Vulnerable Plaques, Inflammation and Newer Imaging Modalities

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Abstract:
Currently, inflammation is considered to be the central player in the pathogenesis of atherosclerosis. It leads to the formation of multiple plaques in the arterial beds including coronary vasculature. Recent studies using the latest imaging techniques have shown that in patients with acute coronary syndromes (ACS) multiple plaques are ruptured and have thrombus formation on them. Various factors make these plaques unstable, these include structural components of plaque like thin fibrous cap, high lipid content of the plaque core and inflammation, both localized and generalized. It has been shown that most of the ACS are caused by plaques causing non-critical stenosis as seen on traditional X-ray angiography. Also, the phenomenon of remodelling makes angiography a poor technique for plaque visualization. Hence newer modalities are required to identify these “vulnerable plaques”. Intravascular ultrasound (IVUS), thermography and Magnetic Resonance Imaging (MRI) are a few such promising techniques. Here we review the invasive and non-invasive modalities that can be helpful in the identification of these plaques before they become unstable and cause ACS, and also the available therapies to stabilize these plaques. (J Postgrad Med 2003;49:361-8)

Key Words: Vulnerable plaque, Coronary artery disease, Intravascular ultrasound.

Coronary artery stenosis is generally asymptomatic until stenosis exceeds 70 or 80%. These large lesions can produce a critical reduction in blood flow to the myocardium, resulting in typical symptoms of angina pectoris. However, acute coronary and cerebrovascular syndromes are often due to the rupture of plaques with less than 50% stenosis.

The ischaemic syndrome results from subsequent thrombus formation. This leads to the concept of “vulnerable plaque” and is supported by findings in post-mortem studies in patients with ACS. The reason behind the rupture of these plaques was originally thought to be the result of localized mechanical shearing and stressing 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. Recently, a lot of research and effort has gone into the identification of those coronary atherosclerotic plaques that might become unstable and thus trigger ACS. This concept of vulnerable plaques is already stimulating the development of imaging and other techniques for their detection before they become unstable.

Does Plaque Size Matter in Acute Coronary Syndrome?
A major finding in the last 2 decades was the recognition that plaque composition, rather than the severity of stenosis may determine the risk of thrombotic complications associated with ACS. It is now well established that disruption of the atherosclerosis lesion and the superimposed thrombus formation play a key role in the pathogenesis of ACS. The coronary artery surgery study used angiography to prospectively evaluate nearly 3000 non-bypassed coronary segments in approximately 300 patients observed over a period of 42 to 66 months. It was shown that less obstructive plaques (< 80% stenotic at baseline) gave rise to more occlusion than severely obstructive plaques because of their greater number. Ambrose et al and Little et al first demonstrated that in approximately 50% of the cases of myocardial infarction, the lesions leading to occlusion were < 50% stenotic. Other groups have shown similar results, and today it is accepted that in approximately 70% of cases, the clot responsible for an acute coronary event occurs in a plaque that is < 50% stenotic. Therefore the assumption that only highly stenotic sites seen on angiography are at risk for thrombotic occlusion and subsequent myocardial infarction, whereas those coronary arteries that do not contain obstructive stenosis (< 50%) are nearly free of risk for thrombotic occlusion is not valid. It is likely that there are other factors that make a non-critically stenotic plaque unstable and prone to rupture.

What Causes the Plaque to be Unstable?
The concept that instability is the consequence of the disrup-
tion of a lipid-rich plaque, resulting from either mechanical stress and/or from inflammatory weakening of its fibrous cap, is now widely accepted. This model, 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. In some patients with ACS, fissure of the culprit lesion is the most dramatic finding of angiography and IVUS, 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. In addition, particularly in younger patients and in women, endothelial erosions are found over stenotic plaques poor in lipids and rich in smooth-muscle cells and proteoglycans but without inflammatory cell infiltrates. Therefore, plaque erosion without the vulnerable plaque features of fissuring or lipid-rich core may lead to ACS. Post-mortem studies in patients with ACS show that most culprit thrombi are composed of platelets or platelets and fibrin. Often, thrombi are composed of multiple layers of different age, suggestive of recent recurrences of weak thrombogenic stimuli.

**Role of Inflammation in Plaque Instability**

There are a number of studies that have shown that inflammation, both localized and generalized, causes the plaques to be unstable. Inflammatory cell infiltrates were found in culprit plaques with and without fissures. Inflammatory activation of metalloproteases can weaken the fibrous cap of lipid-rich 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. 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 eparansulphates) into pathological vasoconstrictor and prothrombotic properties. A transient acute widespread coronary endothelial inflammatory process is suggested by transcoronary activation of neutrophils in patients with unstable angina. Neutrophil activation appears confined to the acute phase of instability, as it is no longer detectable at the time of discharge from the hospital. Such acute endothelial inflammatory activation appears unrelated to coronary atherosclerosis or recurrent ischaemia, as it was not observed in patients with chronic stable angina and multivessel coronary disease or in patients with active variant angina. 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 C-reactive protein (CRP). An acute activation of the clotting system and 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 vivo studies using a thermodilusion catheter. This can be explained as atherosclerosis is a chronic inflammatory process but what causes these “chronically inflamed” plaques to become unstable suddenly is still not clear. Hence the precursors of unstable plaques that trigger ACS are multiple and complex, structurally and functionally.

**Characteristics of Vulnerable Plaques**

**Structurally unstable plaques**

**Fibrous cap:** The cap overlying the atheromatous core is increasingly being recognized as a dynamic structure in which collagen synthesis is modulated by positive and negative growth factors produced by inflammatory cells, and in which collagen is degraded by metalloproteinases derived from activated macrophages. Most of the fissures and fractures occur in eccentric lesions at the shoulder region of the cap. This is usually the thinnest area with reduced collagen content. There is high circumferential stress at the luminal border of the plaque, hence rupture is more likely to occur. It has been shown that circumferential stress increases critically when cap thickness is less than approximately 150 microns. A large lipid core (more than 40%) rich in cholesterol carries high risk of rupture. Lipid in the form of cholesteryl ester softens the plaque, whereas crystalline cholesterol may have the opposite effect. A few studies have shown that a negative relation exists between temperature and core stiffness. If temperature increases, as in inflammation, the core becomes softer. A soft core may be more vulnerable to rupture since it may not be able to bear the imposed circumferential stress, which is then redistributed to the fibrous cap where it may be critically concentrated.

**Functionally unstable 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 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 coronary inflammation and/or of systemic blood thrombogenicity should be considered, which may or may not be superimposed on a baseline structural vulnerability. The presence of multiple inflamed plaques or of widespread endothelial activation and elevated systemic inflammatory markers in some patients with ACS suggests that there may be not only isolated or multiple inflamed vulnerable plaques or a vulnerable endothelium, but also some vulnerable 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 an event may also occur in the absence of inflammatory cell infiltrates and of a central lipid pool.

**Multiplicity of high-risk plaques**

ACS appears to be caused by the rupture of an unstable coronary plaque that appears as a single lesion on angiography. However, there is increasing evidence that systemic effects, such as inflammation, are more widespread within the coronary circulation and this may be leading to the instability of multiple plaques.

**Complex angiographic appearance**

Coronary angiography in patients with ACS often reveals a complex plaque, which is an eccentric-appearing lesion with overhanging edges and irregular borders, ulceration, impaired flow, and often thrombosis. Complex plaques are an indicator of plaque rupture and/or thrombus in patients with unstable symptoms and have been considered to be the “culprit lesion”. Another report showed the presence of multiple complex plaques in the majority of patients with ACS, they required bypass surgery during admission more often and, during the subsequent year, had a significantly higher incidence of ACS. However, some complex plaques that undergo remodelling 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 coronary artery disease (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.

**Remodelling of plaques**

In the early phases of atherosclerosis development, when CAD is minimal, luminal size is not affected by plaque growth because of the expansion of the external elastic membrane (EEM) and enlargement of the vessel size; this represents “positive remodelling”. Further, as CAD becomes moderate there is no increase in the vessel size, but rather the plaque approaches the lumen which shrinks; this is “negative remodelling”. Positive remodelling, larger plaque areas, and echolucent plaques are associated with unstable angina, while negative remodelling and smaller plaque areas are associated with stable angina. Positive remodelling is also seen in acute myocardial infarction at the site of plaque rupture. These findings are consistent with other observations that inflammation, calcification, and medial thinning are primary determinants of positive remodelling, which appears to be a feature of plaque instability.

**Identification of Vulnerable Plaques**

**Invasive Techniques**

**Angiography:** The X-ray coronary angiogram reflects luminal diameter and provides a measure of stenosis with excellent resolution or irregular luminal surface implying the presence of atherosclerotic disease. But this imaging method does not image the vessel wall or provide information about the composition of the atherosclerotic plaque. The phenomenon of remodelling makes angiography a poor technique for assessing the true atherosclerotic burden. The shadows of the coronary lumen seen on angiography provide only indirect and incomplete information concerning the extent of the atherosclerotic process in the arterial wall.

**Intravascular ultrasound (IVUS):** It is a new technology that allows in-vivo visualization of variations in arterial geometry and atherosclerotic plaque by utilizing a miniature transducer at the end of a flexible catheter. IVUS provides a two-dimensional cross-sectional image of the arterial wall and can accurately assess the plaque burden. This issue of multiple complex lesions was addressed in an IVUS study of 72 arteries in 24 patients referred for percutaneous coronary intervention after a first non-ST elevation MI; all had a clearly identified culprit lesion on angiography. IVUS revealed a
mean of 2.1 plaque ruptures per patient; at least one was found somewhere other than in the culprit lesion in 19 (79%), 17 of which were in a different artery from the culprit artery. The ruptures in the non-culprit plaques were less severe, less calcified, and non-stenosing. These observations are consistent with another IVUS study of 32 patients who underwent follow-up catheterisation one month after an acute myocardial infarction (MI). However, the resolution of the ultrasound system is related to its frequency. For high-frequency (40 to 50 Mhz) systems, imaging may be hampered by an increased back scatter of blood. Histopathological studies mostly report low sensitivity for IVUS in detecting lipid-rich lesions although the analysis of IVUS radio-frequency signals may improve tissue characterization. Although axial resolution remains too low for measuring cap thickness of the fibrous cap with its rupture, a recent study reports that the thickness of the fibrous cap with its rupture were visualized.

**IVUS elastography:** IVUS elastography is based on the principle that tissue components that differ in hardness as a result of their different histopathological composition are expected to be compressed differently if a defined pressure is applied. The technique is able to discriminate between soft and hard material and assess the mechanical properties of the vessel wall. Hard and soft regions can be identified using this technique, while in the original image, it is not possible to discriminate the different tissue types. This technique has the potential to identify plaque vulnerability since the detected areas of increased radial strain represent regions of high circumferential stress, a feature of plaque vulnerability. However, a major problem in advancing IVUS elastography to cardiac in vivo applications is the acquisition of data in a pulsating artery located in a contracting heart.

**Angioscopy:** The colour of plaques as detected with angioscopy may vary among patients with different acute syndromes. Xanthomatos plaques (yellowish), which cannot be recognized with arteriography, are more common in patients with acute myocardial infarction and unstable angina. Such plaques are found in all three major coronary arteries, suggesting that the development of these vulnerable plaques is a pan-coronary process. Smooth white plaques are observed in patients with old myocardial infarction and stable angina. A xanthomatos plaque is likely to have a high concentration of cholesterol at its base and the fibrous cap overlying the lipid core may be thin. Plaques with a high concentration of lipid and a thin fibrous cap may be easily cracked by increased shear force at the level of the stenosis and by acute changes in coronary tone or exercise. By comparison, white plaques are less likely to rupture since the increased fibrous content over the lipid core provides stability. Although angioscopy allows visualization of the plaque and thrombus with high sensitivity, it remains a research tool because of its inability to examine the different layers within the arterial wall and to provide an estimation of cap thickness or lipid content.

**Thermography- “Imaging the inflammation”:** A persistent finding in the histopathological specimens of ruptured atherosclerotic plaques has been the presence of activated macrophages within the plaque. Accumulation of these cells reflects the inflammatory process that has been implicated in the pathogenesis of ACS. Since the cardinal sign of inflammation is an increase in temperature, local differences in plaque temperature may be expected depending on the degree of inflammation. Ex vivo studies in human carotid atherosclerotic plaques showed that temperature differences within the plaque were related to the cell density of macrophages. Recently, in vivo studies demonstrated temperature heterogeneity to be determined by plaque composition and more specifically by macrophage mass. The exact mechanism for the increased local temperature in a coronary atherosclerotic plaque is not clearly understood. Neovascularization within the vulnerable plaque as well as expression by activated macrophages of mitochondrial uncoupling proteins (proteins homologous to uncoupling protein-1 that is found in brown fat and is involved in thermogenesis in that tissue) have been implicated in the generation of heat in the inflamed plaque.

The direct measurement of the temperature of the coronary atherosclerotic plaque has become feasible with the use of specially designed thermography catheters. In the first clinical study with the thermography catheter, thermal heterogeneity within atherosclerotic coronary arteries and constant temperature in normal coronary arteries was documented. This heterogeneity was found to be more in unstable angina and acute myocardial infarction patients, implying that it may be related to the pathogenesis of ACS. Another clinical study showed that plaque temperature was higher in patients with ACS and predicted long-term clinical events in patients undergoing Percutaneous Transluminal Coronary Angioplasty (PTCA) and stent implantation. Currently, a study showed a lesser temperature difference between the atherosclerotic
plaques and the normal coronary artery in patients on statins. This finding supports a favourable effect of statins on heat release from the atherosclerotic plaques.\textsuperscript{56}

There is increasing evidence that patients at high risk of ACS have multiple high-risk plaques.\textsuperscript{18,31-35} Based on the above principle, the temperature of the blood that passes through the inflammatory coronary territories and empties into the coronary sinus is expected to be higher in patients with CAD and unstable coronary plaques than in those without coronary lesions.\textsuperscript{57} Patients with significant lesions in the left coronary artery bed had the highest temperature difference between the blood from the coronary sinus and the right atrium.\textsuperscript{58} Thus thermography can develop into a technique to identify “inflamed” patients.

**Optical Coherence Tomography (OCT):** A laser beam is directed at the plaques and the reflected light is analysed. It is capable of visualizing the atherosclerotic lesion with an axial resolution of 2 to 30 microns. The current penetration depth is limited to 1 to 2 mm. Studies revealed that OCT is capable of differentiating lipid tissue from water-based tissues.\textsuperscript{61} Furthermore, the thickness of the fibrous cap overlying an atheroma can be demarcated by OCT.\textsuperscript{61} The limitations of OCT for \textit{in vivo} intravascular imaging include the reduction of image quality when imaging through blood or large volumes of tissue, the relatively slow data acquisition rate, and multiple scattering.

**Raman Spectroscopy:** Raman spectroscopy is ideal for identifying gross chemical changes in tissue, such as in atherosclerosis.\textsuperscript{62} It is an imaging modality in an early stage of development that has great potential to discriminate \textit{in vivo} between lipid-rich, calcified and fibrotic plaques. The penetration depth of Raman spectroscopy in arterial tissue is reported to be 1.0 to 1.5 mm. This would allow the Raman technique to examine tissue types beneath fibrous caps and within the atherosclerotic core. The current limitations of Raman spectroscopy are strong background fluorescence and laser light absorption by the blood.

**Near-Infrared (NIR) Spectroscopy:** Diffused reflectance near-infrared spectroscopy (NIR) has been used extensively to identify the chemical content of biological specimens. NIR spectroscopy (750-2500 nm) is based on the absorption of light by organic molecules. The reflectance spectra from wave lengths between 400 and 2400 nm allows detailed analysis of chemical composition.\textsuperscript{63} The advantage of this technique is its deeper penetration into the atherosclerotic plaque and that it can be combined with other catheter-based techniques, but its use has been limited until now to \textit{in vitro} studies.

**Non-Invasive Techniques**

**Electron beam computed tomography (EBCT):** EBCT is a technique of imaging coronary artery calcium that uses a faster rate of image acquisition than conventional CT. With fast imaging the elimination of cardiac respiratory motion artifacts is accomplished. It has been suggested that in asymptomatic men and women aged 50 to 70, EBCT derived coronary calcium score accurately predicts coronary disease events independently of standard risk factors and can be used to refine the Framingham risk index.\textsuperscript{64} Coronary calcification detected by EBCT is found in individuals who have significant angiographic CAD, with a sensitivity ranging from 90 to 100\%, a specificity of 45 to 76\%, a positive predictive accuracy of 55 to 84\%, and a negative predictive accuracy of 84 to 100\%.\textsuperscript{65-67} Since the finding of calcium on EBCT correlates with the presence of a significant stenosis (≥50\%) on coronary angiography, it may serve as a screening technique prior to invasive angiography and may be particularly helpful in patients with an equivocal exercise test.\textsuperscript{68}

**Limitations:** Calcium severity on EBCT can identify asymptomatic patients at high risk of CHD, but it is not certain if this translates into the identification of asymptomatic patients who have silent ischaemia, which is of importance since the presence of silent ischaemia is predictive of a cardiac event. High-risk plaques often lack calcium and the predictive value of coronary calcification, at least in high-risk subjects, may not be superior to that of standard coronary risk factors. It is expected that the greatest potential for coronary calcium scores appears to be in the detection of advanced coronary atherosclerosis in patients who are apparently at an intermediate risk. The site and extent of calcification do not equate with site-specific stenosis and a calcific plaque does not mean a stable plaque necessarily.

**Magnetic resonance imaging (MRI):** High resolution MRI holds the promise of non-invasively imaging high-risk plaques. High-resolution fast spin echo and optimized computer processing have enhanced the spatial resolution (0.4 mm) during the visualization of atherosclerotic plaques \textit{in vivo}. In experimental studies in small hypercholesterolemic animal models, in atherosclerotic lesions, an excellent agreement was observed between high-resolution MRI (9T system, in plane spatial resolution 97 microns) and histopathology. MRI studies are currently being performed to study the progression and regression of atherosclerotic plaques over time.\textsuperscript{69,70} Using ul-
tra small super paramagnetic particles of iron oxide, macro-
phage accumulation in the aorta could be seen in
hypercholesterolemic rabbits before atherosclerotic lesions
were detected.71 MRI is also used to visualize and characterize
arterial thrombi in vivo.49, 72

High-resolution MRI is an excellent tool to visualize fibrous
cap thickness and rupture in plaques.73,74

Limitations: Although MRI is a promising non-invasive
tool for detecting vulnerable plaques, at present it lacks suffi-
cient resolution (currently 400 microns) for accurate meas-
urements of cap thickness and characterization of the athero-
sclerotic lesion within the coronary circulation. A newer high-
resolution MRI technique shows an 80% agreement with his-
topathology in the analysis of intimal thickness and accurately
determines plaque size.75 Taking advantage of the molecular
processes involved in atherothrombosis, it has recently been
shown that it is possible to target molecules with antibodies
coupled to a contrast molecule, which can be detected by MRI.
These molecular enhancers can potentially boost the ability
of the non-invasive MRI to detect high-risk vulnerable athero-
sclerotic plaques and enhance patients’ risk stratification.76,77
At present, MRI not only provides a non-invasive method of
visualizing plaque and discriminating its components, but also
provides a means of accurately assessing the effects of treat-
ments, such as lipid-lowering therapy, and of timing the activ-
ity of clots to determine when they become inactive. But cer-
tain technical improvements are still desired.

Positron Emission Tomography (PET Scan): The cellular
components of the atherosclerotic plaque, such as
macrophages, exhibit high glucose metabolic activity. Fluoro-
deoxyglucose (FDG) positron emission tomographic (PET)
scans showed an increased vascular FDG uptake in older
patients that was explained by smooth muscle metabolism in
the media, subendothelial smooth muscle proliferation from
senescence, and the presence of macrophages within the
atherosclerotic plaque.78 Further studies are required to sub-
stantiate this observation. Hence the PET scan can evolve into
an important tool for imaging vulnerable atherosclerotic
plaques.

Drugs That May Enhance Plaque Stability
At present there is no proven drug or modality to stabilize the
vulnerable plaques. A number of drugs that are beneficial for
patients with coronary disease may act in part by improving
the stability of plaques that are vulnerable for future rupture.79,80

• Beta blockers lower circumferential wall stress via reduc-
tions in blood pressure, heart rate, left ventricular mass,
and catecholamine surges that occur with stress and ex-
ertion.80
• Angiotensin converting enzyme (ACE) inhibitors lower
the blood pressure and may have plaque-stabilizing ef-
fects by reducing the synthesis of angiotensin II.
• Lipid-lowering therapy, particularly with statins, can sta-
bilize vulnerable plaques or those that have already rup-
tured by improving endothelial function and reducing
thrombogenicity, platelet aggregation, and possibly in-
flammation.81
• Antithrombotic therapy, including antiplatelet agents and
warfarin do not stabilize the vulnerable plaque, but they
do limit thrombosis, which is an important consequence
of plaque rupture.

Conclusion
At present the ideal of these newer modalities for optimum
use remains undefined. The ideal approach would provide
both anatomic and functional data about vulnerable plaques.
It seems that these modalities can provide useful information
for risk stratification. In patients found to be at high risk based
on family history and the presence of co-morbid conditions
like diabetes or high serum CRP level, this information may
add to the “awareness of vulnerability” for the patient and the
physician. This can improve the patient’s compliance with diet
and medications, and can possibly define new treatment goals
for optimum weight, blood pressure, lipids and glucose con-
trol. The presence of vulnerability may merit multiple systemic
therapies, such as aspirin, clopidogrel, ACE inhibitors, [beta]-
adrenergic blockers and statins once their role in plaque
stabilization has been proved further. Another potential use of
these modalities can be the identification of subsets of pa-
tients with atherosclerosis who can benefit the most from the
anti-oxidant therapies.

References
1. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis
of coronary artery disease and the acute coronary syndromes. N Engl
3. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen
artery disease and the development of myocardial infarction. J Am
4. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows
MT, Kahl FR, et al. Can coronary angiography predict the site of a
subsequent myocardial infarction in patients with mild-to-moderate
5. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of
6. Richardson PD, Davies MJ, Born GV. Influence of plaque configura-


15. van der Wal AC, Becker AE, van der Loos CM, DAS PK. Site of initial rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994;89:36-44.


