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**Prologue: Detection of Vulnerable Plaques****C1***Jagat Narula, James T. Willerson***New Opportunities for Identification and Reduction of Coronary Risk:****C2****Treatment of Vulnerable Patients, Arteries, and Plaques***James E. Muller, Ahmed Tawakol, Sekar Kathiresan, Jagat Narula*

Understanding of vulnerable plaque, together with novel diagnostic and therapeutic approaches, creates a new opportunity for prevention. Detection of vulnerable plaques by noninvasive and/or invasive methods, followed by treatments such as stenting, photodynamic therapy, and novel pharmaceutical agents might enhance both primary and secondary prevention. Issues of the focal versus systemic nature of atherosclerosis, the ability of detectors to identify their target and link such a target to clinical events, and the efficacy of specific therapy require further study. If vulnerable plaques and patients can be successfully identified and treated, immense benefits will ensue.

**Pathogenesis of Atherosclerosis****C7***Erling Falk*

Atherosclerosis is a multifocal, smoldering, immunoinflammatory disease of medium-sized and large arteries fuelled by lipid. The most devastating consequences of atherosclerosis, such as heart attack and stroke, are caused by superimposed thrombosis. Approximately 76% of all fatal coronary thrombi are precipitated by plaque rupture. Ruptured plaques are characterized by a large lipid-rich core, a thin fibrous cap that contains few smooth muscle cells and many macrophages, angiogenesis, adventitial inflammation, and outward remodeling.

**Pathology of the Vulnerable Plaque****C13***Renu Virmani, Allen P. Burke, Andrew Farb, Frank D. Kolodgie*

It is now recognized that the three main causes of coronary thrombosis are rupture, erosion, and calcified nodule. The most frequent of these is plaque rupture. The precursor lesion to acute rupture is believed to be a thin cap fibroatheroma (TCFA). Thin cap fibroatheroma are characterized by a lack of thrombus, presence of a necrotic core, and a fibrous cap  $<65 \mu\text{m}$ , which is infiltrated by macrophages. These lesions are located in proximal and mid portions of the three main coronary arteries with  $<75\%$  area luminal narrowing. It is believed that if TCFA can be recognized clinically it might be possible to reduce the incidence of sudden death.

Plasma biomarkers that reflect the clinical potential of atherothrombotic disease may allow more precise risk stratification and prognostication in high-risk populations. High-sensitivity C-reactive protein (hs-CRP) improves vascular risk prediction in primary and secondary prevention across all levels of low-density lipoprotein (LDL) cholesterol, all levels of the Framingham Risk Score, and all levels of metabolic syndrome. Several emerging plasma biomarkers, such as lipoprotein-associated lipoprotein-associated phospholipase A<sub>2</sub>, myeloperoxidase, oxidized LDL, lipoprotein (a), isoprostanes, and small, dense LDL, are being evaluated for their clinical utility. This review will focus on hs-CRP and emerging risk factors and their diagnostic and prognostic ability in cardiovascular disease.

### **Imaging Vulnerable Plaque by Ultrasound**

*Anthony N. DeMaria, Jagat Narula, Ehtisham Mahmud, Sotirios Tsimikas*

Recent intravascular ultrasound (IVUS) studies have suggested that patients presenting with acute coronary syndromes have an approximate 25% incidence of additional ruptured plaques in arteries other than the culprit lesion. New applications of IVUS, such as integrated backscatter, wavelet analysis, and virtual histology, can provide a color-coded representation of plaque characteristics such as lipid, fibrous tissue, calcification, and necrotic core. In addition, targeted contrast agents are being explored to more precisely image aspects of vulnerable plaques. These advances pave the way for future clinical trials to assess the ability of such techniques to diagnose vulnerable plaques and to assess the effects of both pharmacologic and mechanical therapies on plaque characteristics.

### **Atherosclerotic Plaque Characterization by Multidetector Row Computed Tomography Angiography**

*Marco A. S. Cordeiro, João A. C. Lima*

Multidetector row computed tomography angiography (MDCTA) is a potential alternative to current imaging methods to assess vessel anatomy and atherosclerotic plaque composition/morphology. Multidetector row computed tomography angiography correlates well with intravascular ultrasound (IVUS) and histopathology for discrimination between soft, intermediate, and calcified plaques. Plaque area and volume tend to be underestimated by 12-detector row MDCTA and overestimated by 16-detector row MDCTA. However, 64-detector row MDCTA can measure them with greater accuracy. Plaque remodeling is overestimated in small vessels by 12-detector row MDCTA, whereas 16- and 64-detector row MDCTA correlate well with IVUS. Future characterization of atherosclerotic plaque composition and determination of plaque area, volume, and remodeling by MDCTA is quite promising.

**C32**

**C40**

## **Role of Magnetic Resonance and Intravascular Magnetic Resonance in the Detection of Vulnerable Plaques**

C48

*Robert L. Wilensky, Hee Kwon Song, Victor A. Ferrari*

The outstanding soft-tissue-characterizing capabilities of magnetic resonance imaging (MRI) permit depiction of various components of atherothrombotic plaque, including lipid, fibrous tissue, calcium, and thrombus formation. This review discusses the current state of research in noninvasive MRI, the combination of MRI and contrast agents, and the self-contained intravascular MRI catheter.

## **Radionuclide Imaging for the Detection of Inflammation in Vulnerable Plaques**

C57

*John R. Davies, James H. F. Rudd, Peter L. Weissberg, Jagat Narula*

High risk, vulnerable atherosclerotic plaques are characterized by high numbers of inflammatory cells and proteins. Consequently, there is an urgent need for imaging techniques that can identify and quantify levels of inflammation within atheromatous lesions. Nuclear tracer compounds capable of assessing macrophage recruitment, foam cell generation, matrix metalloproteinase production, macrophage apoptosis, and macrophage metabolism have been developed and tested in the carotid and peripheral circulation. But the identification of inflamed lesions within the coronary circulation remains problematic, owing to the small plaque size and lack of a suitable nuclear tracer.

## **Plaque Characterization With Optical Coherence Tomography**

C69

*Debra Stamper, Neil J. Weissman, Mark Brezinski*

The identification of unstable plaque is central in risk-stratifying patients for acute coronary events. Optical coherence tomography (OCT) is a recently introduced imaging modality that has shown considerable promise for the identification of high-risk plaques. Advantages of OCT include its high resolution (4 to 20  $\mu\text{m}$ ), high data acquisition rate, small and inexpensive guidewires/catheters, and ability to be combined with adjuvant optical techniques. This article summarizes the current state of intravascular OCT imaging, focusing on potential markers of instability and current limitations.

## **Intracoronary Thermography for Detection of High-Risk Vulnerable Plaques**

C80

*Mohammad Madjid, James T. Willerson, S. Ward Casscells*

Inflammation is a cornerstone of plaque vulnerability. Inflamed atherosclerotic plaques are hot and their surface temperature correlates with an increased number of macrophages and decreased fibrous-cap thickness. Several animal and human experiments have shown that temperature heterogeneity correlates with arterial inflammation. We review the results of studies using several thermography catheters. Coronary thermography may be used to detect vulnerable plaques, to determine patients' prognosis, and to study the plaque-stabilizing effects of different interventions.

### **Intravascular Palpography for Vulnerable Plaque Assessment**

*Johannes A. Schaar, Anton F. W. van der Steen, Frits Mastik, Radj A. Baldeusing, Patrick W. Serruys*

**C86**

Palpography assesses local mechanical tissue properties. In vitro validation using human specimens revealed a significant difference in strain between fibrous and fatty tissue. High strain at the lumen has 88% sensitivity and 89% specificity for identifying vulnerable plaques. In vivo validation in animals showed higher strain in fatty plaques than in fibrous plaques. High strain at the lumen had high predictive value to identify macrophages. Three-dimensional palpography showed that patients with myocardial infarction or unstable angina have more high strain spots in their coronaries than patients with stable angina. In conclusion, palpography may become a decision-making tool for identifying vulnerable plaques.

### **Near-Infrared Spectroscopy for the Detection of Vulnerable Coronary Artery Plaques**

*Jay D. Caplan, Sergio Waxman, Richard W. Nesto, James E. Muller*

**C92**

This review describes efforts to use near-infrared (NIR) spectroscopy to identify chemical components of coronary artery plaques as a means to assess vulnerability. Studies have confirmed the ability of the technique to identify lipid-rich thin-cap fibroatheromas in aortic and coronary artery autopsy specimens. Initial clinical experience in six stable angina patients with a new catheter-based system demonstrates that high-quality NIR spectra can be safely obtained.

### **Intravascular Radiation Detectors for the Detection of Vulnerable Atheroma**

*H. William Strauss, Carina Mari, Bradley E. Patt, Vartan Ghazarossian*

**C97**

To identify metabolically active atheroma, a beta radiation-sensitive catheter suitable for use in the coronary arteries was developed. Macrophages are a major component of metabolically active atheroma. Specific characteristics of these inflammatory cells, such as increased metabolism, expression of chemotactic receptors, or the high frequency of apoptosis-associated phosphatidylserine expression can be used to localize these cells in vivo using appropriate radiolabeled substrates. A prototype catheter, using a plastic scintillator mated to an optical fiber, had sufficient sensitivity to detect lesions concentrating approximately 0.000001% of the typical 15-mCi dose of <sup>18</sup>fluorodeoxyglucose (FDG), a level of <sup>18</sup>FDG found in mice with experimental atheroma.

### **Epilogue: What Do Clinicians Expect From Imagers?**

*Eugene Braunwald*

**C101**