Treatment Modalities for Diagnosing and Treatment of Vulnerable Plaque

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Features associated with vulnerable plaques

- Large lipid pool (>40% plaque volume)
- Thin fibrous cap (<65 μm)
- Macrophage infiltration
- Activated T cells
- Outward remodeling
- Decreased collagen content of cap
- Necrotic core
- Increased neoangiogenesis
- Calcium nodule
- High mechanical stress
- Low shear stress
Active and inflamed plaque vs. Inactive and non-inflamed plaque

Morphology
- IVUS
- OCT

Histo-Chemistry
- Virtual histology

Activity (physiology)
- Thermography
- VV Imaging

Mechanical properties
- Palpography
- Endothelial SS profiling

Endothelial Dysfunction Imaging

Inactive and non-inflamed plaque

Activity (physiology)
- Endothelial Dysfucntion Imaging

Morphology
- IVUS
- OCT

Histo-Chemistry
- Virtual histology

Activity (physiology)
- Thermography
- VV Imaging

Mechanical properties
- Palpography
- Endothelial SS profiling

Endothelial Dysfunction Imaging
Atheroma Morphology on IVUS

Soft (left), mixed fibrous and calcified (center), and heavily calcified atheromas (right)

Nissen and Yock. Circulation. 2001;103:604
What we see, is not always what it seems
Palpography

High strain region = soft, deformable, fragile, breakable
Low strain = hard, stiff, rigid

Schaar J and Serruys PW
ECG-gated RF acquisition

What’s R.F.

- Sound returns from tissue
- Converted to voltage by transducer
- Travels into console
  - Processed and scan converted to form an image
  - Output to BNC
- Capture with a 500MHz A-D PCI board
Virtual Histology™ IVUS
**VH™ IVUS Plaque Composition**

**Fibrous**
Densely packed bundles of collagen fibers with no evidence of intra-fiber lipid accumulation. No evidence of macrophage infiltration. Appears dark yellow on Movat stained section.

**Necrotic Core**
Highly lipidic necrotic region with remnants of foam cells and dead lymphocytes present. No collagen fibers are visible and mechanical strength is poor. Cholesterol clefts and microcalcifications are visible.

**Fibro-Fatty**
Loosely packed bundles of collagen fibers with regions of lipid deposition present. These areas are cellular and no cholesterol clefts or necrosis are present. Some macrophage infiltration. Increase in extracellular matrix. Appears turquoise on Movat stained section.

**Dense Calcium**
Focal area of dense calcium. Appears purple on Movat. Usually falls out of section, but calcium crystals are evident at borders.
**Intravascular MRI Catheter**

- Catheter based real-time MRI - No external magnets
- High sensitivity & specificity for differentiating:
  - Fibrous tissue
  - Lipid rich necrotic core
  - Calcium
  - Thrombus (next generation)

Virmani et al, JACC 2004 (Submitted)
Presented by RL Wilensky @ TCT 2004
Diffusion Weighted MRI – Concept

Non-restricted diffusion → Fast decay of MR signal → High ADC

Restricted diffusion → slow decay of MR signal → Low ADC
In-vivo porcine femoral arteries: peri-arterial fat wrap

Schneiderman et al
Detection of Lipid-Rich Necrotic Cores

*Ex-vivo* Human Coronaries

**Fibrous Lesion**

**Lipid-Rich Lesion**

* Virmani et al – JACC accepted for publication
### IVMRI Lipid Fraction

**FIM Patients vs. *Ex-vivo* Aortas**

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Number of Measurements</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous</td>
<td>11</td>
<td>25%</td>
</tr>
<tr>
<td>Foam Cells</td>
<td>23</td>
<td>60%</td>
</tr>
<tr>
<td>Lipid</td>
<td>6</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>40</strong></td>
<td><strong>100%</strong></td>
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Optical Coherence Tomography (OCT)

- Uses near-infrared light
- Optical analogue of IVUS

- Greater image clarity & resolution
  - Wavelengths (centre wvl ~1300 nm) bandwidths (~40 nm) of IR light much higher than US signals

- Tissue characterization
  - With spectroscopic and polarization imaging
LightLab OCT Imaging System

ImageWire

Rotary Probe Interface Unit
Superior resolution with OCT

**Strength of OCT:** Visualization of the luminal border and the intimal layer
OCT coronary delivery system

**Occlusion Balloon**

- Very low pressure, over-sized

**Image Wire**

*Limitation: Blood free environment*
OCT Tissue Characterization

- **Fibrous**
  - Homogeneous, Signal-rich

- **Lipid**
  - Echolucent, Diffuse Borders

- **Calcific**
  - Echolucent, Sharp Borders
OCT for Vulnerable Plaque Detection

Histology

OCT

Fibro-fatty plaque
Thin Cap
High lipid content

Renu Virmani et al.
Thin capped Fibroatheroma

Cap < 60µm
Fibrous Cap Thickness
Correlation between OCT and histology

\[ y = 1.02x + 3.8 \]
\[ r = 0.89 \]
\[ p < 0.0001 \]
OCT for Vulnerable Plaque Detection

Vulnerable Plaque – Case 4

Thrombus

Thin cap

Necrotic Core
OCT: Limitations

- The major limitation of OCT is the need for a blood-free environment which necessitates saline injection with or without proximal occlusion.
- OCT has poor (2mm) tissue penetration, therefore can’t provide insight into the deeper areas of the plaque.
- Image-acquisition time is rather long.
White plaque representing fibrous plaque (A). Yellow plaque signifies a lipid-rich core seen through a thin, fibrous cap. The intensity of the image increases as the fibrous cap thins and becomes increasingly transparent (B, C, and D). An irregular or complex lipid-rich plaque is seen in E, and a lipid-rich plaque with associated thrombus is shown in F. A 0.014-in. wire in D provides a reference of scale.

MacNeill et al. *Arterioscl Thromb Vasc Biol.* 2003;23:1333
The InfraReDx NIR Spectroscopy System

- Intra-coronary NIR now possible using:
  - Scanning laser, Fiber-optics
  - Chemometric algorithms

- 3.2Fr IVUS-like rapid-exchange coronary catheter:
  - Can scan artery through blood
  - 5 msec spectra acquisition

- Identifies chemical composition of vessel wall:
  - Sensitivity and specificity > 85% in autopsy specimens
  - Spectra recorded safely in over 70 patients

- 510(k) clearance for NIR examination of coronaries
Detection of Lipid-rich Plaques with Necrotic Cores in Human Coronary Autopsy Specimens with the Use of a Preliminary Algorithm
Vasa vasorum imaging with IVUS

IVUS at t=0

(t₀, P₁)

IVUS after bubbles at same position and cardiac phase timing

(t, P₁)

Differential Echogenecity

Differential Echogenecity
Shear Stress and Palpography

- Shear Stress
- Strain

- high
- low
Focal and Regional Therapy for VP

• *Balloon Angioplasty Plaque Sealing*
• *Stent Design Considerations*
• *Drug-eluting Stents (DES)*
• *Bioabsorbable Stents*
• *Photo Dynamic Therapy (PDT)*
• *Sonotherapy*
• *Cryotherapy*
• *Radiation Therapy*
What are the “treatment imperatives”…

- Must address not merely the vulnerable plaque but also the vulnerable patient

PCI with Balloon or Stents therapy is focal or at most multi-focal can be used for plaque sealing but is obviously limited if a more regional or systemic therapy is required.
The Hypothesis That bare-metal and DES can Stabilize Vulnerable Plaques MUST Be Tested in Animal Models First.
Mechanical Stabilization of Vulnerable Plaques with BMS

Mechanical Objectives for Vulnerable Plaque Stabilization

- Plaque Features
  - Soft Tissular Matrix
  - Thin Fibrous Cap
  - Prominent Lipidic Core
  - Thin Plaque Shoulders

- Mechanical Stabilization
  - Mechanical Compression
  - New Thick “Fibrous Cap” Formation
  - Minimal Lipidic Core
  - Stabilized by Healthy Thin Neointima
Mechanical Stabilization of Vulnerable Plaques with BMS

Experimental Data: Mechanical Stabilization of TCFA in Rabbits

![Graph showing area percentages of Lipid Pool, Old Fibrous Cap, and New Fibrous Cap with comparison between TCFA and BMS, indicating a statistical significance of P < 0.001.]

Echeverri D, Moreno P. ACC 2003
Workhorse Stents Rupture Fibrous Cap & Increase NIH

- 276 struts on TCFA; 188 ruptured the Cap (63%)

- NIH = Neointimal Hyperplasia
  - p = 0.03

- Attenuated by DES
  - p = NS

Fibrous Cap without rupture

Fibrous Cap with rupture

- Moreno et al. TCT 2004
What are the “treatment imperatives”...

- Must be relatively easy to apply and absolutely without early or late toxicity (including significant restenosis)

Most of the DES systems being proposed for VP therapy require the use of drugs or carrier vehicles which are simply too toxic for the proposed application.
Why Self Expanding Stent

Self-expandable Devices are associated with
Lower neointimal hyperplasia
Improved Healing
  reduced inflammation and giant cell formation
  reduced fibrin deposition, and hemorrhage
  increased endothelialization
Very low incidence of strut-induced fibrous cap rupture

Self-expandable devices may be the future for invasive therapy of fibroatheroma.
BVS Fully Bioabsorbable Drug Eluting Stent

- BVS Bioabsorbable Stent Platform
- ML VISION® Balloon SDS
- Everolimus
- Champion™ Bioabsorbable Polymeric Drug Release
Photodynamic Therapy

What are the “treatment imperatives”...

- PDT involves the interaction of a photosensitizing drug, light and tissue oxygen.
- Photosensitizing agents, many of which are porphyrins or chemicals can be given locally or systemically.
- The timing of light delivery is crucial for achieving the biological response.
- PDT generates free radicals, which exerts its cytotoxic effect at the site of the light irradiation, results in changes in proteins and lipids.
Light Infusion Technology™

LS11 activated with endovascular LED
- no need for laser
Properties Specific to LS11

- Ultra-short interval between drug delivery and light activation
  - Activation 5-10 mins after infusion
- Low light dose required
  - Short procedure time with brief blood-flow occlusion for light activation
- Systemic safety in man
- Selective accumulation in atherosclerotic plaque$^{1,2}$
Selective Plaque Accumulation

LS11 revealed in atherosclerotic plaque in rabbit aorta using fluorescence microscopy

Image through courtesy of Dr. K. Aizawa, Tokyo Medical University
Dissociation of plaque lipid after LS11 PDT treatment
(Saito T et al. Tokyo, J)
Motexafin Lutetium (MLu) Phototherpay
A novel experimental therapy
being tested for the treatment of atherosclerosis

- Expanded porphyrin (motexafin lutetium, Antrin®)
- Excited by red light that penetrates tissue and blood
- Water soluble, synthetic
- Enhanced binding to LDL
- Localizes in atheroma
- Short plasma half life
- Far red light ~730 nm light treatment 941 sec to achieve 400 J/cm²
MLu Phototherapy:

Effect on Macrophages

Immunoperoxidase staining with RAM11

2001;49:449-55
MIRVANT PROGRAM

Miravant Light Catheter  +  Miravant Photosensitizer Compound (MV0611)

O₂  →  Cell Depletion

Biological Response
Tissue Distribution of MV0611

- Control
- 4 hours
- 8 hours
- 24 hours

Autofluorescent Drug Localized in Plaques
Increased P53 Expression

1. PDT Induction of Cellular Apoptosis
Intravascular Sonotherapy

- In a swine peripheral stent model, it was shown at 7 days after stent implantation that cellular proliferation was significantly reduced compared with the sham group.
- Sonotherapy has proposed as a treatment to prevent restenosis.
- The data on its use in the treatment of vulnerable plaque has been limited.

Catheter Cardiolvascu Interv 2003;60:9-17.
Proposed Mechanism of Action: Altered Plaque Response

Cold temperatures cause interstitial saline to freeze

Ice forms & expands, creating micro-fractures

Weakened plaque dilates more homogenously

Results

Less Medial Tearing
Less Injury
Less Inflammation
Less Cell Proliferation

- Reduced Post-dilatation
- elastic recoil