Invasive Coronary Imaging Modalities for Vulnerable Plaque Detection

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Greyscale IVUS studies have shown

- Plaque ruptures do not occur randomly or at minimally diseased sites.
- Rather, plaque ruptures (and, therefore, rupture-prone plaques) predictably occur in large, proximal coronary arteries with significant plaque accumulation and positive remodeling. It is only the degree of lumen compromise that is variable and often insignificant.
- Nevertheless, greyscale IVUS cannot predict or even detect a vulnerable plaque.
Proximal

- EEM CSA = 21.0mm²
- Lumen CSA = 9.5mm²
- P+M CSA = 11.5mm²

- Max P+M Thickness=3.0mm
- Plaque burden=0.79
- Remodeling index=1.3

0 → 3mm → 12mm

EEM CSA = 23.5mm²
Lumen CSA = 5.5mm²
P+M CSA = 18.0mm²

EEM CSA = 13.7mm²
Lumen CSA = 9.3mm²
P+M CSA = 4.4mm²
Only the envelope amplitude (echo intensity) is used to form the **gray-scale IVUS** image.

Among reflected ultrasound signals of the same intensity, frequency can also vary depending on the tissue.
Two examples of plaque composition classification trees based on these 8 parameters

- maximum power
- corresponding frequency
- minimum power
- corresponding frequency
- Slope
- y-intercept
- mid-band fit
- integrated backscatter
Eagle Eye (20MHz Electronic Array Transducer)

VH IVUS vs histopathology from fresh 51 fresh, post mortem LADs (115 sections and 407 regions of interest)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous tissue (n=162)</td>
<td>84.0%</td>
<td>98.8%</td>
<td>92.8%</td>
</tr>
<tr>
<td>Fibrofatty (n=84)</td>
<td>86.9%</td>
<td>95.1%</td>
<td>93.4%</td>
</tr>
<tr>
<td>Necrotic core (n=69)</td>
<td>97.1%</td>
<td>93.8%</td>
<td>94.4%</td>
</tr>
<tr>
<td>Dense calcium (n=92)</td>
<td>97.8%</td>
<td>99.7%</td>
<td>99.3%</td>
</tr>
</tbody>
</table>
Fibroatheroma

Fibrotic cap and significant necrotic core
(confluent NC >5% of total plaque volume)
within fibrotic or fibrofatty tissue
Fibroatheroma with evidence of thick fibrous cap

Fibroatheroma without evidence of thick fibrous cap
Thin Cap Fibroatheroma (TCFA)

“Thin Cap Fibro-Atheroma (TCFA)” or “Vulnerable Plaque” -- Necrotic Core >10% of total plaque and located at or near the lumen in 3 consecutive frames. Based on the presence or absence of Ca, the length of the NC, or signs of previous ruptures, TCFA can be further sub-classified for the purpose of risk assessment.

- Confluent NC >20%
- No evidence of fibrotic cap
- Calcium >5%
- Remodeling index >1.05
- >50% plaque burden by IVUS

“Highest Risk TCFA”

“TICFA without significant narrowing” - plaque burden <50% on IVUS and/or less than 25% narrowing on angiogram.

Still further sub-classification can be based on presence of luminal narrowing.

(Pathologic data suggests that TCFA without significant plaque burden are less “vulnerable”)

(Pathologic data suggests that TCFA with significant plaque burden are the most vulnerable)
Multiple small calcific deposits by greyscale IVUS, multiple necrotic cores by VH-IVUS
Healed ruptures are common in patients with acute events

- In 142 men with sudden cardiac death, the mechanism of death was presumed to be acute plaque rupture with acute thrombus in 44, acute plaque erosion with acute thrombus in 23, stable plaque with healed MI in 41, and stable plaque without MI in 34.

- There were 189 healed rupture sites. Healed ruptures were present in 75% of hearts with acute plaque rupture and 80% of hearts with stable plaque and healed MI.

- Of the 44 acute rupture sites, 9 showed 1 healed previous rupture site, 9 showed 2 healed previous rupture sites, 9 showed 3 healed previous rupture sites, and 6 showed 4 healed previous rupture sites.

- Acute ruptures at sites of ≥3 healed previous ruptures demonstrated greater underlying plaque burden (94±4%) than those without healed previous rupture (74±12%).

(Burke et al. Circulation 2001;103;934-40)
26 vulnerable vs 28 non-vulnerable plaques

![Graph showing strain (%) vs specificity and sensitivity]

(R² = 0.68, P < 0.0001)

26 vulnerable vs 28 non-vulnerable plaques

![Box plots for Macrophages, Smooth Muscle Cells, and Collagen]

(Schaar et al. Circulation 2003;108:2636-41)
Independent predictors of strain were macrophages ($p=0.006$) and smooth muscle cells ($p=0.0001$).
VH-IVUS vs Palpography (N=27 patients, 60 high strain spots, and 63 low strain spots)

- Weak inverse correlation between %dense calcium and strain level ($r=-0.20$, $p=0.03$)
- No significant correlation between %necrotic core ($r=0.11$, $p=0.25$) or fibrotic or fibrofatty plaque vs strain level
- Strain was higher when necrotic core was in contact with the lumen ($1.03 \pm 0.5\%$ vs $0.86 \pm 0.4\%$, $p=0.06$)
- Necrotic core in contact with the lumen was the only independent predictor of high strain (OR=5.0, $p=0.003$)
- Sensitivity of VH-IVUS 75% and specificity 44% to detect high strain.

(Rodriguez-Granillo et al. Am Heart J 2006;151:e1-e6)
Integrated Backscatter (IB) IVUS

## Diagnostic accuracy of real-time IB (Integrated Backscatter)-IVUS

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcification (n=144)</td>
<td>95%</td>
<td>99%</td>
<td>93%</td>
<td>99%</td>
</tr>
<tr>
<td>Fibrosis (n=335)</td>
<td>94%</td>
<td>93%</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>Lipid pool (n=205)</td>
<td>90%</td>
<td>92%</td>
<td>85%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Stable Plaque

Vulnerable Plaque Causing ACS

* guidewire artifact

(Sano et al. J Am Coll Cardiol 2006;47:734-41)
Relation between IB-IVUS thickness of fibrous cap, thickness of lipid core, and angioscopic appearance: Angioscopic plaque color reflects thickness of fibrous cap rather than size of lipid core.

**IB-IVUS predictors of vulnerable plaques**

**% Fibrous area**
- Sensitivity: 25%
- AUC = 0.98

**% Lipid area**
- Sensitivity: 65%
- AUC = 0.96

**Remodeling index**
- Sensitivity: 1.25
- AUC = 0.90

**Eccentricity rate**
- Sensitivity: 0.65
- AUC = 0.84

**Plaque burden**
- Sensitivity: 55%
- AUC = 0.85

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>% fibrous area (&lt;25%)</td>
<td>90%</td>
<td>96%</td>
<td>69%</td>
<td>99%</td>
<td>95%</td>
</tr>
<tr>
<td>% lipid area (&gt;65%)</td>
<td>80%</td>
<td>90%</td>
<td>42%</td>
<td>98%</td>
<td>89%</td>
</tr>
</tbody>
</table>

(Sano, K. et al. J Am Coll Cardiol 2006;47:734-741)
Vasovasorum Imaging

Normal

Hypercholesterolemia

Hypercholesterolemia + Statin
Baseline images are acquired for 20 seconds, and regions of interest are assigned.
Contrast is injected, images are acquired for 120 seconds post-injection, and baseline images are subtracted.
The optical analog of IVUS, OCT measures **optical reflections**.
<table>
<thead>
<tr>
<th></th>
<th>IVUS</th>
<th>OCT</th>
<th>OFDI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resolution</strong></td>
<td>100 - 150 µm (axial)</td>
<td>10 µm (lateral)</td>
<td>10 µm (lateral)</td>
</tr>
<tr>
<td></td>
<td>150 - 300 µm</td>
<td>25 - 40 µm</td>
<td>25 - 40 µm</td>
</tr>
<tr>
<td><strong>Size of imaging core</strong></td>
<td>0.8 mm</td>
<td>0.4 mm</td>
<td>0.4 mm</td>
</tr>
<tr>
<td><strong>Dynamic range</strong></td>
<td>40 - 60 dB</td>
<td>90 - 100 dB</td>
<td>90 - 100 dB</td>
</tr>
<tr>
<td><strong>Frame rate</strong></td>
<td>30 frames/s</td>
<td>15 frames/s</td>
<td>400 frames/s</td>
</tr>
<tr>
<td><strong>Scan area</strong></td>
<td>10 - 15 mm</td>
<td>6-7 mm</td>
<td>6-7 mm</td>
</tr>
<tr>
<td><strong>Max. penetration</strong></td>
<td>4 - 8 mm</td>
<td>1 – 1.5 mm</td>
<td>1 – 1.5 mm</td>
</tr>
<tr>
<td><strong>Blood clearing</strong></td>
<td>Not required</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td><strong>Balloon Occlusion</strong></td>
<td></td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td><strong>Flushing</strong></td>
<td></td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td><strong>Pullback</strong></td>
<td>0.5mm/s (no limit)</td>
<td>1mm/s (35mm)</td>
<td>30mm/s (90mm)</td>
</tr>
</tbody>
</table>
Plaque characteristics

Fibrous
• High reflectivity
• Homogenous
• Finely textured

Lipid-rich
• Low reflectivity
• Homogenous
• Diffuse margins

Calcific
• Low reflectivity
• Inhomogenous
• Sharp margins

(or isolated, strong reflections in dark background)
## In vitro Validation

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+ Predictive Value</th>
<th>- Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrous</strong></td>
<td>.87</td>
<td>.97</td>
<td>.88</td>
<td>.96</td>
</tr>
<tr>
<td><strong>Calcific</strong></td>
<td>.95</td>
<td>1.0</td>
<td>1.0</td>
<td>.95</td>
</tr>
<tr>
<td><strong>Lipid Pool</strong></td>
<td>.92</td>
<td>.94</td>
<td>.81</td>
<td>.97</td>
</tr>
</tbody>
</table>

Interobserver $k = 0.88$; Intraobserver $k = 0.91$

(Yabushita et al. Circulation 2002;106:1640-5)
Correlation between OCT and Histology Measures of Fibrous Cap Thickness

Histology (microns)

OCT (microns)

\[ y = 1.02x + 3.8 \]
\[ r = 0.89 \]
\[ p < 0.0001 \]
Thick-capped fibroatheroma

- High lipid content
- Fibrotic intima

Thin-capped fibroatheroma

- High lipid content
- Thin fibrous cap with Ca beneath

Histology courtesy of E. Mont and R. Virmani, Armed Forces Institute of Pathology, Washington, DC
Macrophages by OCT

Stable Angina

Post-MI

Lumen

LP
NIR Spectroscopy can identify the chemical composition of unknown substances and distinguish cholesterol from collagen.
Chemogram Showing NIR Detection of Lipid-rich Plaque

Coding Based on Histology (LRP=Lipid-rich Plaque)
Identification of lipid-rich plaque by NIR in 9 test hearts
Intravascular MRI

Conventional MRI Scanner

- Bo Field*
- B1 Field
- Time-Varying Gradient
- Bo Field

Intravascular MRI Probe

- Magnets
- Tx/Rx Coil
- Static Gradient
- B1 Field
- Bo Field

Blank et al, Magnetic Resonance in Medicine, June 2005
ADC vs. Histology in Human Aortas
Lipid fraction index (LFI) per patient and per lesion. LFI does not correlate with angiographic diameter stenosis.

- **Low Lipid**
- **Moderate Lipid**
- **High Lipid**

The image shows a bar chart and a graph indicating the distribution of lipid fraction index (LFI) and its correlation with angiographic diameter stenosis (QCA %DS). The correlation coefficient is given as \( r^2 = 0.035 \).
No study has shown the predictive value of any of the previously mentioned technologies. In addition, thin-capped fibroatheromas (TCFAs) represent only an estimated 70% of vulnerable plaques.