Imaging the Vulnerable Plaque: The Future is Here

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The risk of a vulnerable patient is affected by vulnerable plaque and/or vulnerable blood and/or vulnerable myocardium

Different types of vulnerable plaque as underlying cause of acute coronary events (ACS) and sudden cardiac death (SCD)

70% of all vulnerable plaques
30% of all vulnerable plaques

Correlation between frequency of plaques, degree of stenosis, and risk of complication per plaque as a function of plaque progression
The Most Common type of Vulnerable Plaque

▪ A vulnerable plaque has a thin fibrous cap and a large and soft lipid pool underlying the cap (rupture-prone plaque)
  – The most frequent cause of a cardiac event following rupture of a vulnerable plaque is blood clotting on top of the site of the ruptured plaque that blocks the lumen of the artery.

Despite major advances in treatment of coronary heart disease patients, a large number of victims of the disease who are apparently healthy die suddenly without prior symptoms

▪ Repeated atheroma rupture and healing is one of the mechanisms, perhaps the dominant one, which creates artery stenosis.

How do a Vulnerable Plaque form?

▪ Lipoprotein particles are absorbed by the artery wall, past the endothelium lining, cholesterol is released and then oxidized. This process typically starts in childhood.

▪ Oxidized cholesterol causes the release of proteins called cytokines.

▪ The cytokines make the artery wall sticky, which attracts immune-system white blood cells (specifically monocytes).

▪ The monocytes squeeze into the artery wall. Once inside, they transform into eating cells called macrophages and ingest the oxidized cholesterol droplets.

▪ The macrophages dye in place, releasing their fat laden membranes into the intracellular space. This attracts more macrophages.

▪ In some regions of increased macrophage activity, macrophage induced enzymes erode away the fibrous membrane beneath the endothelium so that the cover separating the plaque from blood flow in the lumen becomes thin and fragile.
Schematic figure illustrating the most common type of vulnerable plaque characterized by thin fibrous cap, extensive macrophage infiltration, paucity of smooth muscle cells, and large lipid core, without significant luminal narrowing.

A large lipid core (>40%) rich in cholesterol is at a 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. If temperature increases, as in inflammation, the core becomes softer. A soft core may be more vulnerable to rupture because it may not be able to bear the imposed circumferential stress.
Angiography and stress testing

- Because artery walls typically enlarge in response to enlarging plaques, these plaques do not usually produce much stenosis of the artery lumen. Therefore, they are not detected by cardiac stress tests or angiography.

Plaques with nearly similar morphology in terms of lipid core and fibrous cap (middle panel) may look similar with diagnostic imaging aimed at morphology only (bottom panel).
Non-Invasive Techniques for Assessing Vulnerable Plaque

▪ Multislice computed tomography (MSCT)
  – X-ray-based technology with good temporal resolution that has been improved in the next generation of CT scanners.
  – Volumetric CT scanners will have a temporal resolution under 50 milliseconds, a scan time of just one heartbeat, and an isotropic resolution (all three dimensions) of 0.2 millimeter.
  – While this level of sensitivity can detect a fibrous cap, it will not be enough to identify an inflamed thin-cap fibroatheroma (TCFA), and some data can be lost in signal processing.

▪ Magnetic resonance imaging (MRI)
  – Better signal-to-noise and contrast-to-noise ratios
  – allow visualization of smaller vessels and branches.
  – in-plane resolutions of 0.6 mm x 0.6 mm are adequate for differentiating some plaque features
  – out-of-plane resolution (slice thickness) is 1.5 mm. This is not sensitive enough to identify thin caps on the order of 100 microns.

Invasive Techniques for Assessing Vulnerable Plaque

▪ Invasive technologies provide the best methods for the detection of vulnerable plaque in coronary arteries

▪ Technologies included in this group are
  – optical coherence tomography (OCT)
  – near-infrared (NIR) spectroscopy
  – intravascular MRI
  – intravascular ultrasound (IVUS)
  – virtual histology
  – Palpography

Most of these techniques are used primarily in research settings and clinical studies, and are not yet available in clinical practice.
Optical Coherence tomography

▪ “Optical coherence tomography is a light-based technique that has excellent spatial resolution and can identify thin fibrous caps and detect macrophages.

▪ The location and density of macrophages in a plaque can be detected based on speckle analysis in OCT images

▪ Researchers are studying macrophage density in patients with ST-elevated MI, acute coronary syndrome, and stable angina. Using OCT, they have shown that macrophage density is higher in acute clinical syndromes and lower in the stable group.

▪ OCT cannot scan through blood, the vessel of interest must first be cleared of blood by flushing or with a balloon

▪ OCT cannot image the entire vessel at one time.”

Optical coherence tomography shows macrophage density in a plaque.
Near-infrared spectroscopy (NIR)

- Near-infrared spectroscopy (NIR) is a light-based technique that employs an IVUS-like rapid-exchange coronary catheter that rotates the light beam.
- Spectra acquisition is rapid, about 5 milliseconds.
- Absorbance is plotted against wavelength to produce a spectrum that correlates to attenuation through the tissue.
- A well-validated method, NIR is frequently used to assess the chemical composition of the vessel wall. When used in autopsy specimens, TCFA sensitivity and specificity was greater than 85%.
- Unlike OCT, NIR is able to scan through blood. The availability of laser, fiber-optic, and chemometric technologies make intracoronary use feasible.

Four Tissue Classifications

- Normal
- Lipid
- Fibrotic
- Calcific
NIR Spectra of Human Aorta Samples

Source: Infraredx, 2002

Summary Prediction Results

<table>
<thead>
<tr>
<th></th>
<th>NIR (+)</th>
<th>NIR (-)</th>
<th>Results (a)</th>
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<tr>
<td>Lipid Pool (+)</td>
<td>164</td>
<td>16</td>
<td>Sensitivity: 91%</td>
</tr>
<tr>
<td>No Lipid Pool (-)</td>
<td>66</td>
<td>484</td>
<td>Specificity: 88%</td>
</tr>
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intravascular MRI

- intravascular MRI is a newer catheter-based real-time technique that does not require external magnets.
- Intravascular MRI has a high sensitivity and specificity for differentiating fibrous tissue and lipid rich necrotic cores.
- The technique requires time to position the catheter with a balloon inside the vessel wall.
- Also, because it is a somewhat “noisy” technique, data assessment requires relatively more time.

Noninvasive MRI of carotid plaque macrophages using dextran-coated iron oxide MNPs

Experimental MRI of inflammation in atherosclerosis using multimodality magnetofluorescent nanoparticles (MFNP)

Intravascular Ultrasound and Vulnerable Plaque

- Intravascular ultrasound (IVUS) allows in vivo visualization of variations in arterial geometry and atherosclerotic plaque. It provides a two-dimensional cross-sectional image of the arterial wall and can accurately assess the plaque burden.
- IVUS permits the investigation of plaque morphology and the direction and extent of arterial remodeling with much accuracy.
- The resolution of the ultrasound system is related to its frequency.
  - Axial resolution is approximately 100 µm and 200 µm for 40-MHz and 20-MHz systems, respectively.
  - Lateral resolution varies widely.
  - For high-frequency (40-50 MHz) systems, imaging may be hampered by an increased back-scatter of blood.
  - Histopathologic studies mostly report low sensitivity for IVUS in detecting lipid-rich lesions, although IVUS radiofrequency signal analysis may improve tissue characterization.

Virtual histology IVUS

- Virtual histology using intravascular ultrasound (VH IVUS) relies upon a radiofrequency analysis of the intravascular ultrasound spectra to identify plaque components including fibrous tissue, fibrous fatty tissue, the necrotic core, and dense calcium.
- This technique allows much more complete lesion assessment, including plaque composition, on top of the traditional IVUS plaque descriptors, minimal luminal diameter (MLD), proximal and distal vessel diameter, and plaque dimensions themselves.

Palpography (1)

- Palpography uses ultrasound to “palpate” a vessel from the inside. The images are correlated to levels of deformation (strain) using Young’s Modulus (E), which provides a measure of relative hardness that differentiates tissue components.
- Atheroma, for example, is lipid-rich and soft, having an E of 4 kPa; fibrous intimal tissue is more than 100 times harder (E=483 kPa), and calcified regions are 1000 times harder (E=4000 kPa) than atheroma.
- A high degree of deformation may be associated with a thin-cap fibrous atheroma.
- Palpography has been shown to be very sensitive and specific, detecting TCFA 90% of the time.
- In addition to the thin cap, it captures information about other hallmarks of VP including macrophages and smooth muscle cells.
- Results from in vitro studies showed that higher levels of macrophages, fewer smooth muscle cells, and thinner caps all produced higher strain levels. In vivo studies revealed that the number of high strain spots in a vessel was directly related to the patient's condition and to CRP levels.
Palpography (2)

- In a study that utilized integrated technologies (multislice CT, grayscale IVUS, virtual histology, palpography, biomarkers) to monitor stable, unstable, and ST-elevated MI patients (N=52), palpography was the only technology that was able to show a treatment effect.
  - The ST-elevated MI group showed a 50% reduction in the Schaar, Mastik, van der Steen (SMS) index, which is a measure for the instability of a vessel based on palpographic measurements, at 6 months compared to baseline.
  - In contrast, compared to baseline, neither the stable nor the unstable group showed significant changes in SMS index at 6 months. These results probably reflect the fact that 11 of the 12 patients in the ST-elevated MI group were naïve to medication at baseline, while patients in the other groups were already being treated with medications (primarily statins) at baseline.

Emerging Other Techniques

- **Thermography.** The warmer the plaque, the more likely it will crack or rupture
- **Wall thickness,** usually abbreviated IMT in portions of larger arteries closest to the skin, such as the carotid or femoral arteries
- **Vulnerable plaque** has a low pH (is more acidic) and that such acidic plaques are more likely to rupture. A fiberoptic catheter that will allow measurement of the pH of a plaque is being developed.
Prevention of rupture of vulnerable Plaque

▪ Aspirin
▪ eat a proper diet
▪ quit smoking
▪ begin an exercise program.
▪ Better control of Obesity and diabetes which are linked to high levels of C-reactive protein
▪ Statins, ACEI, ARB all reduce cardiovascular events
▪ “COURAGE trial: "optimal medical therapy" (not PTCA) produced the most effective results in terms of improving human survival and quality of life for those who have been identified as having already developed advanced cardiovascular disease with many vulnerable plaques”

Summary

▪ “The concept of “vulnerable plaque” is changing the way that cardiologists treat coronary artery disease.
▪ Potential biomarkers that offer predictive, clinically useful information about VP and disease progression are being evaluated.
▪ The role of imaging in VP therapy is still a matter of debate; however, there’s no doubt that a combination of imaging and biomarkers will be important in clinical trials and drug development.
▪ These research activities will determine what treatments are indicated, when they should be initiated, and how to better quantify an individual patient’s risk for acute cardiovascular events.”