Pathogenesis, Detection, and Treatment of Vulnerable Plaque: IVUS, VH, and other IVUS-based Imaging Diagnostics

Gary S. Mintz, MD

Cardiovascular Research Foundation
New York City, NY
Disclosures

- Boston Scientific
- Volcano
- Light Lab
- Terumo
“Vulnerable Plaque” = thrombosis-prone plaque and plaque with a high probability of undergoing rapid progression

70% of ACS culprit lesions

30% of ACS culprit lesions

IVUS profile of ruptured plaques: Insights into pre-rupture morphology
<table>
<thead>
<tr>
<th></th>
<th>Mean ±1SD</th>
<th>CoV</th>
<th>10&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
<th>90&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen CSA</td>
<td>11.7±3.5</td>
<td>0.29</td>
<td>8.1</td>
<td>15.3</td>
</tr>
<tr>
<td>EEM CSA</td>
<td>20.2±5.6</td>
<td>0.27</td>
<td>14.2</td>
<td>26.7</td>
</tr>
<tr>
<td>P&amp;M CSA</td>
<td>8.5±3.0</td>
<td>0.35</td>
<td>4.9</td>
<td>12.4</td>
</tr>
<tr>
<td>Plaque Burden</td>
<td>0.42±0.75</td>
<td>0.18</td>
<td>0.31</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Lesion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen CSA</td>
<td>4.9±2.7</td>
<td>0.55</td>
<td>2.1</td>
<td>8.6</td>
</tr>
<tr>
<td>EEM CSA</td>
<td>20.8±6.0</td>
<td>0.29</td>
<td>14.3</td>
<td>28.5</td>
</tr>
<tr>
<td>P&amp;M CSA</td>
<td>15.9±4.9</td>
<td>0.31</td>
<td>9.8</td>
<td>22.4</td>
</tr>
<tr>
<td>Min P&amp;M Th</td>
<td>0.5±0.3</td>
<td>0.58</td>
<td>0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Max P&amp;M Th</td>
<td>2.3±0.6</td>
<td>0.25</td>
<td>1.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Eccentricity</td>
<td>0.32±0.23</td>
<td>0.71</td>
<td>0.09</td>
<td>0.66</td>
</tr>
<tr>
<td>Plaque Burden</td>
<td>0.76±0.10</td>
<td>0.12</td>
<td>0.63</td>
<td>0.88</td>
</tr>
<tr>
<td>AS</td>
<td>0.57±0.19</td>
<td>0.34</td>
<td>0.28</td>
<td>0.80</td>
</tr>
<tr>
<td>RI</td>
<td>1.10±0.20</td>
<td>0.18</td>
<td>0.87</td>
<td>1.38</td>
</tr>
<tr>
<td>Arc of Ca++</td>
<td>46.9±51.2</td>
<td>1.09</td>
<td>0</td>
<td>106.7</td>
</tr>
</tbody>
</table>

99% of ruptured plaques fit 4 of these 5 parameters
• The 10th or 90th percentile parameters of the 5 variables with the narrowest coefficient of variance were
  • Reference lumen area > 8.1 mm²
  • Lesion EEM area > 14.3 mm²
  • Lesion max plaque thickness > 1.6 mm
  • Lesion plaque burden > 0.63
  • Remodeling index > 0.87

Unfortunately, it is impossible to determine whether this lesion has the histologic and mechanical substrates for a rupture-prone plaque.
Only the envelope amplitude (echo intensity) is used in formation of the gray-scale IVUS image.

Eight amplitude and frequency parameters are used in Virtual Histology.

Frequency of echo signal can also vary, depending on the tissue.
Thin plate spline morphing after which the computer was taught to recognize four basic tissue types.
Fibroatheroma without evidence of thick fibrous cap

Fibroatheroma with evidence of thick fibrous cap
Positive correlation between lipid core and remodeling - negative correlation between fibrous tissue and remodeling

Lesion types and remodeling

Positive Remodeling (RI>1.05)

Negative Remodeling (RI<0.95)

Fibrocalcific
Intimal thickening
Fibroatheroma
TCFA

Frequency of TCFA in secondary non-obstructive lesions (<50%DS, n=55)

- 99 TCFA identified
- No relationship between TCFA and gender, diabetes, smoking, hypercholesterolemia, hypertension, family history
- Located within
  - 1st 10mm in 35%
  - 10-20mm in 31%
  - 20-30mm in 19%
  - 30-40mm in 14%

On average the proximal 35mm of the artery was imaged

Changes in Plaque Content at Distances from the Ostium of the Coronary artery

Valgimigli et al. Eur Heart J 2006 27:655-663
### Diagnostic accuracy of real-time IB (integrated Backscatter)-IVUS

<table>
<thead>
<tr>
<th>Condition</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 in press)
Plaque Vulnerability

Compositional properties

- Large lipid pool
- Thin fibrous cap
- Presence of macrophages

Mechanical properties

- High strain region
Principles of Palpography

IVUS at 85mmHg

(t₁, P₁)

(t₂, P₂)

IVUS at 90mmHg

Processing

IVUS elastogram
26 vulnerable vs 28 non-vulnerable plaques

Independent predictors of strain were macrophages ($p=0.006$) and smooth muscle cells ($p=0.0001$)

Three-dimensional IVUS images and color mapping of longitudinal stress distribution assessed using finite element analysis

Relationship between stress distribution and plaque shape, luminal stenosis, or vessel remodeling
Effect of lipid core on stress distribution

A1: plaque model
- vessel wall
- plaque
- lipid core

A2: equivalent stress distribution (relative mapping)

B1: plaque model
a. 

B2: equivalent stress distribution (absolute mapping)

Equivalent stress
- min
- max

60 100 140 180 220 260 300 (kPa)
Effect of fibrous cap thickness and surface calcific deposits on stress distribution
Vasovasorum Imaging

Normal

Hypercholesterolemia

Hypercholesterolemia + Statin
Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta

Moreno P et al, Circulation 2004; 110:2032-8
Plaque blush, branch location, and calcification were angiographic predictors of progression of mild to moderate coronary stenoses in 68 patients.

Predictors of progression

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque blush</td>
<td>12.2</td>
<td>0.0015</td>
</tr>
<tr>
<td>Calcification</td>
<td>6.1</td>
<td>0.0235</td>
</tr>
<tr>
<td>Branch point</td>
<td>13.9</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

Casscells et al. Am Heart J 2003;145:813-20
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.
Pre-injection (Frame #200)
Background motions are cancelled

Peak Injection (Frame #600)
Lumen subtracted (microbubble shadow effect is not calculated)

Post-injection (Frame #800)
The enhancement lasts for at least 25 seconds.
Time-activity curves with quantitative monitoring of plaque perfusion

Intimo-Medial and Plaque Area

Adventitia Area
The PROSPECT Trial
Providing Regional Observations to Study Predictors of Events in the Coronary Tree

Natural history study in pts with ACS
Multiple imaging techniques
Multiple serum markers
Prolonged follow-up

Principal sponsor: Guidant Corporation
Co-sponsor: Volcano Therapeutics, ?3rd
700 pts with ACS and 1 or 2 vessel CAD undergoing PCI will have QCA of entire coronary tree, culprit artery imaging (post PCI), and both non-culprit arteries also imaged using IVUS, Virtual histology, Palpography, ± Thermography (EU only).

F/U: 1 mo, 6 mo, 1 yr, 2 yr, ±3-5 yr (event driven)

Repeat imaging in pts with events

Meds Rx
Aspirin
Plavix 1yr
Statin

F/U: 1 mo, 6 mo, 1 yr
<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Angiography</th>
<th>IVUS+VH+Stress+VV Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active inflammation</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Thin cap with large lipid core</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Endothelial denudation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fissured plaque</td>
<td></td>
<td>±</td>
</tr>
<tr>
<td>Stenosis &gt;90%</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Minor criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial calcified nodule</td>
<td></td>
<td>+</td>
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<tr>
<td>Glistening yellow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraplaque hemorrhage</td>
<td></td>
<td>+</td>
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<tr>
<td>Endothelial dysfunction</td>
<td></td>
<td></td>
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<tr>
<td>Positive remodeling</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Three vessel imaging</td>
<td>+</td>
<td>±</td>
</tr>
</tbody>
</table>
Conclusion

- Conventional grey scale IVUS cannot detect vulnerable plaques
- Other IVUS based imaging modalities have the potential to detect vulnerable plaques, including
  - VH+IB IVUS
  - Palpography/Stress imaging
  - Vasovasorum Imaging