Editorials

Advances in the Detection of the Vulnerable Coronary Atherosclerotic Plaque

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Atherosclerosis is currently considered a systemic disease involving several arterial beds. Recent advances in intravascular imaging have enabled us to detect *in vivo* the primary atherosclerotic changes in the coronary arterial wall and to confirm that a multisite involvement is also true for the coronary arterial bed. Moreover, not only the disease affect more than a single point but there is also discrepancy between the angiographic appearance and the intravascular image, which underscores the limited value of this technique to provide lesion characteristics in detail. This limitation becomes more prominent when we consider that acute myocardial infarction often involves atherosclerotic plaques, which do not have significant stenosis. As a result we cannot reliably predict which of the atherosclerotic plaques are prone to plaque rupture. It has therefore become a clinical challenge to distinguish the "stable" from the "unstable" plaque.

The lesion that is rupture-prone cannot not be clearly defined yet. However, several morphologic and immunologic determinants specific for the vulnerable plaque have been reported[1-9]. Currently we know that an advanced atherosclerotic lesion is characterized by a core of extracellular lipid with an overlaying fibrous collagen-rich cap.

The development of acute coronary syndromes is created in the majority of cases by rupture or erosion of the fibrous cap with subsequent formation of a thrombus and transformation of a former stable coronary atherosclerotic plaque into a complex type of lesion. A smaller percentage of myocardial infarction also appears to arise from vulnerable plaques with somewhat thicker caps that erode or a vulnerable plaque that has an intact cap but suffers from an intraplaque hemorrhage leading to sudden luminal thrombosis and occlusion.

The vulnerable plaque

Thickness of the 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[3]. When there is also high circumferential stress at the luminal border of the plaque, plaque rupture is more likely to occur[10-11]. It has been shown that circumferential stress increases critically when cap thickness is less than approximately 150 μm[10-11].

Size, composition and effect of temperature on the atheromatous lipid core: A large lipid core (more than 40%), rich in cholesterol is at high risk for rupture. Also, lipid in the form of cholesteryl ester softens the plaque, whereas crystalline cholesterol may have the opposite effect.

A negative relation exists between temperature and core stiffness[12-13]. 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[11].

Inflammation within or adjacent to the fibrous cap: An inflammatory-cell infiltrate is a marker of plaque vulnerability. Some factors, including oxidized lipoproteins, infectious agents or autoantigens may provoke a chronic inflammatory reaction in the atherosclerotic plaque, while others including endothelial cells, monocytes and T cells play a role in the promotion of inflammation. As a result a heavy local infiltration by macrophages and often by T-lymphocytes is observed atherosclerotic plaques that are at risk of rupture. Furthermore, elaboration of cytokines and matrix-degrading proteins, lead to a weakening of the connective-tissue framework of the plaque. Smooth-muscle cells may counteract some of these effects by producing matrix, collagen and inhibitors of the matrix-degrading enzymes called metalloproteinases[14].

In conclusion, it is clear that a hemodynamically non-significant coronary atherosclerotic plaque can be ruptured and produce a cardiac event long before it produces significant lumen narrowing and angina pectoris, if the above mentioned plaque characteristics are met. It is therefore important that newer imaging techniques based on recent insights into the vulnerable plaque, become available in clinical practice.

Invasive techniques for evaluation of the atherosclerotic vulnerable plaques

The angiographic recognition of the vulnerable plaque

Most myocardial infarctions occur as a result of occlusion of arteries that did not previously contain a significant stenosis (50%)[15].

Therefore the assumption that only highly stenotic sites 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.

Other limitations of coronary angiography in recognition of the vulnerable atherosclerotic plaque are due to the fact that coronary angiography is only luminography and gives little information about arterial wall pathology. The phenomenon of remodeling makes angiography a poor technique with which to assess the true atherosclerotic burden[16-17]. In addition, the shadows of the coronary lumen provide only indirect and incomplete information concerning the extent of the atherosclerosis process in the arterial wall.

High-frequency (20 to 40 MHz) intravascular ultrasound

The accuracy and reproducibility of intravascular ultrasound to quantitatively assess lumen area, plaque area and vessel area as well as morphologic features like dissections and calcifications before and after balloon angioplasty has been documented.

Intravascular ultrasound is the only imaging modality that provides images in which variations in arterial geometry and atherosclerotic plaque along the artery can be studied *in vivo*[16-17]. This catheter-based imaging technique provides two-dimensional cross-sectional tomographic images of the arterial wall and can accurately assess plaque burden[18].

However, the resolution of the ultrasound system is related to its frequency. Axial resolution is approximately 100 μm to 200 μm for 40-MHz and 20-MHz systems, respectively. Lateral resolution varies widely. For high-frequency (40 to 50 MHz) systems, imaging may be hampered by an increased backscatter of blood[19].

Histopathologic studies mostly report low sensitivities for intravascular ultrasound in detecting lipid-rich lesions although intravascular ultrasound radiofrequency signal analysis may improve tissue characterization[20-21]. Although axial resolution remains too low for measuring cap thickness, a recent study reports that the thickness of the fibrous cap with its rupture were visualized[22]. An intriguing relation between locally altered vessel size and histopathologic and clinical markers for plaque vulnerability has been found with the use of ultrasound[23].

Angioscopy

Although angioscopy allows visualization of the plaque and thrombus with high sensitivity, it re-

mains a research tool because of the inability to examine the different layers within the arterial wall and to provide estimation of cap thickness or lipid content[24].

Thermography

Background

A persistent finding in the histopathological specimens of ruptured atherosclerotic plaques has been the presence of activated macrophages within the plaque[2]. The accumulation of these cells reflects the inflammatory process that has been implicated in the pathogenesis of acute coronary syndromes. Since the cardinal sign of inflammation is increase in temperature it is logical to assume that 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[25].

Recently, *in vivo* studies demonstrated temperature heterogeneity to be determined by plaque composition and more specifically by macrophage mass[26].

The exact mechanism for the increased local temperature in the 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[27]. Regardless of the exact mechanism, heat produced in the plaque may contribute to the vulnerability of the plaque by softening of the lipid core and redistributing and critically concentrating circumferential stress on the fibrous cap, in addition to reflecting the degree of inflammatory process.

Clinical studies

The direct measurement of the temperature of the coronary atherosclerotic plaque has become feasible with the use of a specially designed thermography catheters of 3F size (Figure 1)[28]. A hydrofoil configuration was constructed opposite to the thermistor in order to facilitate contact of the thermistor against the vessel wall.

Figure 1. Thermography catheter with the thermistor on one side at the distal part (two arrows), and the hydrophoil construction at the opposite side (one arrow).

The technical characteristics of the polyamide thermistor included (1) temperature accuracy, 0.05ºC; (2) time constant, 300 ms; (3) spatial resolution, 0.5 mm; and (4) linear correlation of resistance versus temperature over the range of 33ºC to 43ºC.

With the thermography catheter measuring the temperature of the atherosclerotic plaque *in vivo* is feasible.

In the first clinical study with the thermography catheter, thermal heterogeneity within human atherosclerotic coronary arteries and constant temperature in normal coronary arteries was documented. This heterogeneity was found to be larger in unstable angina and acute myocardial infarction patients, implying that it may be related to the pathogenesis of acute coronary syndromes[28].

In another clinical study, using the thermography catheter, the impact of increased local temperature of the atherosclerotic plaque on clinical events, after PTCA and stent implantation, was evaluated[29]. The temperature difference (ΔT) between the atherosclerotic plaque and the healthy vessel wall was greater in patients with adverse cardiac events than in patients without events. Moreover, ΔT was greater in the patients with exertional angina and unstable angina with adverse cardiac events as compared with those without events. ΔT was a strong predictor of adverse cardiac events during the follow-up period (OR 2.14, 95% confidence interval 1.31 to 6.85, $p=0.043$). Sensitivity and specificity analysis showed that the threshold of the ΔT value (cut-off point) above which the risk for an adverse outcome after the intervention was significantly increased, was 0.5ºC (ROC area=77%). The sensitivity for this cut-off point was 86% (18 of 21 patients), and the specificity was 60%. The incidence of adverse cardiac events in patients with $\Delta T>0.5$ºC was 41%, as compared with 7% in patients with $\Delta T<0.5$ºC ($p<0.001$). A Cox survival plot adjusted for ΔT and stratified for the cut-off point showed a

clear relationship between ΔT and event-free survival (Figure 2).

This study showed that plaque temperature was higher in patients with acute coronary syndromes and predicted long term clinical events in patients undergoing PTCA and stent implantation.

Recently, the effect of therapy with statins on atherosclerotic plaque was studied in 72 patients presented with effort angina, unstable angina and myocardial infarction[30]. A progressive increase in difference between the atherosclerotic plaque and the proximal vessel wall was observed regardless of the treatment with statins. However, those who were on statin therapy had smaller differences between the atherosclerotic plaque and the proximal vessel wall compared to those who were not treated with statins. The effect of statin therapy was independent of the clinical syndrome. Thus, a favorable effect of statin therapy, on heat release from atherosclerotic plaques, was documented[30]. This could not be attributed to the lipid lowering effect of statins since there was no correlation between temperature measurements and cholesterol levels.

In addition to the cascade of new information that we were able to obtain by the thermography catheter, we were able to identify factors that could influence *in vivo* measurement of coronary atherosclerotic plaque temperature. Indeed, coronary flow influences thermography measurements and the authors have observed increase in thermal heterogeneity by coronary flow interruption. This observation substantiated the cooling effect of coronary flow on thermal heterogeneity and led us to the creation of a newer version of the thermography

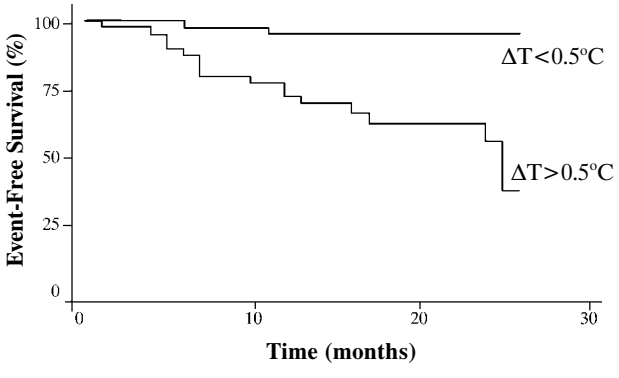

Figure 2. Cox survival plot adjusted for ΔT and stratified for the cut-off point of 0.5°C. The risk of an adverse cardiac event in patient with ΔT>0.5°C is significantly increased as compared with that in patients with ΔT<0.5°C.

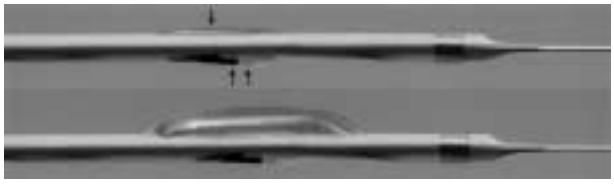

Figure 3. Top: Thermography catheter with the thermistor on one side at the distal part (two arrows), and the inflatable balloon at the opposite side (one arrow). Bottom: Thermography catheter with balloon inflated.

catheter. This catheter is designed in a way that a balloon which is positioned opposite to the thermistor can be inflated and produce interruption of blood flow while facilitating contact of the thermistor with the arterial wall (Figure 3)[31]. Therefore, temperature measurements during coronary flow interruption, thus unaffected from the cooling effect of blood can be obtained *in vivo*. In authors' preliminary experience with the balloon thermography catheter an almost 60% increase was found in thermal heterogeneity of atherosclerotic plaques in patients with effort angina.

Thermography for detection of the vulnerable patient

Postmortem studies have documented a multifocal inflammatory cell infiltration in several coronary branches in patients dying of an acute myocardial infarction[32]. Recently, in patients with unstable angina an extensive spread of the inflammatory process was also detected[33]. These findings challenge the concept of a single vulnerable plaque in patients with acute coronary syndromes and underscore the need for techniques that will detect the "vulnerable patient" rather than the "vulnerable plaque". One way to approach it is the application of the thermographic concept to the blood of the coronary sinus. According to this concept, 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 coronary artery disease and unstable coronary plaques than in those without coronary lesions. Indeed, using a specially designed thermography catheter (7F diameter) with a steering arm at the proximal end and a maneuverable distal tip we were able to position the catheter into the coronary sinus and obtain local blood temperature in 60 patients (Figure 4). Subsequently, blood temperature was obtained in the right atrium and compared with that of the coronary sinus. Preliminary analysis of the data documents higher tem-

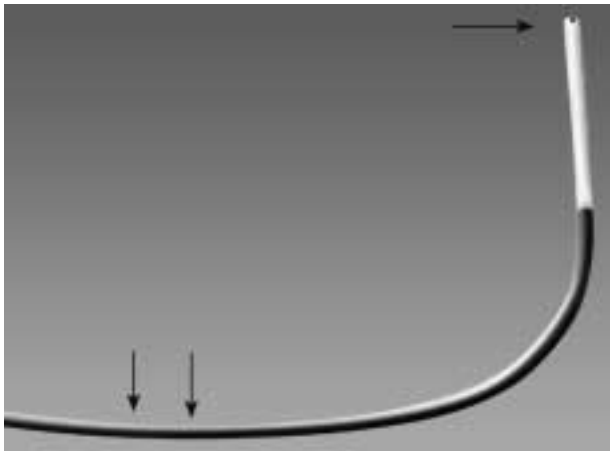

Figure 4. Coronary sinus thermography catheter. The thermistor is positioned at the distal edge of the catheter (one arrow). The shaft of the catheter (two arrows), at the distal part is flexible and is displayed in flexion.

perature of blood in the coronary sinus than in the right atrium, with the highest difference of blood temperature being detected in patients with significant lesions in the left coronary arterial bed. Although coronary sinus thermography is still in its infancy, it is an attractive technique for a global evaluation of the "vulnerable coronary arterial bed" and the "vulnerable patient".

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[34]. The technique is able to discriminate between soft and hard material and assess the mechanical properties of the vessel wall[35]. Hard tissues (calcifications and collagen) will be compressed less than soft-tissue types (lipids).

Using the radiofrequency data of ultrasound images that have been obtained mainly in diastolic part of the heart cycle, strain images are constructed using the relative local displacements, which are estimated from the time shifts between grated echosignals acquired. 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[36].

This technique has the potential to identify plaque vulnerability since the detected areas of increase radial strain represent regions of high circumferential stress, a feature of plaque vulnerability. However a major problem in advancing intravascular elastography to cardiac *in vivo* applications is the acquisition of data in a pulsating artery located in a contracting heart.

Optical Coherence Tomography (OCT)

Using a laser as light source a beam of low coherent infrared spectrum is directed and reflected within the tissue and the intensity of the reflected infrared light rather than acoustic waves is measured.

The intravascular device is capable of visualizing the atherosclerotic lesion with an axial resolution of 2 to 30 μm depending on the spectral width of the source and a lateral resolution of 5 to 30 μm determined by the beam waist. 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[37]. Furthermore, the thickness of the fibrous cap overlying an atheroma can be demarcated by OCT[37]. There are some limitations of optical coherence tomography for *in vivo* intravascular imaging including the reduction of image quality when imaging through blood or large volumes of tissue, the relative slow data acquisition rate and the multiple scattering.

Raman spectroscopy

Raman spectroscopy is ideal for identifying gross chemical changes in tissue, such as in atherosclerosis[38]. It is an imaging modality in an early stage of development that has great potential to discriminate *in vivo* among lipid-rich, calcified and fibrotic plaques. Raman spectra uses light of a single wavelength from a laser that is directed onto the tissue sample via glass fibers. Light scattered from the sample is collected in fibers and launched into a spectrometer. It may be considered the acquisition of a molecular fingerprint.

Penetration depth of the 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 atheromatous core.

Current limitations of Raman spectroscopy are the strong background fluorescence and the 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 allow detailed analysis of chemical composition[39]. 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 into *in vitro* studies.

Non-invasive techniques

Ultrafast computed tomography (UFCT)

UFCT takes advantage of a faster rate of image acquisition than conventional computed tomography (CT). With fast imaging elimination of cardiac and respiratory motion artifacts was accomplished. Since there is an association between coronary calcium and obstructive CAD, it has been suggested that the amount of coronary calcium is a predictor of risk of coronary events.

Therefore, measurements of the amount or volume of calcium in the coronary arteries by electron-beam CT (EBCT), with 3 mm thick slices from the aortic root to the apex of the heart, or fast-gated helical or spiral CT and non-EBCT, using multidetector arrays systems, were performed. Histological and UFCT studies support the association of calcified plaques with tissue densities >130 Hounsfield units[40]. However, it must be admitted that high-risk plaques often lack calcium and that the predictive value of coronary calcification, at least in high-risk subjects, may not be superior to that of standard coronary risk factors. High calcium score is sensitive but not a specific marker for coronary stenosis. 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 intermediate risk. 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 (MR)

High resolution MRI holds the best 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 visualization of atherosclerotic plaques *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 μm) and histopathology. Magnetic resonance imaging studies are currently being performed to study the progression and regression of atherosclerotic plaques over time.

Although MRI is a promising non-invasive tool for detecting vulnerable plaques it lacks sufficient resolution (currently 400 μm) for accurate measurremnts of cap thickness and characterization of the atherosclerotic lesion within the coronary circulation. To improve the signal-to-noise ratio, an intravascular catheter coil has been developed that enhances image resolution to 250 to 300 μm. This intravascular MRI technique shows an 80% agreement with histopathology in analysis of intimal thickness and accurately determines plaque size[41].

More recent studies have reported in-plane resolutions of 117x156 μm for high-resolution intravascular MRI imaging, which is comparable to resolutions as obtained with IVUS. Thus, although difficulties remain with *in vivo* imaging, it may be a matter of time before MRI is used for identification of vulnerable plaques in human coronary artery disease.

Treating the vulnerable coronary atherosclerotic plaque

In view of the current developments and the oncoming new techniques in the evaluation of the atherosclerotic plaque, new treatment strategies may arise. Our knowledge on the cell biology of the plaque rupture suggests that there are many routes to plaque stabilization. Interventional techniques relieve symptoms and may alter the cellular and inflammatory process in the unstable atherosclerotic plaques. However the combination of revascularization and lipid lower therapy will stabilize even more unstable coronary atherosclerotic plaques. Aggressive lipid therapy may stabilize plaque and reduce the risk of further acute coronary events. We now recognize that most plaque disruptions are clinically unapparent. However, when thrombosis occurs, the transforming growth factor-β and the platelet-derived growth factor that are released promote procollagen formation, which results in the thickening of the fibrous cap and decrease in lumen size. This results in stable

but stenotic plaque. Lipid lowering therapy affords the opportunity to reverse cholesterol transport and shrink the lipid core. The inflammatory cells can egress or die by apoptosis. These events can produce a thickened fibrous cap with a preserved lumen. The additive role of antioxidants and anti-inflammatory agents are in need of further clinical research.

Inherrant in the issue of detection of the atherosclerotic plaque is the question what should be done with a "hot" atherosclerotic plaque, at a key site in a coronary artery, which is not causing considerable stenosis. The day of prophylactic angioplasty has not yet arrived - although it may come. In the mean time, aggressive lipid therapy, antiplatelet agents and medications that improve endothelial function would seem the most reasonable approach for this type of lesion.

In the future, thermography may be used for the detection of the vulnerable plaque or even better the vulnerable patient. However, its widespread use will depend on the clinical proof that treatment of the vulnerable plaque or patient as detected by this technique, prevents detrimental outcomes such as acute ischemic coronary syndromes and sudden death.

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