lipid core growth process. Additionally, this study showed that plaque rupture has not to be considered as a consequence of external pressure alone, but rather of a subtle combination of external loading and intraplaque RS/S.

Impact of pressure variation

For a given fibrous cap thickness, the normalized cap peak circumferential stress (PCS) stayed almost constant for pressure (P) values in the physiological
range (6 to 20 kPa). Above this range, the results showed that geometric non-linearity (the geometric complexity of the structure) was of negligible impact. This means that there is an almost linear relation 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.

PCS is proportional to plaque loading. Changes in blood pressure can tilt a plaque from stability into instability and rupture. Many triggers for sudden coronary events have been identified clinically and pathologically: exertion [17], vigorous exertion [18], anger and wake-up [19], and fear. What these all have in common is sympathetic neurohormonal activation responsible for hemodynamic changes, which can rupture vulnerable atherosclerotic plaque [20]. A drop of about 5-6 mmHg diastolic blood pressure is enough to obtain a significant decrease in vascular mortality [21].

**Study of the mechanism of positive remodeling**

Positive arterial remodeling was first described by Glagov, et al. [22], who differentiated two aspects: arterial widening (the more the plaque grows, the wider the artery becomes), and an associated compensatory mechanism that more or less conserves lumen area as long as the plaque does not exceed 30% to 40% of the total arterial area. In Varnana, et al.’s [23] elegant histopathological study, the coronary arteries were perfusion-fixed at physiological pressure before dissection and pathological analysis. The lumen thus remained circular, while the total vessel cross-section was distorted into an ellipse because of outward plaque growth. Despite this suggestive appearance, Varnana and colleagues, on the basis of these findings, argued that positive remodeling could be due to the plaque-free segment of the vessel wall dilating around the fixed point of the plaque.
The present study (fig. 7) found that the length of the plaque-free segment of an eccentric plaque with positive remodeling significantly affected the kinematics of the wall and lumen, that the kinematics of the atherosclerotic plaque had only a slight impact, inversely proportional to the plaque burden (indicative of the mechanical rigidity of the plaque and artery), and finally that the degree of arterial pressure showed a strong stretching effect on plaque-free segment kinematics but very little on the plaque. Plaque-free segment stretching contributes to the so-called compensatory remodeling, Glagov originally described. As long as the healthy arc is large enough, stretching remains possible, thus avoiding a too rapid reduction in lumen area – under the condition that the plaque burden does not exceed 40%. These findings fully agree with Glagov’s experimental histological data for sections of the left main coronary trunk [22].

**Coronary plaque stability**

Beta-blockers reduce arterial flow loading and pressure-related and circumferential coronary artery wall stress, and prove highly effective in secondary prevention after myocardial infarction [24].

Core composition is actually highly heterogeneous, with serial reworking: variable cell concentration because of apoptotic or necrotic mechanisms of cell death, peripheral macrophage foam-cell infiltration, or change in lipid content by transformation into cholesterol crystals [25]. The present study shows that quite small changes in the core Young’s modulus produce considerable reductions in circumferential stress. The plaque stability range is reached with a core Young’s modulus exceeding 200 kPa, whatever the cap thickness would be. If, however, fibrous cap thickness is already critical (≤ 60 μm), then a very slight (1-25 kPa) increase in Young’s modulus will bring peak circumferential stress down below the critical rupture values [13]. Many recent studies have demonstrated the beneficial effects of lipid reduction on plaque composition by reducing lipid content, cell death and inflammation rates, and increasing collagen content [26].

**Coronary plaque instability or stability: a ‘vulnerable’ balance**

There have been many studies on structural variation in the fibrous cap and lipid core, being 1) negative – inflammatory processes aggravating plaque progressions [27, 28].

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**FIG. 7** – Numerical model of the positive remodeling mechanism. Models for normal and atherosclerotic arteries (with eccentric or concentric plaques, in line with Glagov’s data) show how, with a physiological loading of 100 mmHg, positive remodeling does not involve plaque progression but rather the healthy arc stretching, facing the eccentric plaque. No such remodeling is found with concentric plaques. Thus, stretching of the healthy arc is directly dependent on the length of its angular arc.

**Fig. 7** – Modèle numérique du mécanisme de remodelage positif. Les modèles d’artère normale et athéromateuse (avec plaques excentriques ou concentriques, selon les données de Glagov) montrent comment, avec une charge physiologique de 100 mmHg, le remodelage positif n’implique pas la progression de la plaque mais plutôt un étirement de l’arc sain, à l’opposé de la plaque excentrique. Un tel remodelage ne se retrouve pas dans une plaque concentrique. Ainsi, l’étirement de l’arc sain est directement lié à sa longueur.
vulnerability – and 2) positive – statin treatment enhancing plaque stability [27]. The exponential variations in PCS with cap thickness and core elasticity 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 that sort are to be observed in the clinical setting, with multiple coronary plaque rupture following acute coronary syndrome [28], 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) [29].

KEYWORDS: Coronary vessels, hemodynamics, angioplasty, stent design.

CONCLUSION

The mechanism of vulnerable plaque rupture can thus be considered as highly complex, due to its multifactor nature. Such complexity virtually rules the prediction in individual cases out: chaos theory and sensitivity to initial conditions prevail. Diagnostic imagery, therefore, needs to be used to predict rupture only with the greatest caution, as it involves a purely morphological approach. As in vulcanology, effective prediction cannot be made from a snapshot, but only from a series of both morphological and biological observations that enable trends to emerge. Additionally, these observations should, theoretically, be non-invasive.

References


