Is There a Vulnerable Plaque?
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The identification of potential triggers of acute coronary syndromes (ACS) represented by unstable angina (UA), myocardial infarction (MI) (preceded or not by UA), and sudden coronary death (SCD) is a rapidly growing area of research.

Issues of Nomenclature
Coronary plaque disruption and subsequent thrombosis is the major recognized pathogenetic component of “unstable plaques,” which characterize the transition from stable coronary artery disease (CAD) to ACS. However, in the presence of unstable or even stable plaques, a thrombogenic state or “high-risk blood” may contribute, at least in some cases, to the development of ACS.

Furthermore, thrombosis is also an integral component of the chronic atherothrombotic progression of atherosclerosis.

Although the observation that plaque disruption leads to ACS goes back a number of decades, the notion of “vulnerable plaques” was first developed a little over a decade ago on the basis of post-mortem observations in patients with ACS. At the site of culprit coronary lesions, a rupture was often found at the shoulder of atheromatous plaques with a large pultaceous lipid core and a thin fibrous cap. Such rupture was originally thought to be the result of localized mechanical shear stress forces. However, on the basis of emerging evidence of a prevalent inflammatory component in ACS, inflammatory mechanisms of plaque instability began to receive considerable attention.

The acquisition of knowledge does not necessarily makes things more comprehensible, but rather often adds novel complexities. Yet, when confronted with a pressing issue, such as predicting major future adverse events, there is a natural inclination to accept generalizations not yet justified by available data.

The intriguing concept of a vulnerable plaque, as a potential short-term precursor of unstable plaques, derives from the theoretical possibility of identifying those coronary atherosclerotic plaques that might become unstable and thus trigger ACS. The notion of vulnerable plaques is already stimulating the development of imaging and other techniques for their detection before they become unstable, and eventually for their passivation. However, efforts to detect vulnerable plaques require a clearer definition of this concept. In particular, it should be clarified whether vulnerable or high-risk coronary plaques may (1) become unstable because of a structural or an inflammatory vulnerability or because of other yet unknown causes; (2) be present simultaneously in multiple coronary arteries; (3) remain vulnerable for weeks, months, or years; and (4) be also fibrotic, without a lipid-rich core and thin fibrous cap, thus, better fulfilling the generic term high-risk plaque rather than the traditional term vulnerable plaque, which tends to imply the presence of a soft lipid core.

To define more precisely the concept of vulnerable or high-risk plaques as potential precursors of the unstable lesions that may trigger ACS, it is useful to consider the distinctive structural and functional features of the culprit unstable coronary plaques and the distinctive clinical presentation of ACS.

Distinctive Structural and Functional Features of Unstable Coronary Plaques
The most obvious features that distinguish patients with ACS from those with stable CAD are (1) complex coronary stenoses; (2) coronary plaque fissures; (3) fresh thrombi; and (4) plaque inflammation. Such findings, being both common and plausible pathogenetic mechanisms, led to the widely accepted unifying paradigm that instability is the conse-
quence of the disruption of a lipid-rich plaque, resulting from either mechanical stress and/or from inflammatory weakening of its fibrous cap. This paradigm, which implies a single type of culprit coronary plaque as a cause for instability, does not appear to adequately fit the findings of comprehensive reviews of post-mortem studies.5,6

**Complex Coronary Stenoses**
Represented by a variable combination of plaque fissure and thrombosis, complex coronary stenosis is the most striking morphological feature of ACS. Some complex plaques that undergo remodeling may become smooth, whereas others may remain complex but eventually become functionally stable, as angiographically complex lesions can also be found in a substantial percentage of patients with stable CAD. Thus, outside of clinically unstable phases, neither complex stenoses nor severe flow-limiting stenoses, which are typical of chronic stable angina, represent plausible, isolated, morphological markers of instability. However, in ACS, the presence of multiple complex stenoses at coronary angiography, suggestive of a possible multiplicity of acutely unstable plaques, was found to be correlated with elevated C-reactive protein (CRP) levels7 and with recurrent instability.8

**Coronary Plaque Fissures and Erosions**
In some patients with ACS, fissure of the culprit lesion is the most dramatic finding of angioscopic and intravascular ultrasound techniques, as well as of post-mortem studies. However, in other patients with ACS, post-mortem studies reveal endothelial erosions underneath a variety of plaques with inflammatory cell infiltrates, some with a lipid core, others entirely fibrous.9 In addition, particularly in younger patients and in women, endothelial erosions are found over stenotic plaques, increasing the likelihood of their rupture. In this event, thrombus growth would be related to the size and thrombogenicity of the fissured plaque, as well as to the number and activation of exposed inflammatory cells.1 Alternatively, enhanced inflammation of the circulating blood may lead to activation of the clotting system, whereas inflammatory activation of the endothelium can modify its physiological vasodilatory and antithrombotic properties (production of endothelial-derived relaxing factor [EDRF], prostacyclin [PGI2], tissue plasminogen activator or [tPA], or epeparanesulphates) into pathological vasoconstrictor and prothrombotic properties (no production of vasodilator and antithrombotic mediators, production of endothelin-1, plasminogen activator inhibitor [PAI-1], tissue factor [TF], and adhesive molecules for leukocytes and platelets).

In patients with severe unstable angina, a transient acute widespread coronary endothelial inflammatory process is suggested by transcoronary activation of neutrophils.16,17 Neutrophil activation appears confined to the acute phase of instability, as it is no longer detectable at the time of hospital discharge.14 Such acute endothelial inflammatory activation appears unrelated to coronary atherosclerosis or recurrent ischemia, as it was not observed in patients with chronic stable angina and multivessel coronary disease or in patients with active variant angina.17 The hypothesis of widespread acute coronary endothelial inflammation would be consistent with the evidence of multiple complex stenoses, multiple thrombi, and multiple fissured plaques involving different coronary branches in ACS reported above. The causes of such acute coronary endothelial inflammation are unknown, but both neutrophil activation and the number of inflamed coronary plaques correlated with the systemic level of CRP.7,16

Stimuli, leading to local aggregation of platelets which, being only 400,000 per m³ of blood, take a long time to accumulate. Often, thrombi are composed of multiple layers of different age, suggestive of recent recurrences of weak thrombogenic stimuli. Less frequently, red thrombi, rich in fibrin and red cells, are found at the site of disrupted plaques with a large pultaceous core, suggesting very strong thrombogenic stimuli. Multilayered platelet thrombi and red thrombi are likely to be related to distinct pathogenetic mechanisms.

As intriguing as the multiple coronary fissures observed in some patients with ACS is the observation by intracoronary angioscopy of multiple thrombi.13 In addition, although some thrombi may complicate significant stenotic and non-fissured coronary plaques, although with superficial erosions, pathological specimens and imaging technology suggest similar phenomena in carotid and peripheral artery plaques, thus implying a high-risk blood associated with such non–lipid-rich but high-risk plaques.
Finally, an acute activation of the clotting system and/or of the endothelium by inflammatory cytokines might not necessarily be related to the presence of chronic inflammatory cell infiltrates within plaques, as such infiltrates were not found in some unstable plaques. Conversely, plaque inflammation can often be found in patients with stable coronary disease, as suggested at autopsy, and in in vivo studies using a thermistor catheter. The very common findings of chronically inflamed plaques in stable patients is not surprising, considering the fact that atherosclerosis is largely a chronic inflammatory process and as they are common they are unlikely to explain by themselves the very occasional burst of instability.

**Distinctive Clinical Presentation of ACS**

At one end of the spectrum of clinical presentation of ACS are patients with SCD or with a totally unheralded MI occurring like lightening out of a blue sky, without a single warning episode of angina, and not followed by recurrent instability. At the other end of the spectrum are patients who develop an MI after a period of unstable angina of several days or weeks, and who often develop post-infarction angina and/or reinfarction. The triggers of instability in such extreme groups of patients may not be the same. For example, the prevalence of elevated CRP serum levels is about 70% in patients with Braunwald class IIIB unstable angina (in the absence of elevated troponin); it is nearly 100% in patients with very early acute MI preceded by UA (also in the absence of elevated troponin), but is less than 50% in patients with very early MI not preceded by UA. Moreover, the persistence of elevated systemic inflammatory markers predicts recurrence of instability. Waxing, waning, and persistence of acute inflammatory stimuli would fit the clinical picture of the instability in UA and in MI preceded by UA, as would the simultaneous presence of multiple complex or fissured plaques and of thrombi with layers of different age. Conversely, the absence of elevated systemic inflammatory markers in most patients with totally unheralded MI and without recurring ACS suggests a subclinical or a less prevalent role of persistent or recurrent inflammatory mechanisms.

**Potential Precursors of Unstable Plaques**

Collectively, the data reviewed above suggest that the precursors of unstable plaques that trigger ACS are multiple and complex, structurally and functionally. Moreover, in some cases, unstable or otherwise stable plaques may require a thrombogenic high-risk blood to trigger ACS. Such potentially diverse origins of plaque vulnerability have relevant implications for their temporal evolution of vulnerability, as well as for the selection of diagnostic and passivation strategies.

**Structurally Vulnerable Plaques**

Plaques with a central lipid core (>40% of the total lesion area and a cap thickness ~65 to 150 μm) may also rupture when they cause a stenosis not visible by x-ray angiography. They are potentially vulnerable to mechanical stress and/or to inflammatory weakening of their collagen structure. The prevalence of structurally vulnerable plaques is also high in stable patients and is related to the total atherothrombotic burden. However, it is impossible to predict whether structurally vulnerable plaques may become unstable weeks, months, or years after their detection, and whether they will rupture as a result of mechanical stress, spasms, acute inflammatory endothelial activation, or the chronic inflammatory component of atherosclerosis.

**Functionally Vulnerable Plaques**

Thrombosed plaques without detectable fissures represent a substantial percentage of culprit lesions found post-mortem, yet they must have been thrombogenic enough to lead to an ACS. Their vulnerability is most likely caused by a thrombogenic or high-risk blood and/or local proinflammatory cytokines that promote thrombosis, sometimes also in the absence of intraplaque inflammatory cell infiltrates and in the absence of a lipid core.

In patients with multiple fissured plaques and/or thrombi with layers of different ages, the possibility of a widespread waxing and waning of coronary inflammation and/or of systemic blood thrombogenicity should be considered, which may or may not be superimposed on a baseline structural vulnerability. The association of multiple inflamed plaques or of widespread endothelial activation and elevated systemic inflammatory markers in some patients with ACS suggests there may be not only isolated or multiple inflamed vulnerable plaques or a vulnerable endothelium, but also some inflamed patients who remain vulnerable for a period of weeks and months and who could be identified by persistent elevation of systemic inflammatory markers. In such inflamed patients, it may be difficult to identify which coronary plaque may suddenly flare up and become unstable, particularly if such event may occur also in the absence of inflammatory cell infiltrates and of a central lipid pool.

**Conclusions**

The recently developed concepts of vulnerable or high-risk plaques and possibly of vulnerable patients are still evolving. Until the multiple triggers of ACS, their pathogenetic components, and the likelihood and time course of their vulnerability are more clearly understood, attempts to translate these concepts into clinical practice should be considered with great caution.

**References**


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