Unstable or High Risk Plaque: How Do We Approach It?

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MJAFI 2006; 62 : 2-7

Key Words : Unstable plaque; High risk plaque; Acute coronary syndrome

Vulnerable Plaque: Issue of Nomenclature

Every year, >1 million people in the United States and >19 million others worldwide experience a sudden cardiac event (acute coronary syndrome and / or sudden cardiac death) resulting in > 450 000 deaths annually in the United States. A large portion of this population has no prior symptoms [1]. This is due to non flow limiting vulnerable/unstable plaques rupturing and setting up the cascade of thrombosis producing subtotal or total occlusion and leading to Acute Coronary Syndrome (ACS).

The term 'vulnerable' plaque was coined by Muller and colleagues, to describe a plaque that by becoming disrupted has a high likelihood of starting the adverse cascade [2,3]. There is disagreement over the meaning of this term, and several terms like high risk plaque, culprit plaque and unstable plaque have been used interchangeably to indicate the same pathological lesion.

The term 'unstable plaque' basically connotes an unstable clinical situation. It should therefore, be used only when vulnerable plaque has already initiated the clinical cascade of ACS. Because the term also has well-accepted clinical usage to describe unstable angina pectoris, confusion between the clinical syndrome and plaque is inevitable. Therefore it is proposed that the term 'unstable' be reserved for the clinical syndrome and not for the plaque. The term 'culprit plaque' indicates that the clinical syndrome has set in and the plaque has played causative role. The classical 'vulnerable plaque' has certain well defined histopathology namely a thin fibrous cap, extensive macrophage infiltration, paucity of smooth muscle cells, large lipid and calcified nodule which are likely as a result of repetitive plaque rupture and healing, causing shrinkage of vessel lumen with consecutive high grade coronary stenosis [4].

The correct terminology should be 'high risk plaque' because it would encompass all varieties of histopathologic plaques that are likely to disrupt. In the literature, the most widely used terminology is

'vulnerable plaque' and for the sake of avoiding confusion we would use the same term in this article.

The results from recent studies have proposed the following histopathologic and clinical criteria for the definition of vulnerable plaque.

Major Criteria

1. Active Inflammation (monocyte/macrophage infiltration) [5]: Plaques with active inflammation may be identified by extensive macrophage accumulation. Possible intravascular diagnostic techniques include thermography (measurement of plaque temperature), contrast-enhanced (CE) MRI, and fluorodeoxyglucose positron emission tomography. It has recently been shown that optical coherence tomography (OCT) reflects the macrophage content of the fibrous cap.
2. A thin cap with a large lipid core [6]: These plaques have a cap thickness of <100 μ m and a lipid core accounting for >40% of the plaque's total volume. Possible diagnostic techniques include OCT, intravascular ultrasonography (IVUS), MRI, angiography, near infrared (NIR) spectroscopy and radiofrequency IVUS analysis.
3. Endothelial Denudation with Superficial Platelet Aggregation [4]: These plaques are characterized by superficial erosion and platelet aggregation or fibrin deposition. Possible intravascular diagnostic techniques include angiography with dye and OCT. Noninvasive options include platelet/fibrin-targeted single photon emission computed tomography and MRI.
4. Fissured/Injured Plaque [4]: Plaque with a fissured cap that did not result in occlusive thrombi may be prone to subsequent thrombosis. Possible diagnostic techniques include OCT, IVUS, angiography and MRI. Fissured coronary plaques can be found in up to 25% of patients with CAD who died of non-cardiac causes [7].

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5. Severe Stenosis : On the surface of plaques with severe stenosis, shear stress imposes a significant risk of thrombosis and sudden occlusion. The current standard technique is resonance angiography. Noninvasive options include multislice CT and magnetic resonance angiography with or without a contrast agent.

Minor Criteria

1. Superficial Calcified Nodules [4]: These plaques have a calcified nodule within or very close to their cap and this structure protrudes through and can rupture the cap. This event may or may not be associated with severe coronary calcification and a high calcium score.
2. Yellow Colour (on Angioscopy) [8]: Yellow plaques, particularly glistening ones may indicate a large lipid core and thin fibrous cap, suggesting a high risk of rupture. However, because plaques in different stages can be yellow and because not all lipid-laden plaques are destined to rupture or undergo thrombosis, this criterion may lack sufficient specificity.
3. Intraplaque Hemorrhage [4]: Extravasation of red blood cells or iron accumulation in plaque may represent plaque instability. Possible diagnostic technique include NIR spectroscopy, tissue Doppler methods and MRI.
4. Endothelial Dysfunction [9]: Vulnerable plaques have sites of active inflammation and oxidative stress and are likely to be associated with impaired endothelial function. Possible diagnostic techniques are endothelium-dependent coronary artery dilatation and measurement of flow-mediated dilatation by brachial artery ultrasonography.
5. Expansive (positive) Remodeling: Many of the nonstenotic lesions undergo “expansive,” “positive,” or “outward” remodelling i.e. compensatory enlargement before compromising significantly on the vascular lumen. As the luminal area was not affected, this phenomenon was considered as positive remodelling. Several studies have suggested that such remodelling is a potential surrogate marker of plaque vulnerability [10]. IVUS was used in these studies to evaluate remodelling in coronary arteries.

Relation to the AHA classification of atherosclerotic lesions

The AHA classification [11], which is based on histologic features rather than functional significance, divides plaques into six types with increasing complexity.

1. Type I: initial changes

2. Type II: fatty streak
3. Type III: pre atheroma
4. Type IV: atheroma
5. Type V: fibroatheroma
6. Type VI: complicated plaque

Most vulnerable plaque exhibit a Type IV or Type V histologic appearance.

Diagnosing the vulnerable plaque:

Rupture of vulnerable plaques is the main cause of ACS. Identification of vulnerable plaque is therefore important to enable the development of treatment modalities to stabilize such plaque.

Invasive Modalities

Coronary Angiography

Coronary angiography has been the gold standard to assess the severity of luminal narrowing. Studies have shown that the culprit lesion prior to an MI has been, in 48-78% of all cases, a stenosis smaller than 50% [12,13]. 70% of acute coronary occlusions are in areas that were previously angiographically normal [14]. Angiography therefore, has a low discriminatory power to identify vulnerable plaque.

Angioscopy

Intracoronary angioscopy offers direct visualization of the plaque surface and intraluminal structures like tears and thrombi. It allows assessment of the colour of the plaque and thrombus with higher sensitivity compared to angiography [15]. In a 12 month follow up of 157 patients with stable angina, ACS occurred more frequently in patients with yellow plaques than in those with white plaques [16]. Limitations of Angioscopy are difficulty to perform, invasive, limited part of vessel can be investigated and to enable clear visualization of the vessel wall, the vessel has to be occluded and the remaining blood flushed away with saline, thereby potentially inducing ischemia.

Intravascular Ultrasound (IVUS)

IVUS provides some insight into the composition of coronary plaque. In IVUS images lipid depositions are echolucent and detected with sensitivity between 78-95% and specificity of 30% [17]. Plaque calcification, characterized by a bright echo signal with distal shadows can be detected with a sensitivity of 86% [18]. Ruptured plaque is characterized by an echolucent area within the plaque and a tear of the thin fibrous plaque. It can be confirmed by injecting contrast medium and seeing filling of the plaque cavity on IVUS. Potential of ultrasound radiofrequency signal analysis for tissue characterization has been studied. It offers better tissue characterization with improved differentiation of

atheroma with high lipid contents from atheroma with low lipid contents.

Thermography

Inflammation produces a rise in temperature in the affected tissue. A vulnerable plaque is very active and temperature differences between atherosclerotic plaque and healthy vessel walls increased progressively from patients with stable angina to patients with acute MI with a maximum difference of $1.5 \pm 0.7^\circ\text{C}$ [19]. Limitation is in vivo coronary temperatures are influenced by coronary flow which has a “cooling effect”. Proximal balloon occlusion can overcome this problem but interrupts coronary flow.

Optical Coherence Tomography (OCT)

OCT is analogous to ultrasound, measuring the intensity of back reflected infrared light rather than acoustical waves. It can clearly identify the thin intimal plaque (as little as 30 microns diameter) above the high risk plaques. It can also define fissuring within the plaque and can generate high contrast between lipid and non lipid tissues, therefore identify lipid collections within the plaque. A lipid pool generates decreased signal areas and a fibrous plaque produces a homogenous signal. In vitro comparison of OCT with IVUS demonstrated superior delineation by OCT of structural details like thin caps or tissue proliferation [20]. Limitations include low penetration depth and light absorption by blood that needs to be overcome by saline infusion or balloon occlusion with associated potential for ischemia.

Near Infra Red (NIR) Spectroscopy

It provides qualitative and quantitative results on plaque composition. The sensitivity and specificity for the histologic features of plaque vulnerability are 90% and 93% for lipid pool, 77% and 93% for thin cap, and 84% and 89% for inflammatory cells respectively [21].

Intravascular Elastography/Palpography

Elastography measures the mechanical properties of tissue using ultrasound. For detection of a deformable plaque that is prone to rupture, it is important to differentiate between hard and soft tissue.

Non-invasive Modalities

Magnetic Resonance Imaging (MRI)

Combining information from T1 and T2 weighted imaging permits in vitro identification of the atheromatous core, collagenous cap, calcification, media, adventitia and perivascular fat. MRI differentiates plaque components on the basis of biophysical and biochemical parameters. Plaque imaging and characterization has been performed using Black blood MRI. The signal from blood flow is rendered black to better image the adjacent

vessel wall. Bright blood imaging can be employed to assess fibrous cap thickness. This sequence enhances the signal from flowing blood and highlights the fibrous cap as a dark band. Calcification is well defined by signal loss in all sequences (T1w, T2w). Contrast enhanced MRA with use of gadolinium based contrast agents may provide additional information for plaque characterization by identifying neovascularisation in the atherosclerotic plaque and improve differentiation between necrotic core and fibrous tissue. Imaging of coronary artery is difficult because of cardiac and respiratory motion, small plaque size and acquisition problems due to location of coronary arteries.

Computerized Tomography (CT) plaque imaging:

Electron Beam CT (EBCT) or Multi detector CT (MDCT) has high sensitivity for detection of calcified plaques. The total burden of calcified atherosclerotic plaques in all coronary arteries can be identified by ultrafast CT. Lipid rich, fibrous and calcified plaques can be differentiated reliably. However, sensitivity is lower for earlier stages of atherosclerosis (type III and IV plaques). For plaques with and without calcification detected on IVUS, EBCT yielded a sensitivity of 97% and 47% and a specificity of 80% and 75% respectively [22].

Nuclear Scintigraphic Techniques:

Radioisotopes offer potential for imaging atherosclerotic lesions. Positron emission tomography (PET) and Single photon emission computed tomography (SPECT) have high sensitivity for application to molecular imaging, but lower spatial resolution than other technologies. Fluorodeoxyglucose [18 FDG] has been shown to accumulate in plaques of patients with symptomatic carotid atherosclerosis. Another emerging technique is measurement of transcoronary gradient (difference in conc. between coronary ostium and coronary sinus or between proximal and distal segments of each coronary segment) of various factors, including cytokines, adhesion molecules, temperature, etc.

All techniques are under development and none can identify a vulnerable plaque alone. Thus the combination of several modalities will be of importance in future to ensure high sensitivity and specificity in detecting vulnerable plaque.

Clinical Implications:

The coronary lesion responsible for infarction is usually only mildly stenotic suggesting that plaque rupture with superimposed thrombosis is the primary determinant of acute occlusion rather than lesion severity. It is therefore, important to identify plaques that are likely to

become vulnerable, to find out how long they will stay vulnerable, and to be able to target therapy to those plaques most likely to develop thrombosis. Also, factors that protect plaques from becoming vulnerable need to be identified.

Therapeutic Options:

Lipid modifying agents:

Statin treatment is established in treating atherosclerosis. Angiographic studies of statin treatment on coronary artery plaque have shown modest reduction in plaque dimension referred to as plaque regression, with clinical benefit [23], suggesting plaque stabilisation (pleiotropic effect) which is multifactorial with diminution of plaque lipid-rich core, reduction in inflammation with decreased macrophage and foam cell formation and promotion of fibrous cap thickening, improvement in endothelial function and decreased platelet reactivity. Although improvement in endothelial function is instantaneous, reduction in thrombotic events takes up to 3 months and reduction in the plaque lipid pool up to 6 months. Animal studies of cholesterol reduction demonstrate changes in plaque structure including reduction of macrophage numbers and MMP-1 expression and increases in interstitial collagen content resulting in increased plaque stability. Clinical studies of statin treatment, utilising IVUS, have consistently demonstrated increases in hyperechogenicity index (suggesting an increase in fibrous tissue), reduction in the plaque lipid pool, but only modest reduction in plaque volume [24]. These changes in plaque structure have translated into improved outcomes in both the MIRACL and the PACT studies of early cholesterol reduction in ACS [25], which are likely to relate to beneficial effects on plaque stabilization, probably by improved endothelial function and possibly by reduced platelet thrombogenicity. Other cholesterol reducing agents, such as nicotinic acid and ezetimibe, may improve plaque stabilisation by reducing the lipid pool and improving endothelial function, but whether this will extend to improved outcome in ACS has yet to be established.

Treatments which raise high density lipoprotein (HDL) cholesterol, such as niacin and fibrates, also improve cardiovascular outcome in high risk groups with low HDL cholesterol, either in combination with simvastatin, or in isolation.

Antithrombotic/Antiplatelet agents

An important part of the process leading to arterial thrombotic occlusion is exposure of the subendothelial extracellular matrix, which occurs with either deep plaque rupture or superficial plaque erosion. Exposure of subendothelial tissue introduces platelet adhesion

molecules and tissue factors to the circulation, thereby activating the clotting cascade leading to atherothrombotic disease. Antithrombotic agents act by reducing intravascular haemostasis, but may also have a direct passivating effect on the vascular wall. Both unfractionated (UFH) and low molecular heparin (LMWH) improve outcome in ACS. Aspirin has antiplatelet and anti-inflammatory properties, by covalent binding of cyclo-oxygenase and reducing interleukin-6, C reactive protein (CRP), and macrophage colony-oxygenase and reducing interleukin-6, C reactive protein (CRP) and macrophage colony stimulating factor. Adenosine diphosphate (ADP) receptor antagonists, such as clopidogrel and ticlopidine, inhibit platelet activation, degranulation and release of prothrombotic and inflammatory mediators, while preventing activation of the glycoprotein (Gp) II b / III a receptor. These translated into clinical benefit when used in combination with aspirin, and their rapid onset of beneficial effect suggest an effect on plaque stabilisation as well as passivation [27].

Gp II b/III a inhibitors block the platelet Gp II b-III a receptor, preventing fibrinogen binding and thus platelet aggregation. This class of drugs exhibits their greatest benefit in those patients undergoing percutaneous coronary intervention (PCI). These beneficial effects may extend beyond inhibition of platelet binding. As platelets promote the accumulation of inflammatory cells, the antiplatelet aggregation activity of Gp II b/IIIa inhibitors reduces plaque macrophage burden.

Angiotensin Converting Enzyme (ACE) inhibitors

ACE inhibitors may improve plaque stability by inhibiting the endothelial dysfunction and oxygen-free radical production caused by angiotensin, while also decreasing macrophage activity and inhibiting smooth muscle cell lipooxygenase activity. The Heart Outcomes Prevention Evaluation (HOPE) trial has demonstrated added benefit with ACE inhibitors in ACS out of proportion to the modest degree of blood pressure lowering seen, in patients without significant left ventricular systolic dysfunction, but at high cardiovascular risk [28]. It could be postulated that this is either due to plaque stabilization, perhaps in part due to up-regulation of type III collagen synthesis, or an anti-atherogenic effect which demonstrated significant reduction in the rate of carotid intimal medial thickening.

Calcium antagonists

Calcium antagonists may stabilise plaques by interfering with lipid oxidation and reducing foam cell formation, with the significant increase in transmembrane calcium transport seen in ACS implying an anti-

atherogenic role. Amlodipine significantly reduced the rate of carotid intimal medial thickening and reduced ACS admissions in a high cardiovascular risk group [29].

Other oral agents

Oral antioxidants may contribute to plaque stabilization by inhibiting oxidation of low density lipoprotein (LDL) cholesterol and stabilizing vascular reactivity. Despite this, studies have consistently failed to show a benefit; yet diets rich in antioxidants, such as the Mediterranean diet reduce cardiovascular events, an effect possibly mediated by high concentrations of the n-3 class of essential fatty acids [30]. Oral treatment with corticosteroids also improves clinical outcome and reduces in-stent restenosis, in patients with high CRP concentration [31]. Oral administration of immunomodulatory agents (rapamycin) showed no beneficial effect on clinical and angiographic end points [32].

Percutaneous Coronary Intervention:

Heparin coated stents, where heparin is covalently bound to the polymer coating thereby preventing elution, were developed to reduce stent thrombosis, while reducing or eliminating systemic anticoagulation. The feasibility of using heparin coated stents in combination with oral antiplatelet treatment to reduce acute stent thrombosis was successfully tested by the Benestent II study [33]. Heparin coated stents have demonstrated utility in other settings, such as in small coronary arteries and vein grafts, but failed to show significant advantages over uncoated stents. The significant degree of inflammation seen in a vulnerable plaque means that local drug delivery (LDD) of anti-inflammatory agents holds great potential interest. Reduced in-stent restenosis and a low major adverse cardiac event (MACE) rate, when compared with similar studies, have been demonstrated with a dexamethasone eluting stent in a study group with a high incidence of ACS (40%) [34]. The study subgroup with ACS showed reduced in-stent restenosis, suggesting that LDD of dexamethasone has a greater effect in vulnerable or inflamed plaques, which may relate to plaque stabilisation. Local immunomodulation and plaque stabilisation may partially explain the significant reduction of in-stent restenosis and low MACE rates seen with sirolimus eluting stents [35].

Should we treat the vulnerable plaque with angioplasty?

About 90% of clinically relevant MI are caused by lesions in the proximal third of the major coronary arteries. An immediate decision is warranted whether to proceed with a preventive angioplasty to transform

this vulnerable plaque mechanically into a scar tissue by intentionally cracking the fibrous cap under controlled condition to induce a scar which is immune to future fissures or rupture (plaque sealing) [36]. Thus once the acute effect with its inherent risk of acute occlusion has passed, the subsequent risk of plaque rupture is markedly reduced compared with that of an untreated plaque. There is little published evidence for the plaque sealing concept. Mercado et al have investigated the clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty and stenting in comparison with moderate to severe stenosis. The one year event rate (mortality, rate of non fatal MI, and repeat revascularization) was same for significant and non significant stenoses [37]. The potential risk of performing angioplasty and for causing significant restenosis in such non significant lesions should be taken into account. The advent of the drug eluting stents offers advantage in favour of mechanical sealing by reduction of restenosis rate.

Future Therapy

- Gene therapy : Genetic therapy has seen advances in lowering LDL, increasing HDL, increasing endothelial Nitric Oxide synthase and decreasing Vascular Cell Adhesion Molecule. One study showed that intravenous administration of HDL inhibited progression and promoted regression of aortic lipid deposits and fatty streaks [38].
- Metalloproteinase (MMP) inhibitors: Despite being an attractive target from a therapeutic standpoint, the increasing number and complexity of the MMP family of enzymes makes it challenging to determine precisely which enzyme should be targeted.
- CD 40 pathway inhibitors: Large randomised clinical trials will be needed to further elucidate the clinical role of interrupting the CD-40 signalling system on atherosclerosis and plaque stabilization.

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