Treatment Modalities for Diagnosing and Treatment of Vulnerable Plaque

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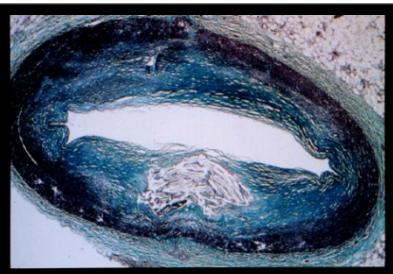
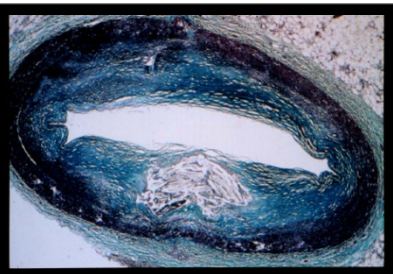
Features associated with vulnerable plaques

- 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

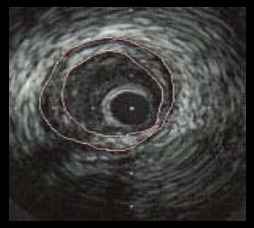


VS.

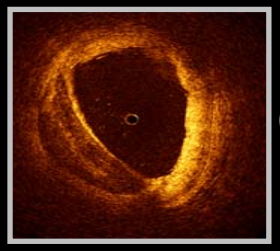


Inactive and non-inflamed plaque

Morphology

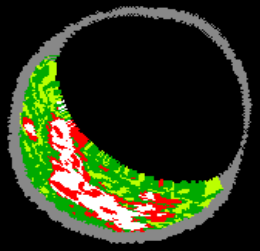


IVUS

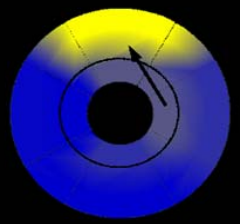


OCT

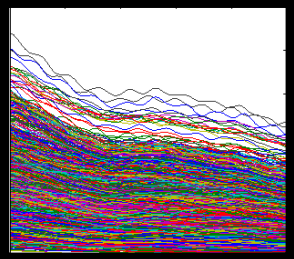
Histo-Chemistry



Virtual histology



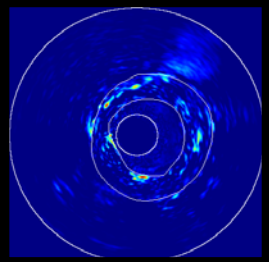
IV MRI



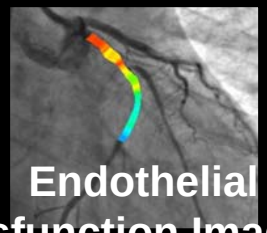
Spectroscopy

Activity (physiology)

Thermography

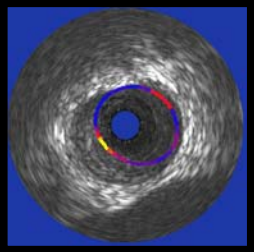


VV Imaging

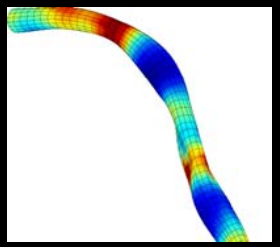


Endothelial Dysfunction Imaging

Mechanical properties

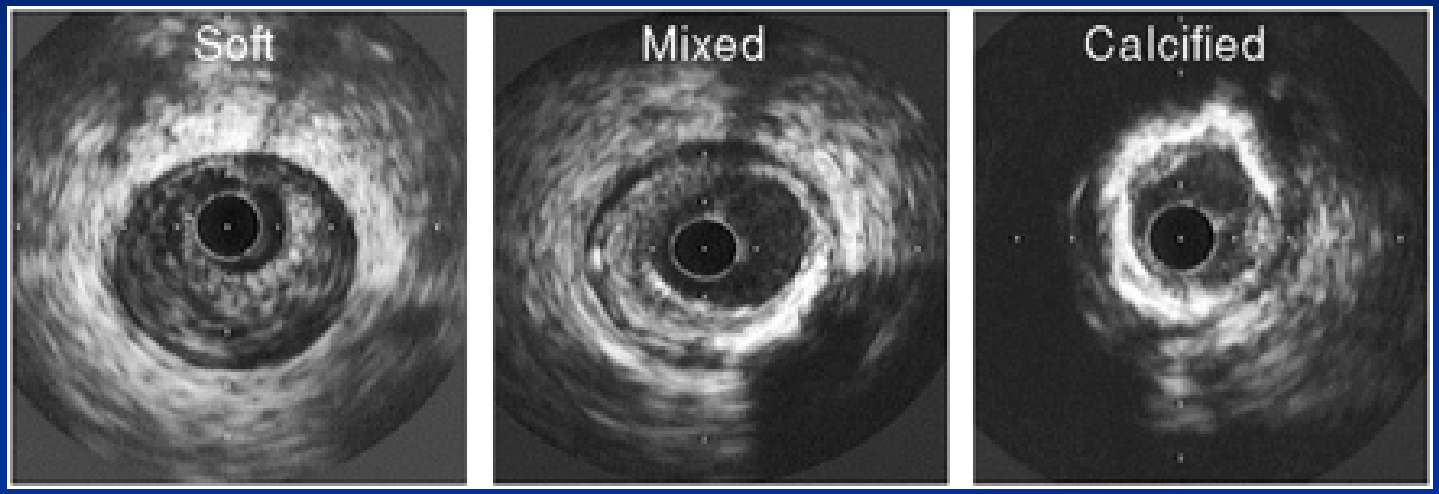


Palpography



Endothelial SS profiling

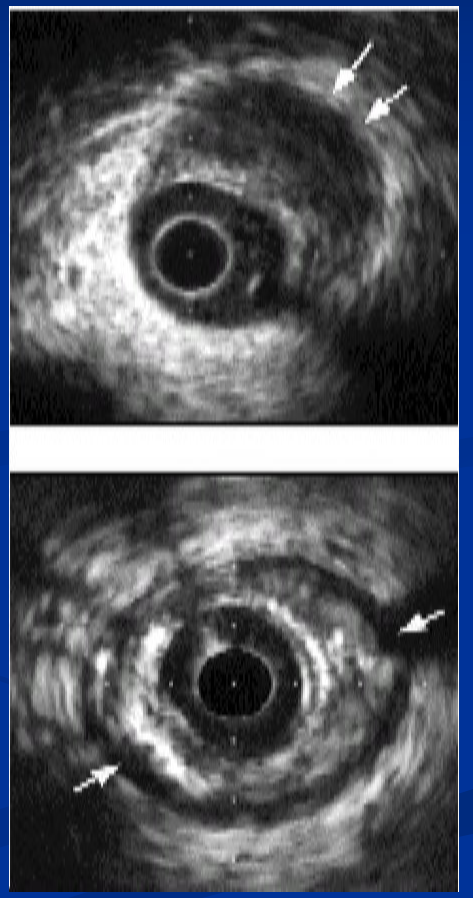
Atheroma Morphology on IVUS



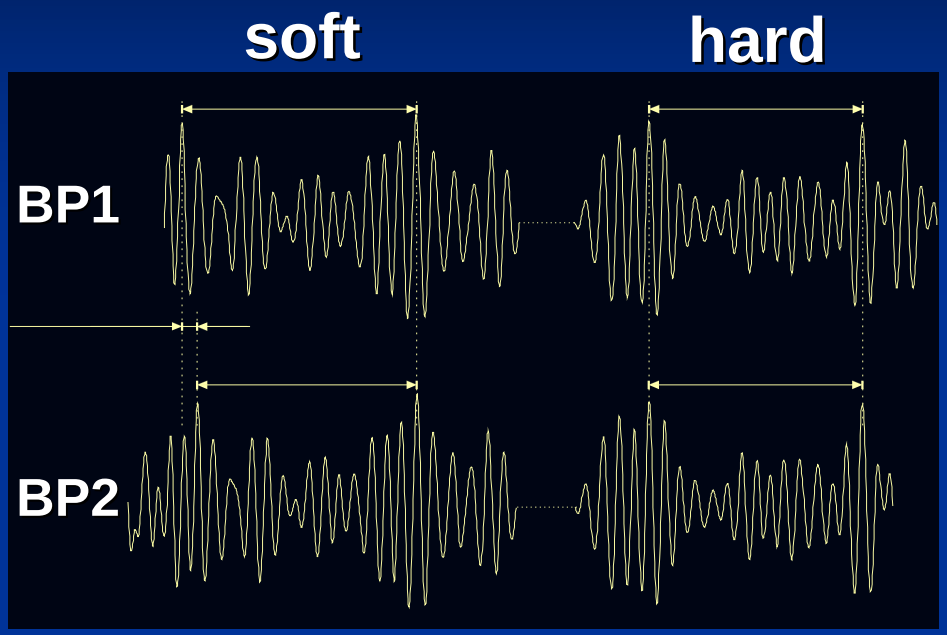
Soft (left), mixed fibrous and calcified (center), and heavily calcified atheromas (right)

Nissen and Yock. Circulation. 2001;103:604

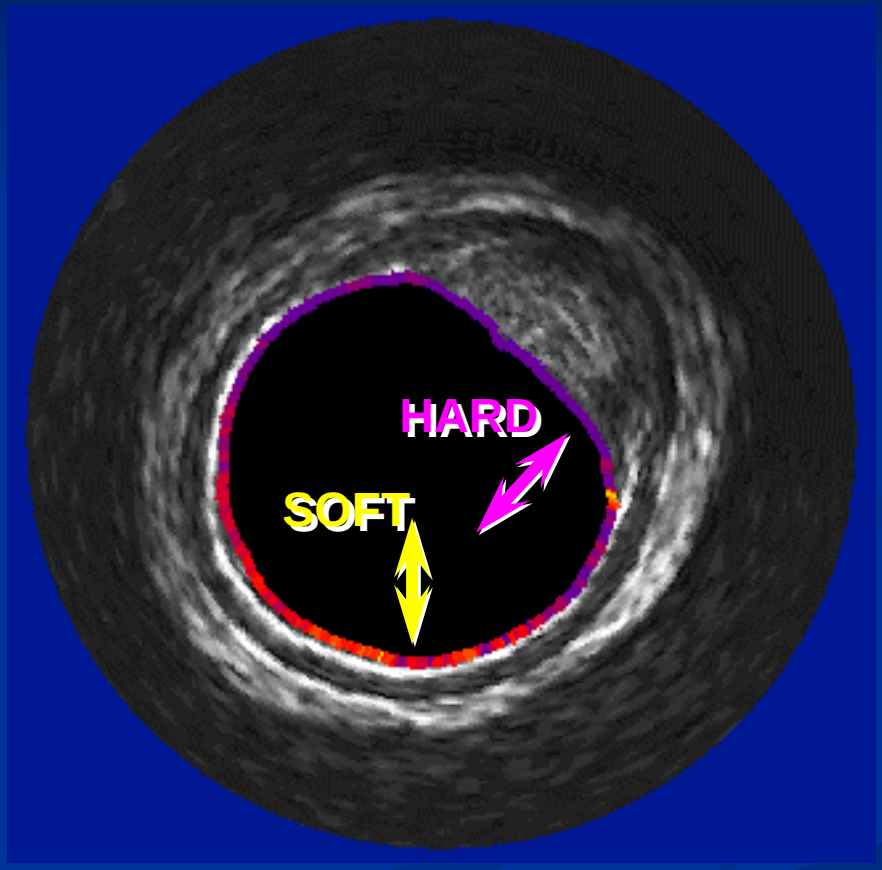
What we see, is not always what it seems



Palpography



Backscattering of radiofrequency signal at 2 levels of blood pressure

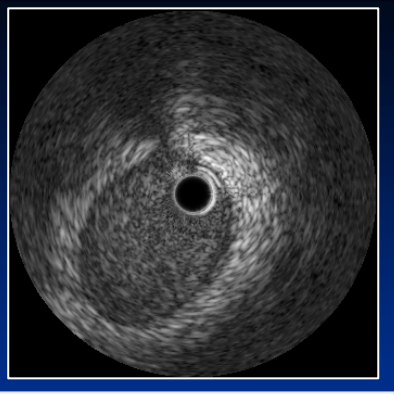


High strain region = soft, deformable, fragile, breakable

Low strain = hard, stiff, rigid

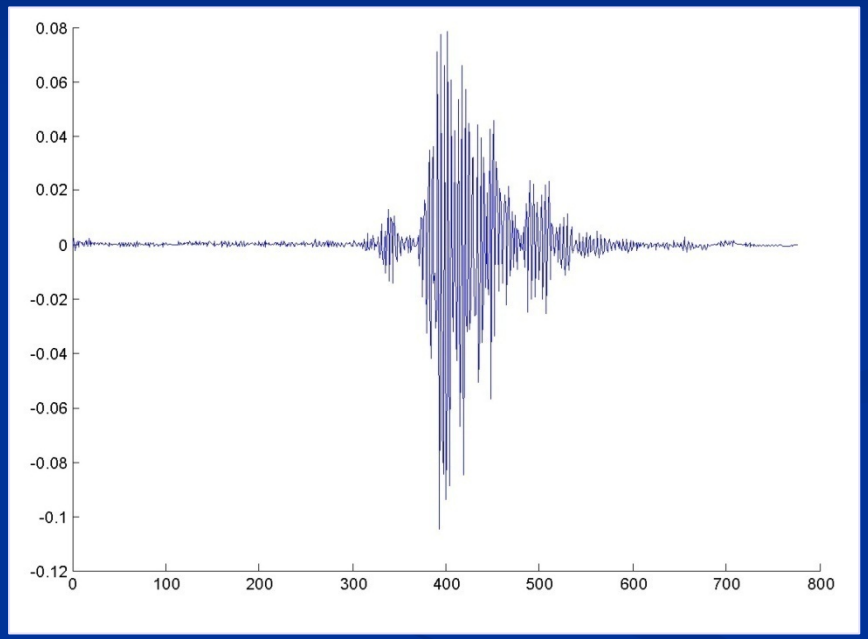
Schaar J and Serruys PW

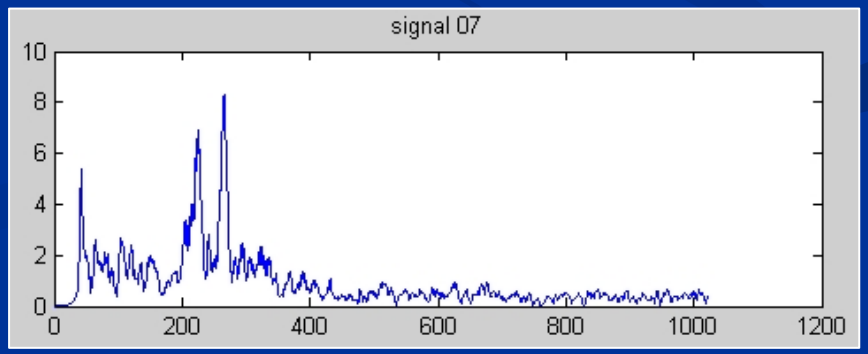
ECG-gated RF acquisition



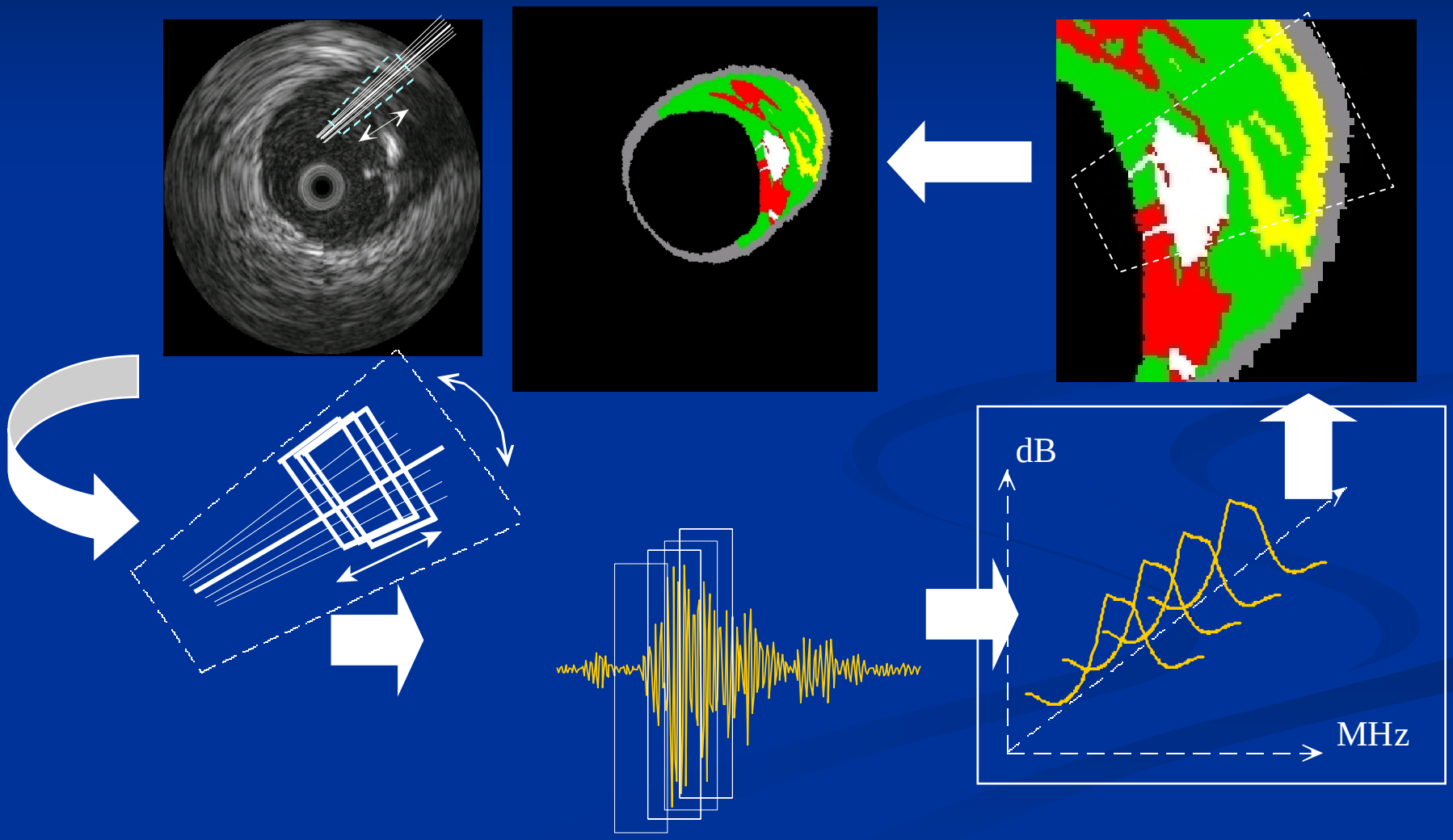
What's R.F.

- 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





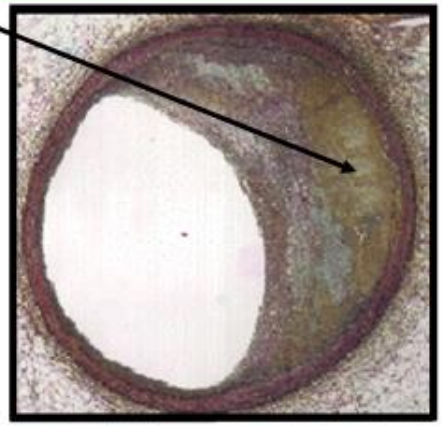
Virtual Histology™ IVUS



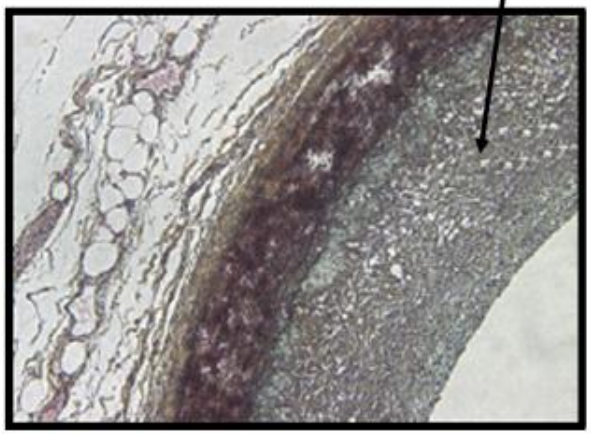
VH™ IVUS Plaque Composition

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.

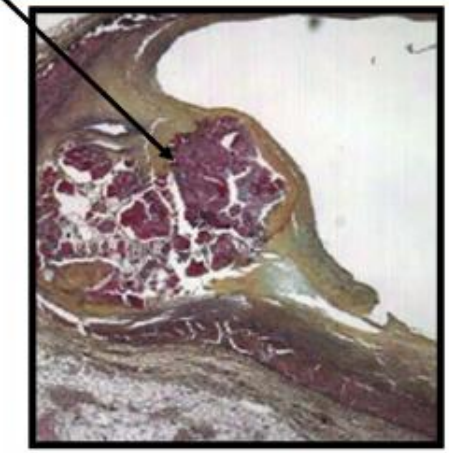


Fibro-Fatty



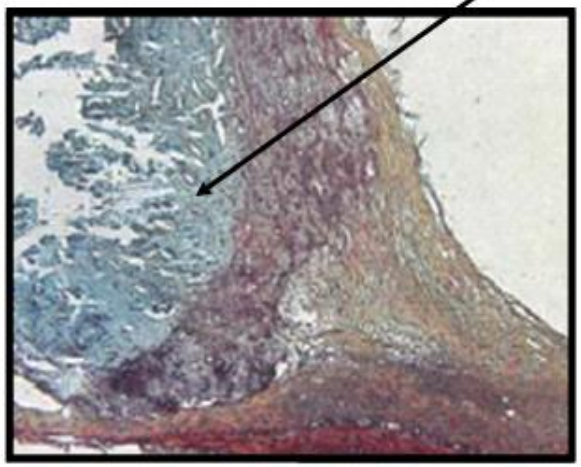
Loosely packed bundles of collagen fibers with regions of lipid deposition present. These areas are cellular and no cholesterol clefts or necrosis are present. Some macrophage infiltration. Increase in extracellular matrix. Appears turquoise on Movat stained section.

Necrotic Core



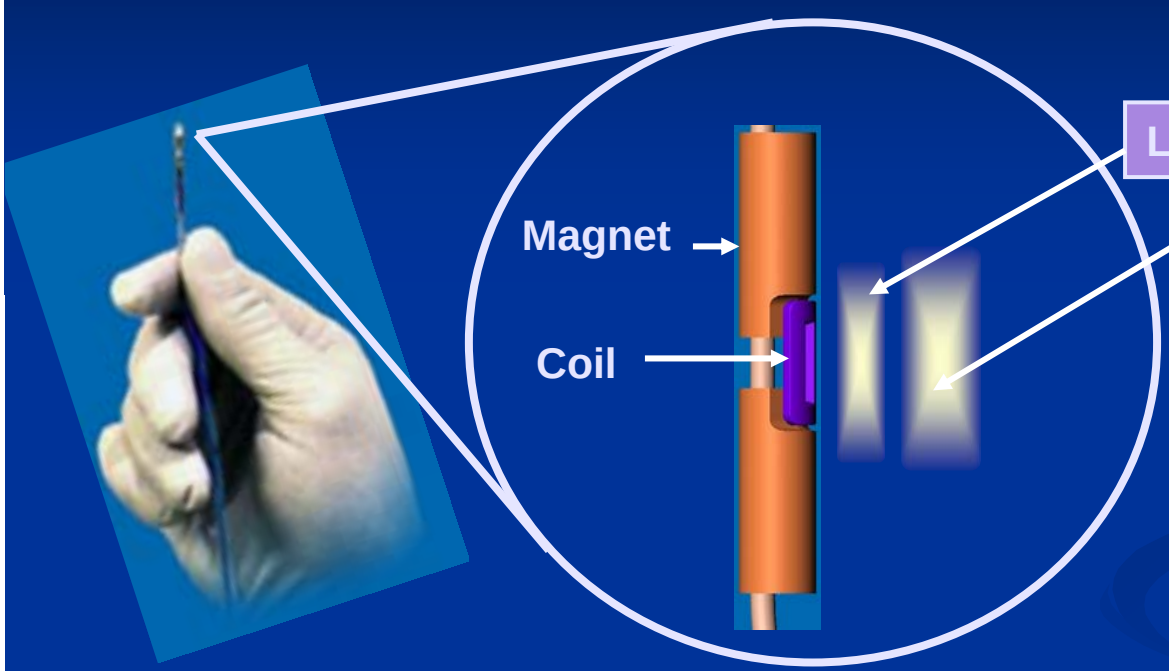
Highly lipidic necrotic region with remnants of foam cells and dead lymphocytes present. No collagen fibers are visible and mechanical integrity is poor. Cholesterol clefts and micro calcifications are visible.

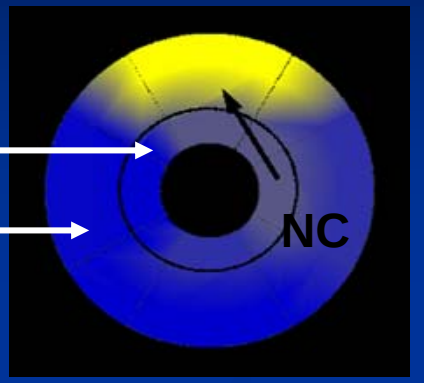
Dense Calcium

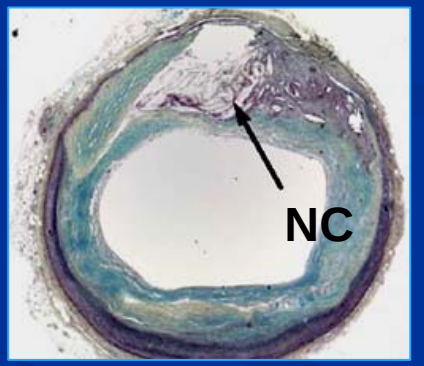


Focal area of dense calcium. Appears purple on Movat. Usually falls out of section, but calcium crystals are evident at borders.

Intravascular MRI Catheter



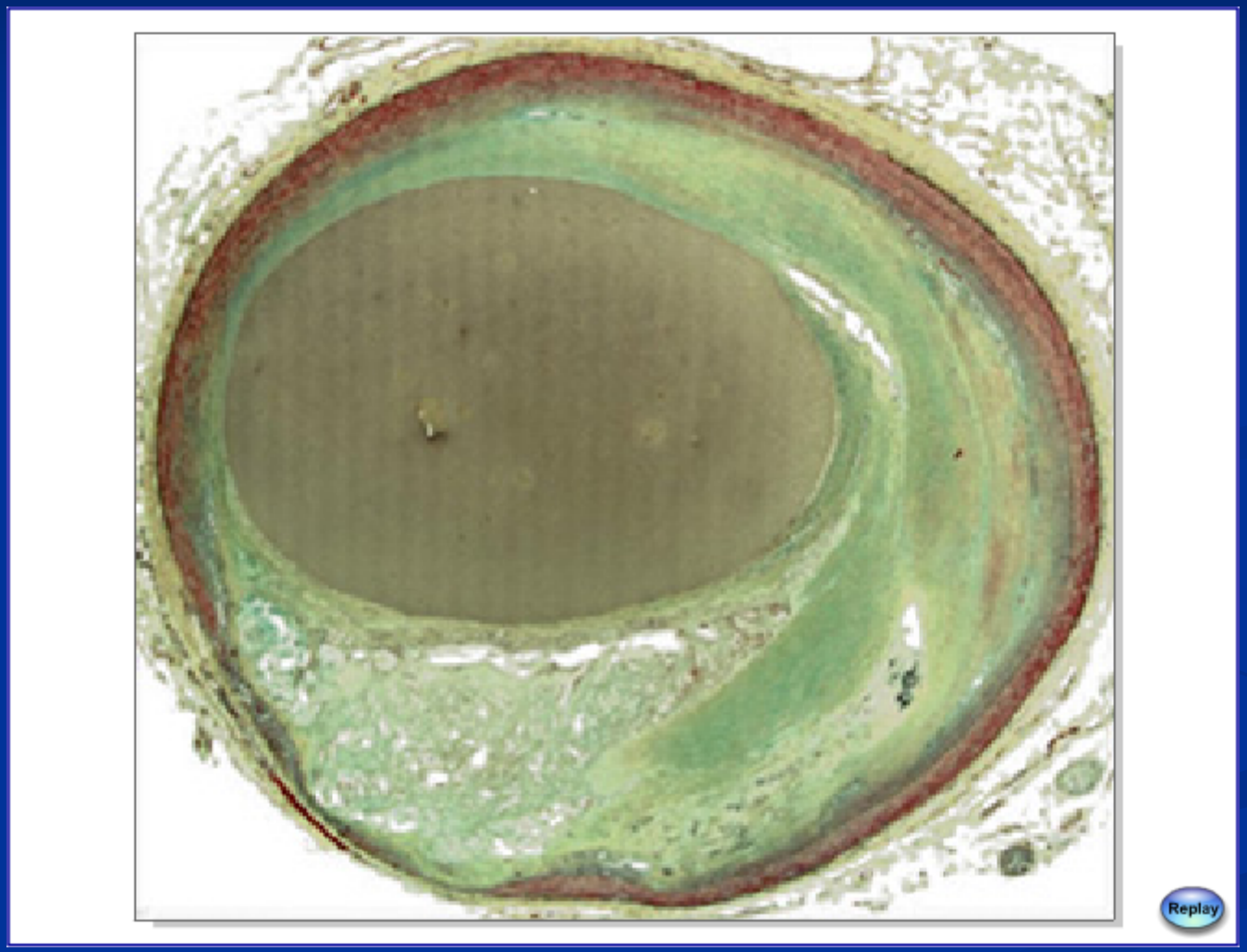




- Catheter based real-time MRI - No external magnets
- High sensitivity & specificity for differentiating:
  - Fibrous tissue
  - Lipid rich necrotic core
  - Calcium
  - Thrombus (next generation)

Virmani et al, JACC 2004 (Submitted)
Presented by RL Wilensky @ TCT 2004

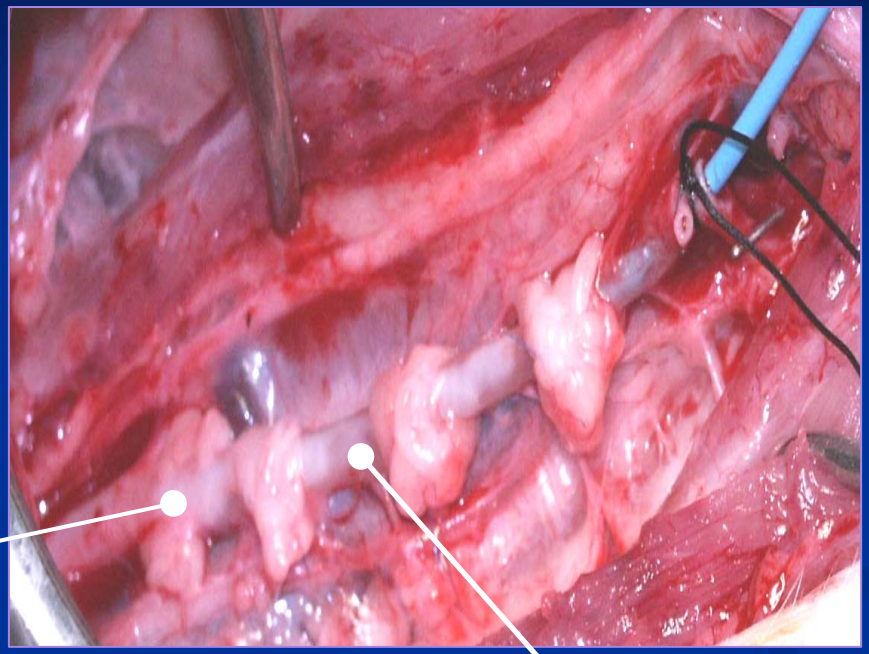
Diffusion Weighted MRI – Concept

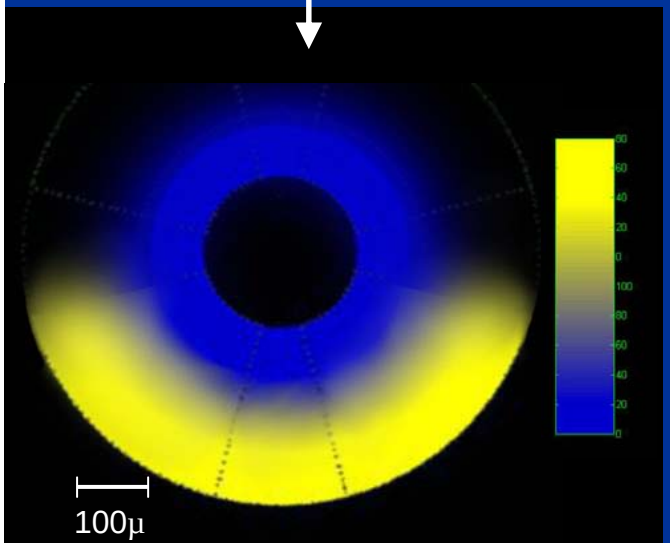


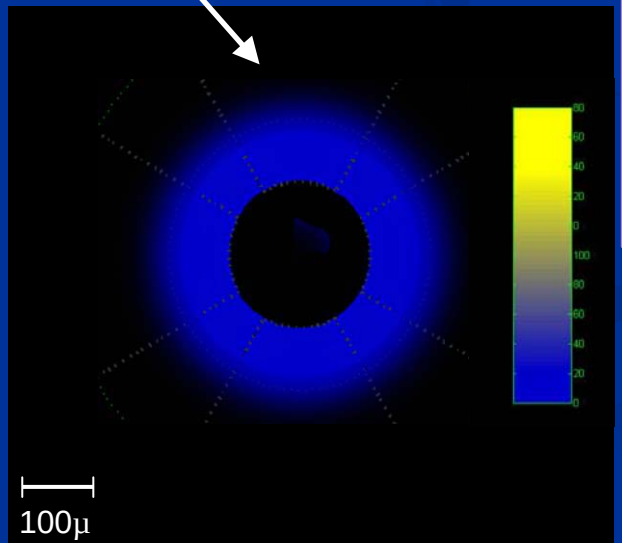
Non-restricted diffusion → Fast decay of MR signal → High ADC

Restricted diffusion → slow decay of MR signal → Low ADC

In-vivo porcine femoral arteries: peri-arterial fat wrap



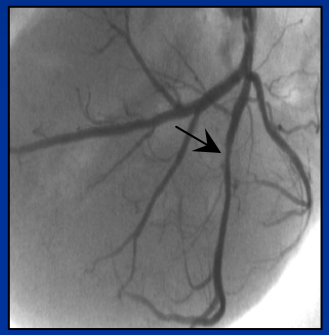


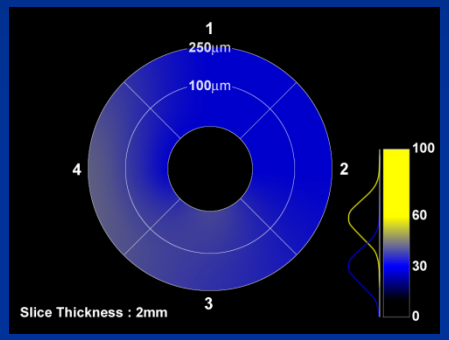


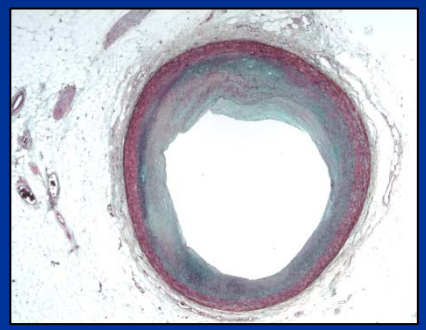
Schneiderman et al

Detection of Lipid-Rich Necrotic Cores
Ex-vivo Human Coronaries*

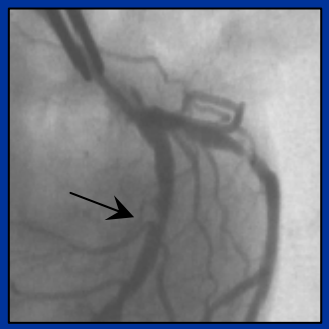
Fibrous Lesion

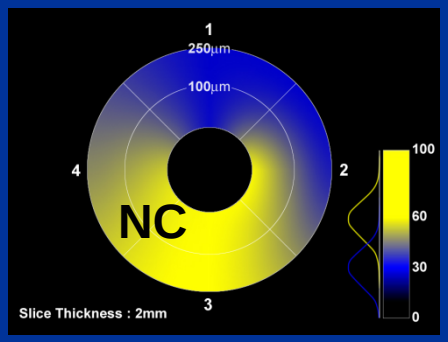


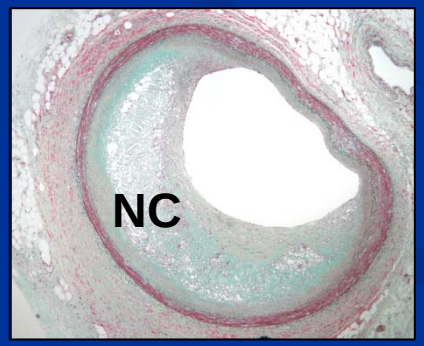


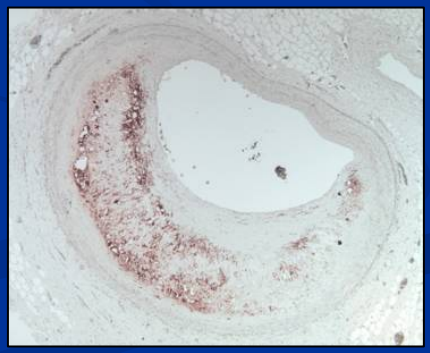


Lipid-Rich Lesion





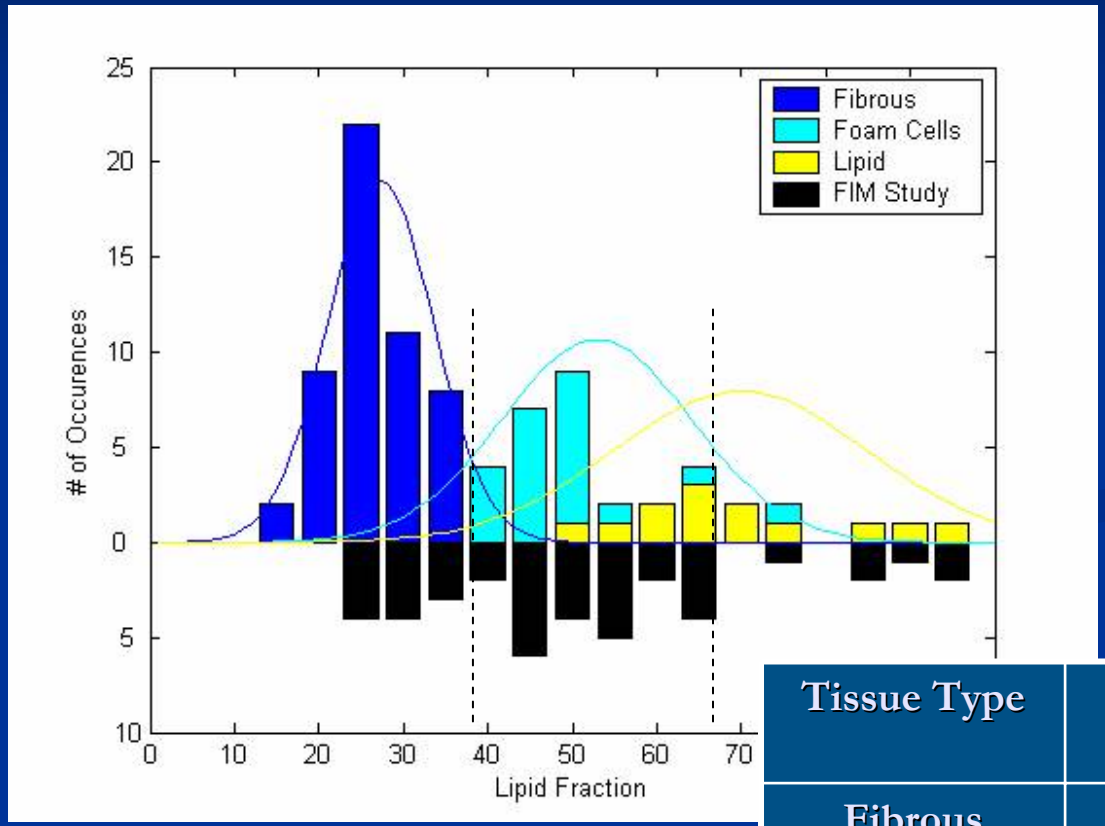




Angiogram **IVMRI** **Histopathology**

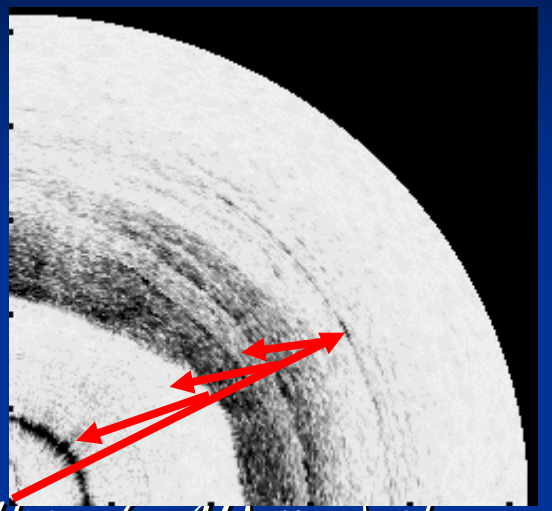
* Virmani et al – JACC accepted for publication

IVMRI Lipid Fraction
FIM Patients vs. *Ex-vivo* Aortas



Tissue Type	Number of Measurements	Prevalence
Fibrous	11	25%
Foam Cells	23	60%
Lipid	6	15%
Total	40	100%

Optical Coherence Tomography (OCT)

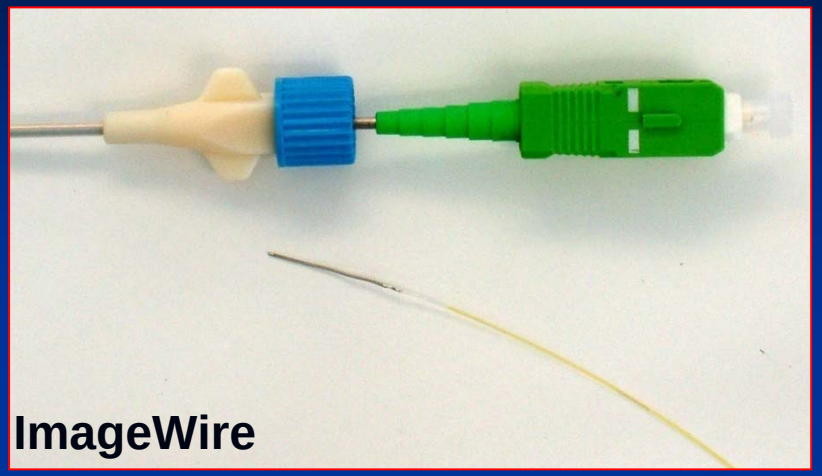


- **Uses near-infrared light**
- **Optical analogue of IVUS**

- **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

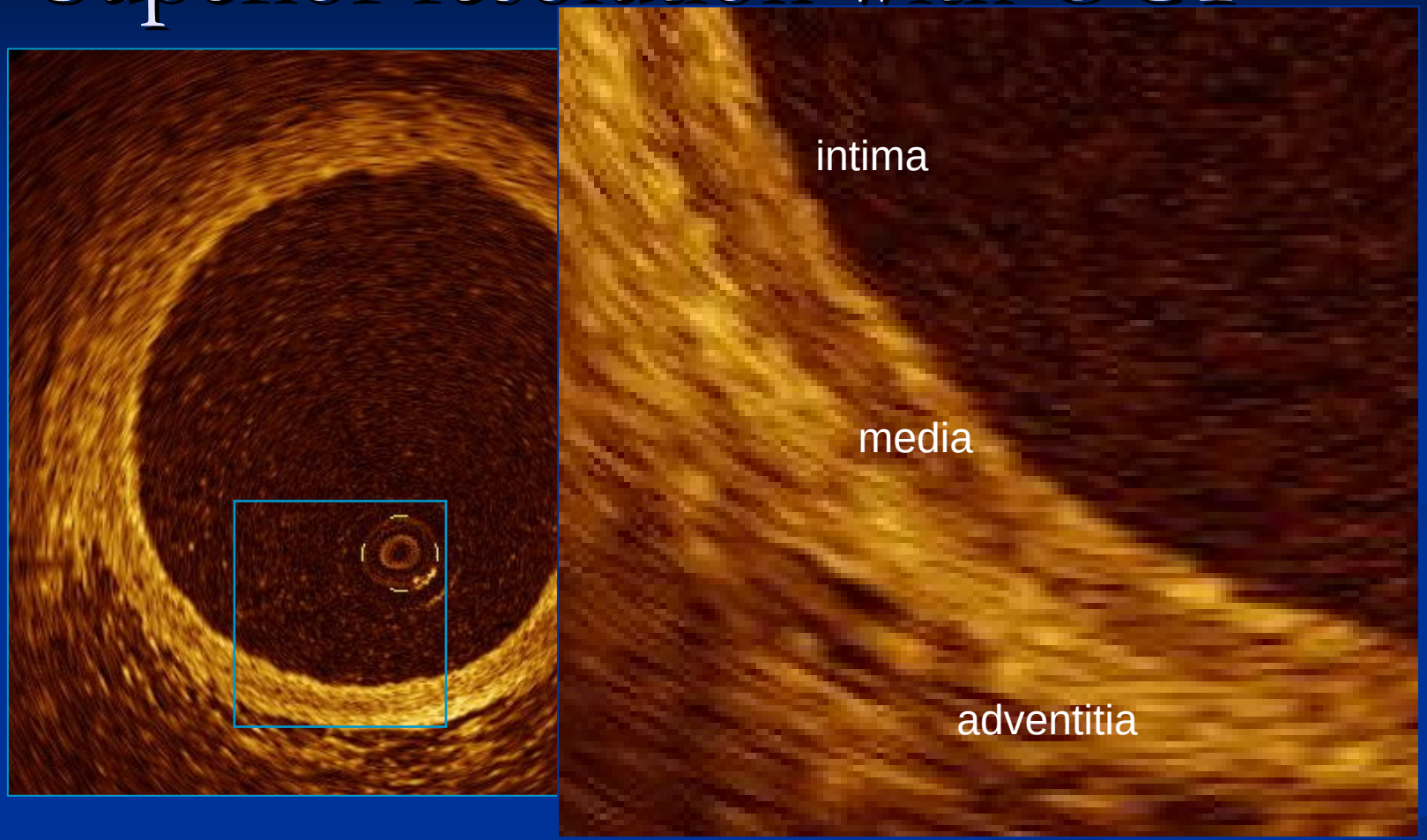
LightLab OCT Imaging System



ImageWire

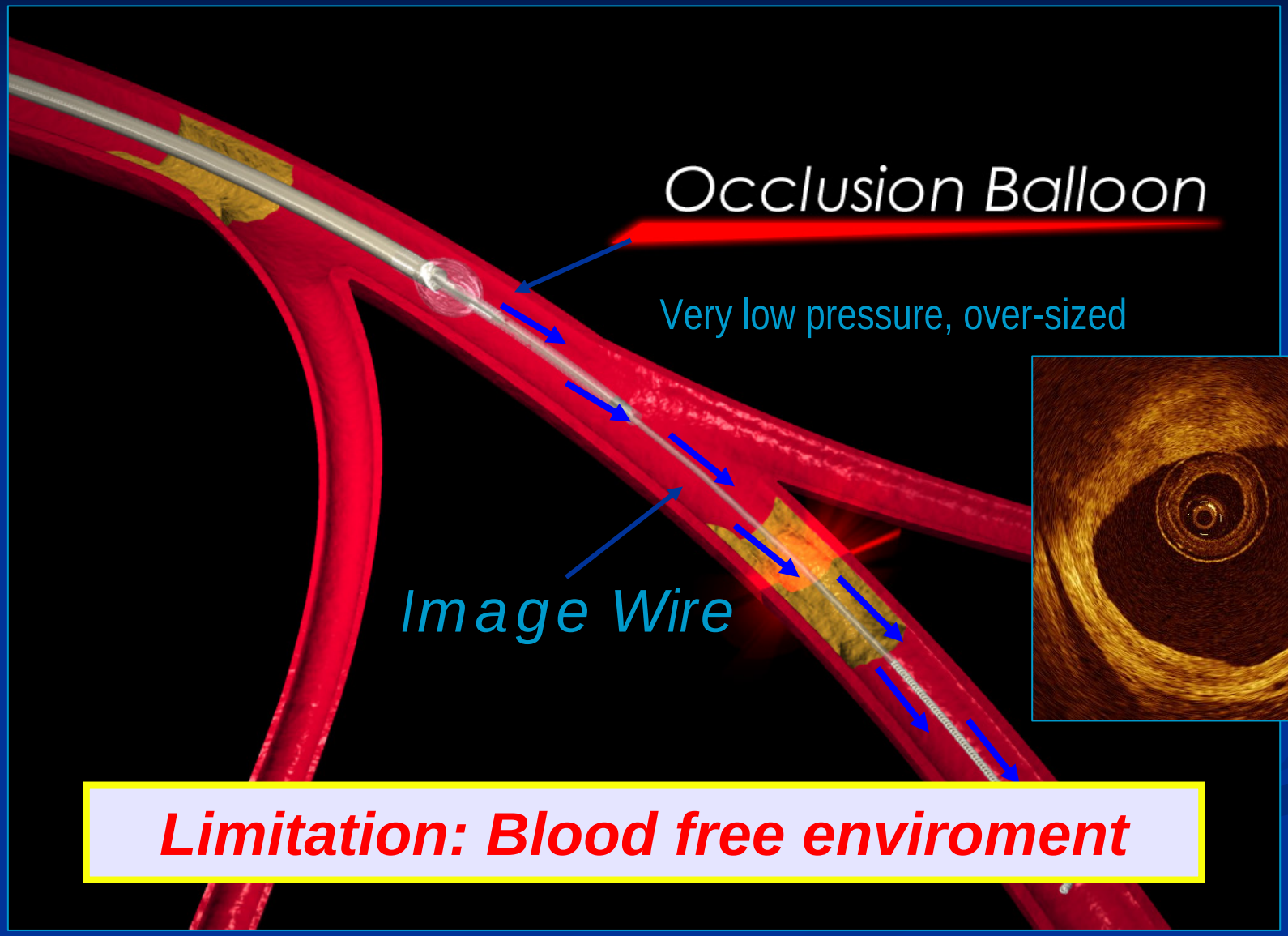
Rotary Probe Interface Unit

Superior resolution with OCT



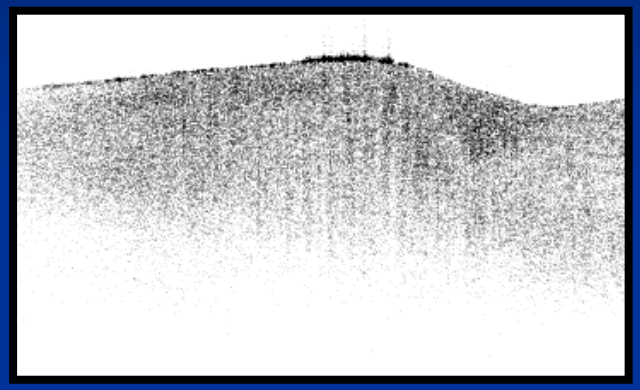
Strength of OCT: Visualization of the luminal border and the intimal layer

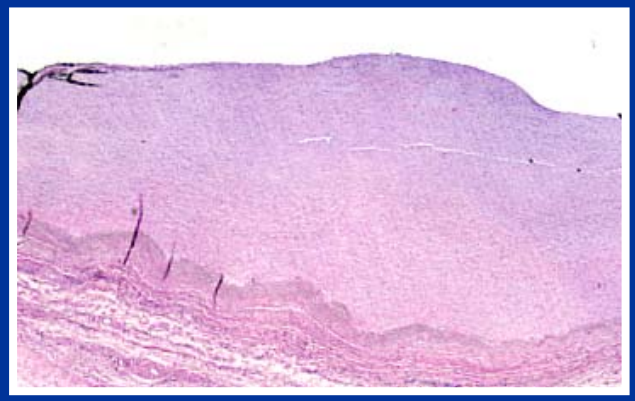
OCT coronary delivery system



OCT Tissue Characterization

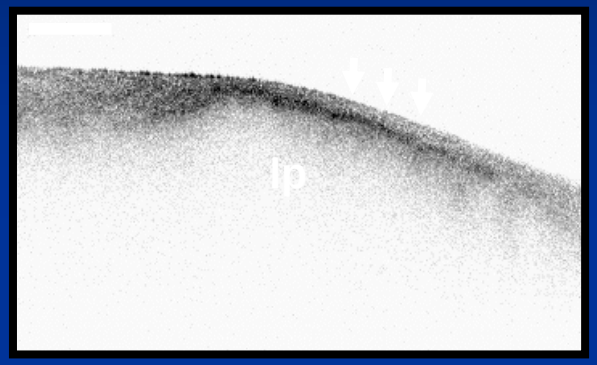
Fibrous





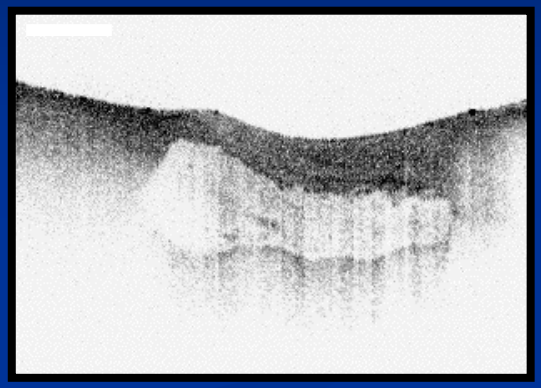
Homogeneous,
Signal-rich

Lipid



Echolucent,
Diffuse Borders

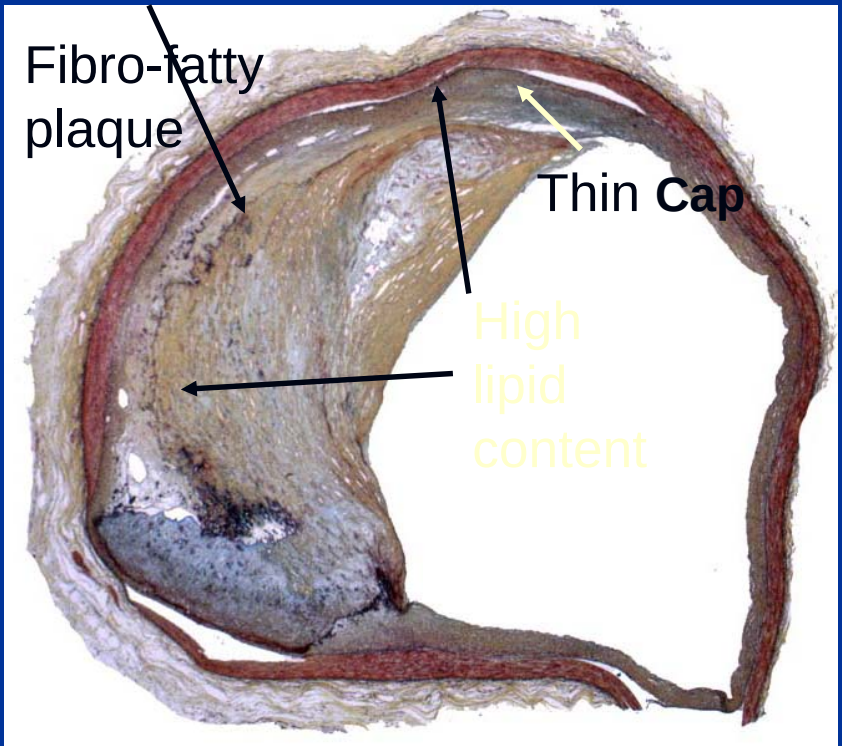
Calcific

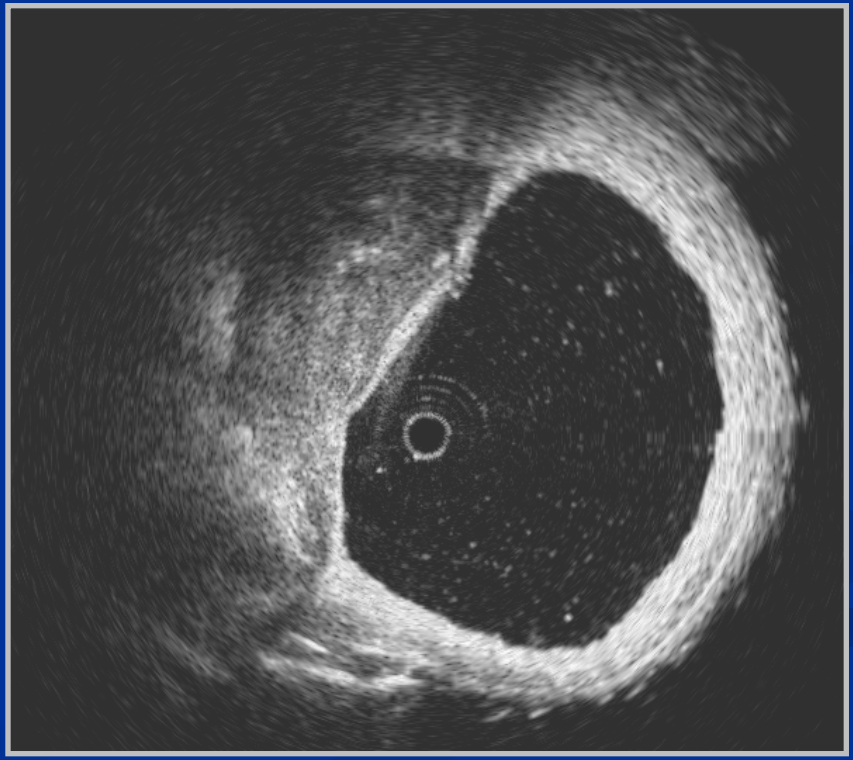


Echolucent,
Sharp Borders

OCT for Vulnerable Plaque Detection

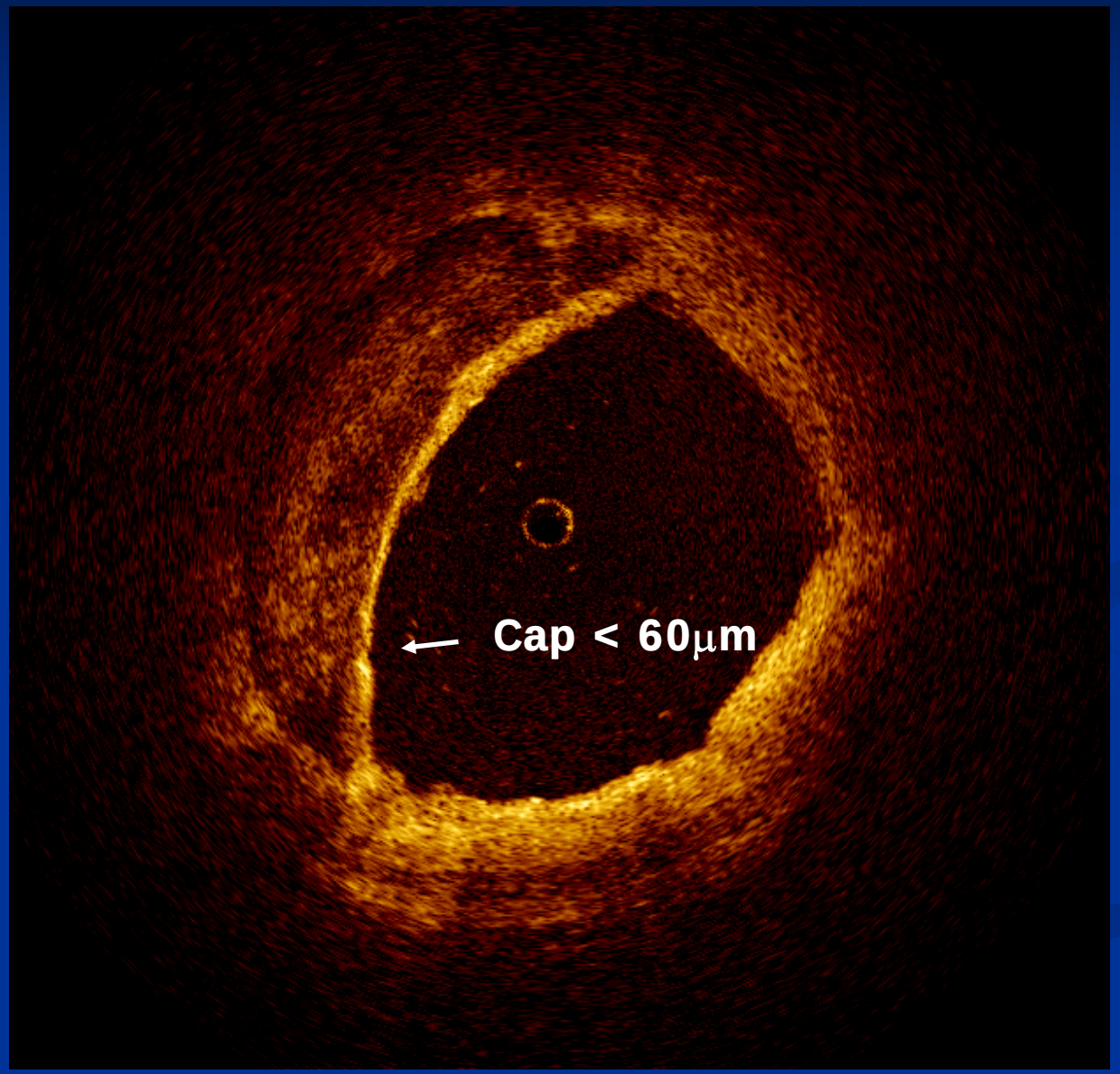
Histology **OCT**





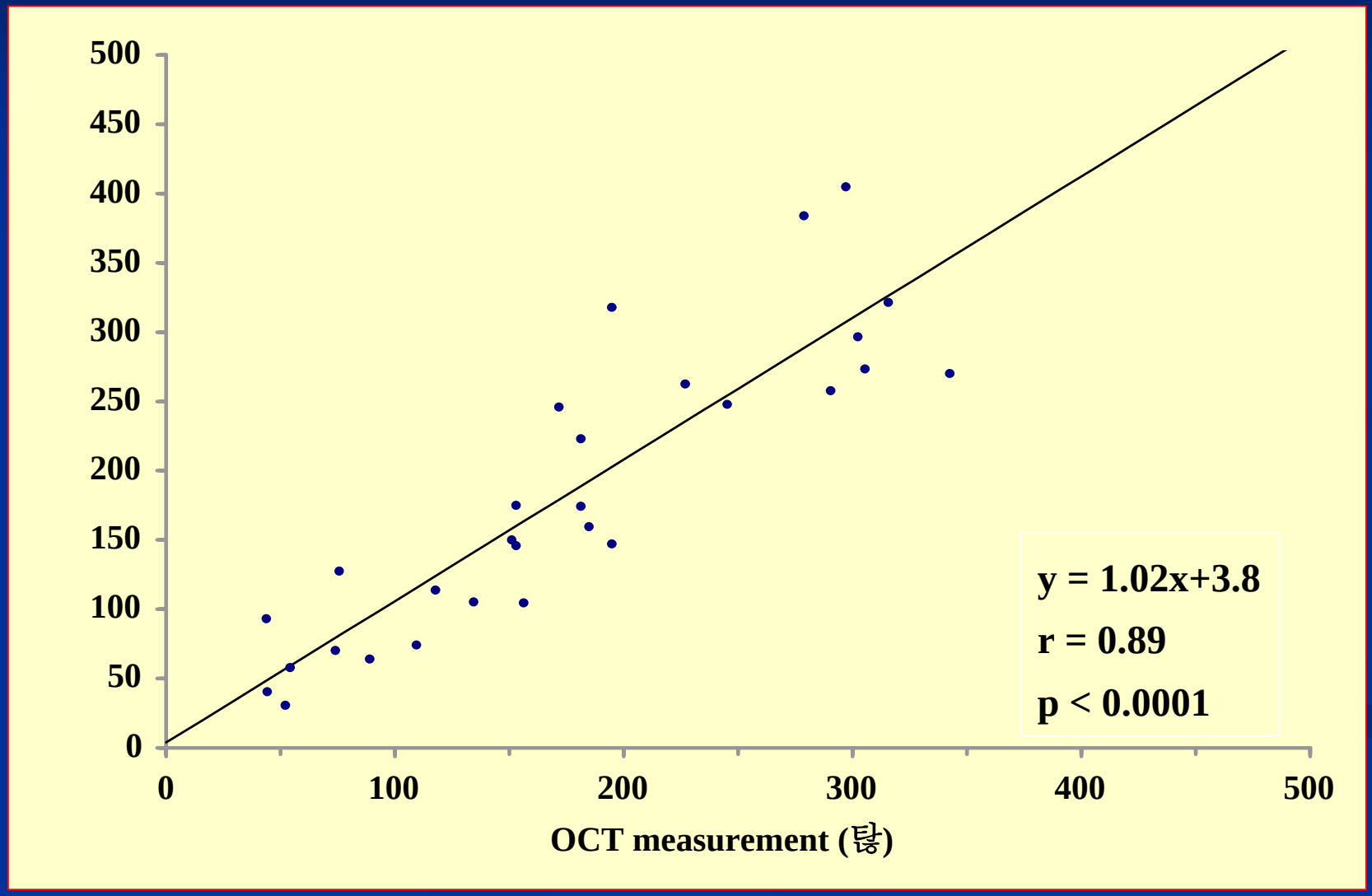
Renu Virmani et al.

Thin capped Fibroatheroma



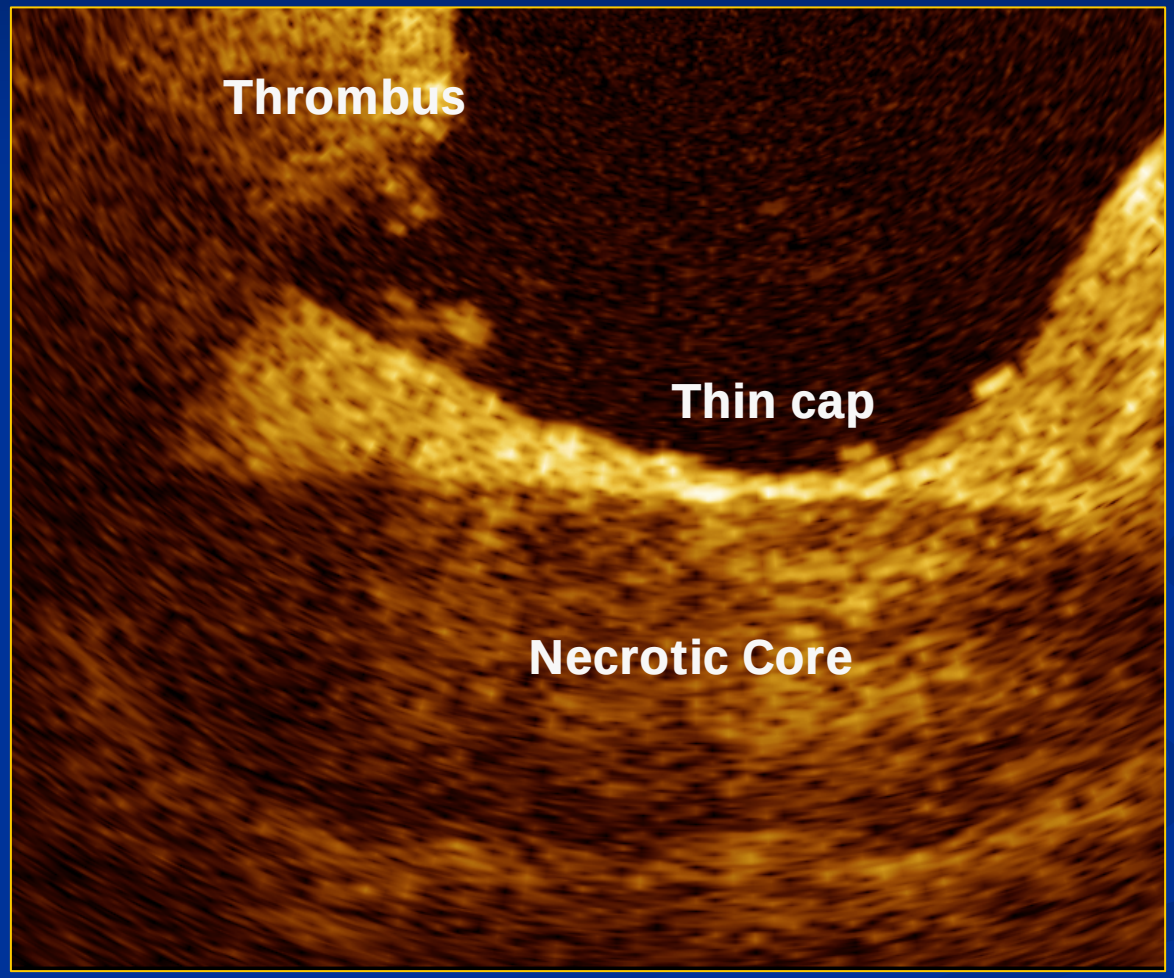
Fibrous Cap Thickness

Correlation between OCT and histology



OCT for Vulnerable Plaque Detection

Vulnerable Plaque – Case 4

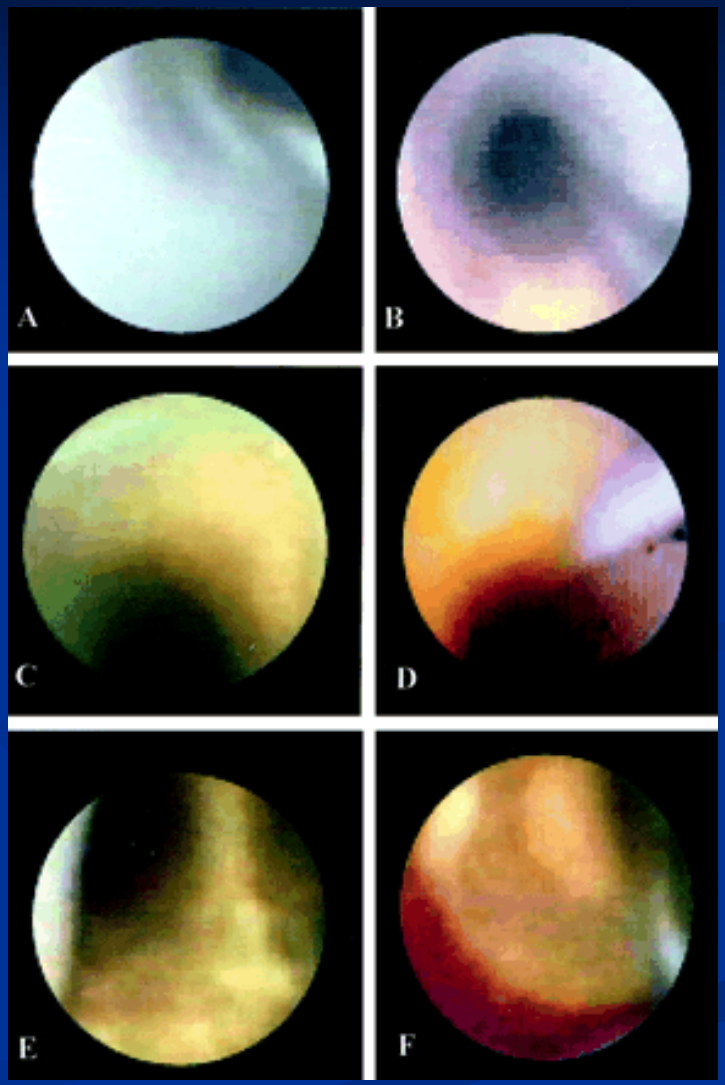


OCT: Limitations

- 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.

Angioscopic color grading of coronary plaques

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

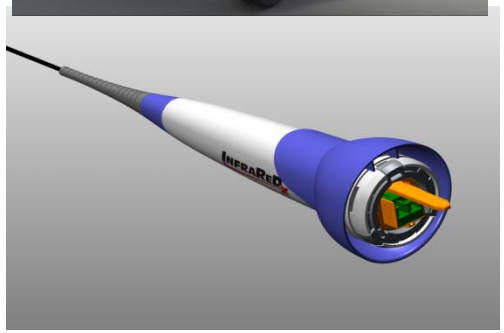
The InfraReDx NIR Spectroscopy System

- **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

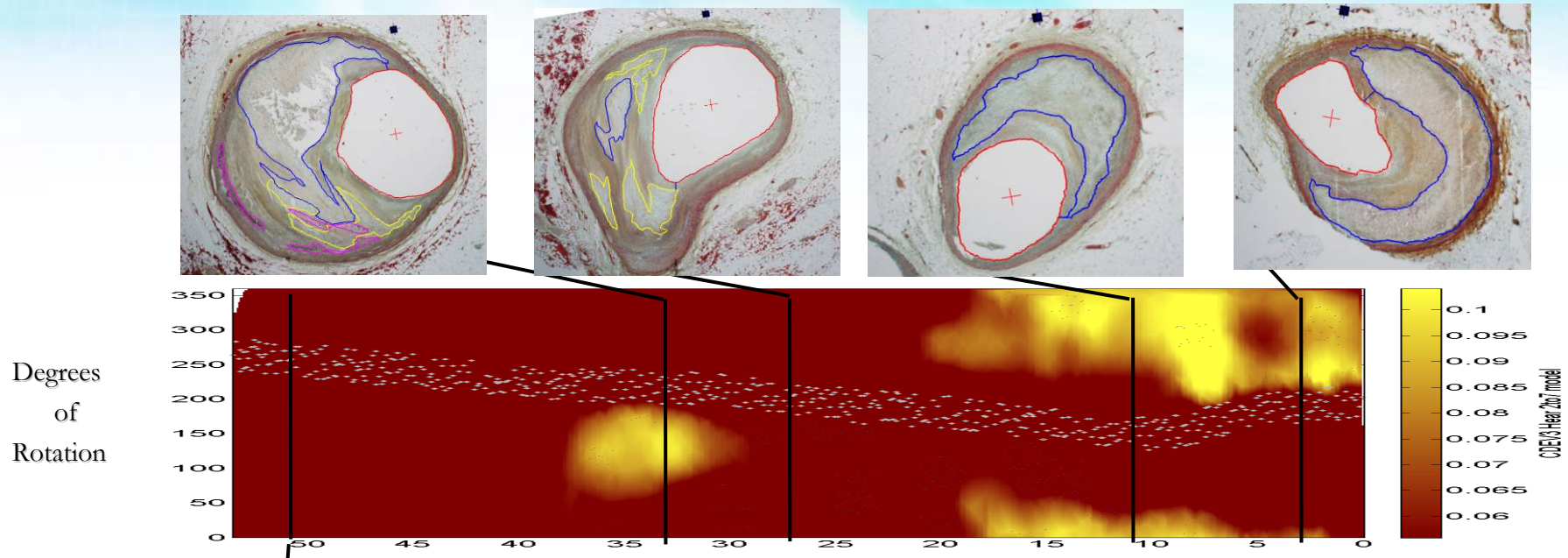
- **Identifies chemical composition of vessel wall:**
  - Sensitivity and specificity > 85% in autopsy specimens
  - Spectra recorded safely in over 70 patients

- **510(k) clearance for NIR examination of coronaries**

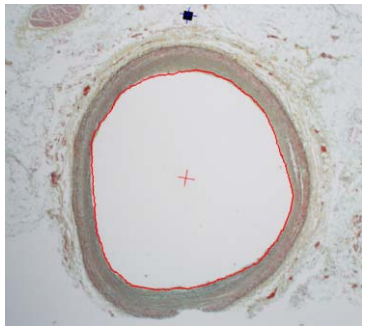


INFRAREDX

Detection of Lipid-rich Plaques with Necrotic Cores in Human Coronary Autopsy Specimens with the Use of a Preliminary Algorithm



Normal area Correctly detected

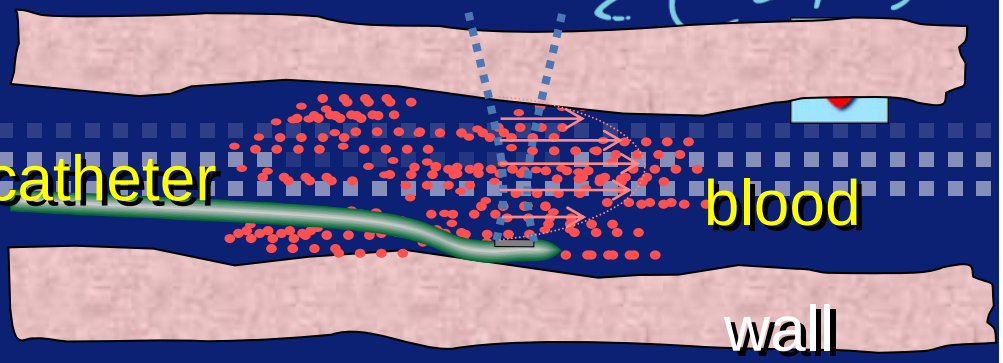


Necrotic Core Correctly Detected

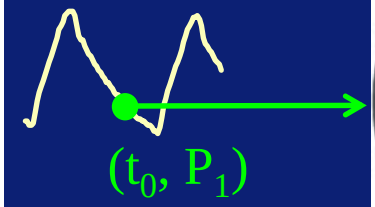
INFRAREDx

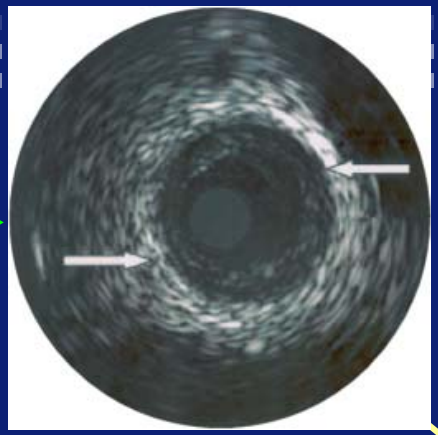
Vasa vasorum imaging with IVUS

Erasmus MC



IVUS at t=0





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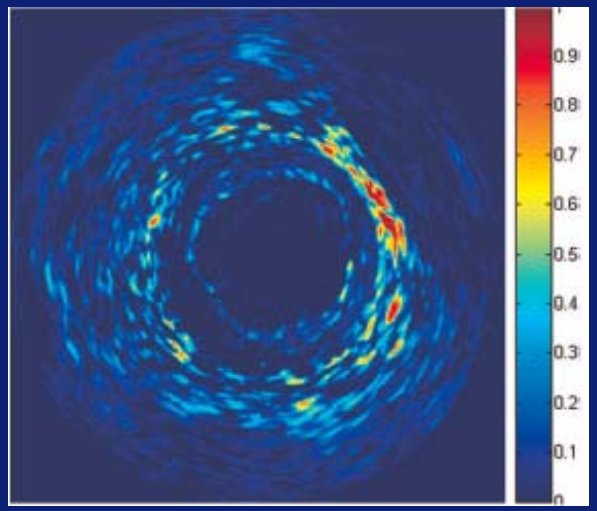
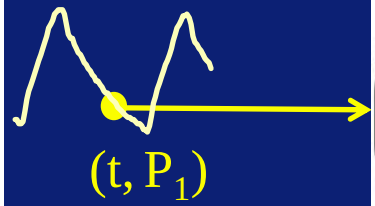
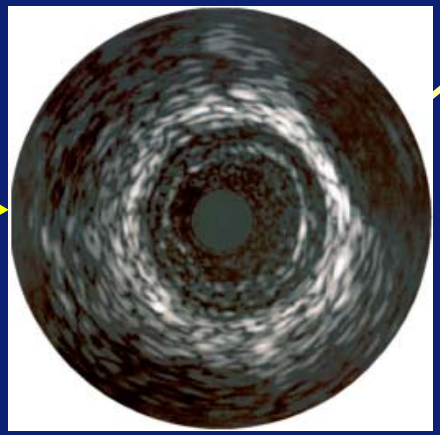


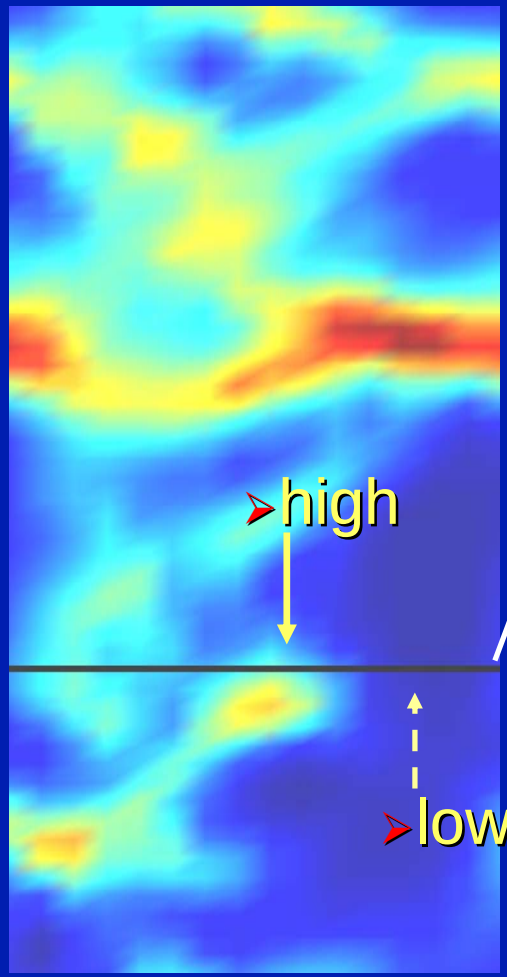
Differential Echogenecity

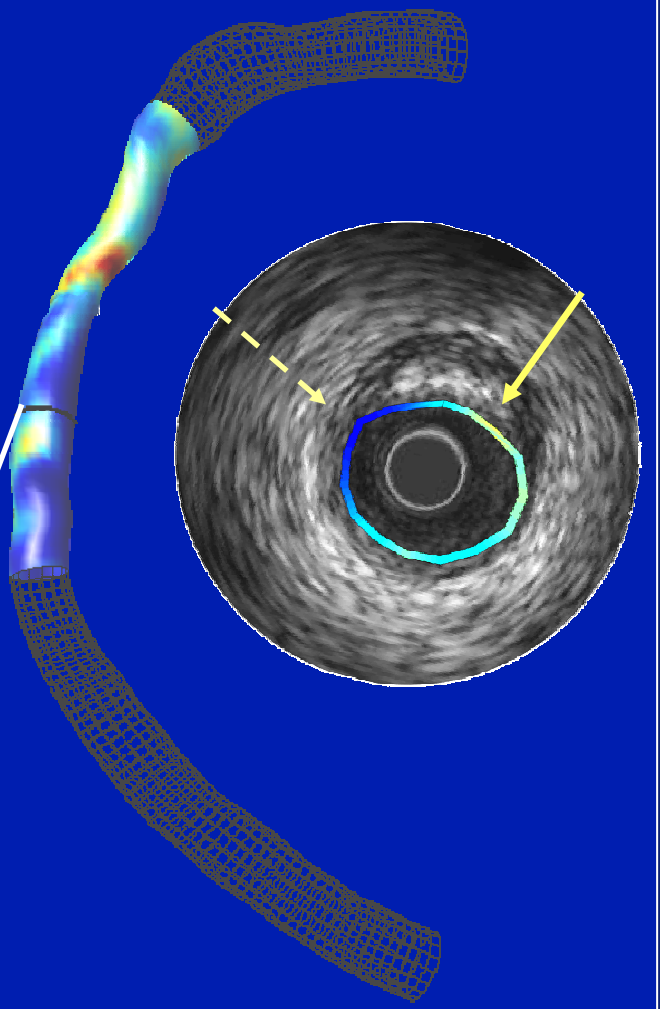




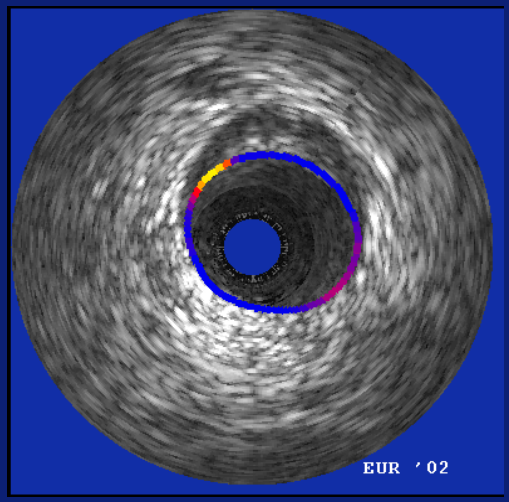
IVUS after bubbles
at same position
and cardiac phase timing

Shear Stress and Palpography





Shear Stress

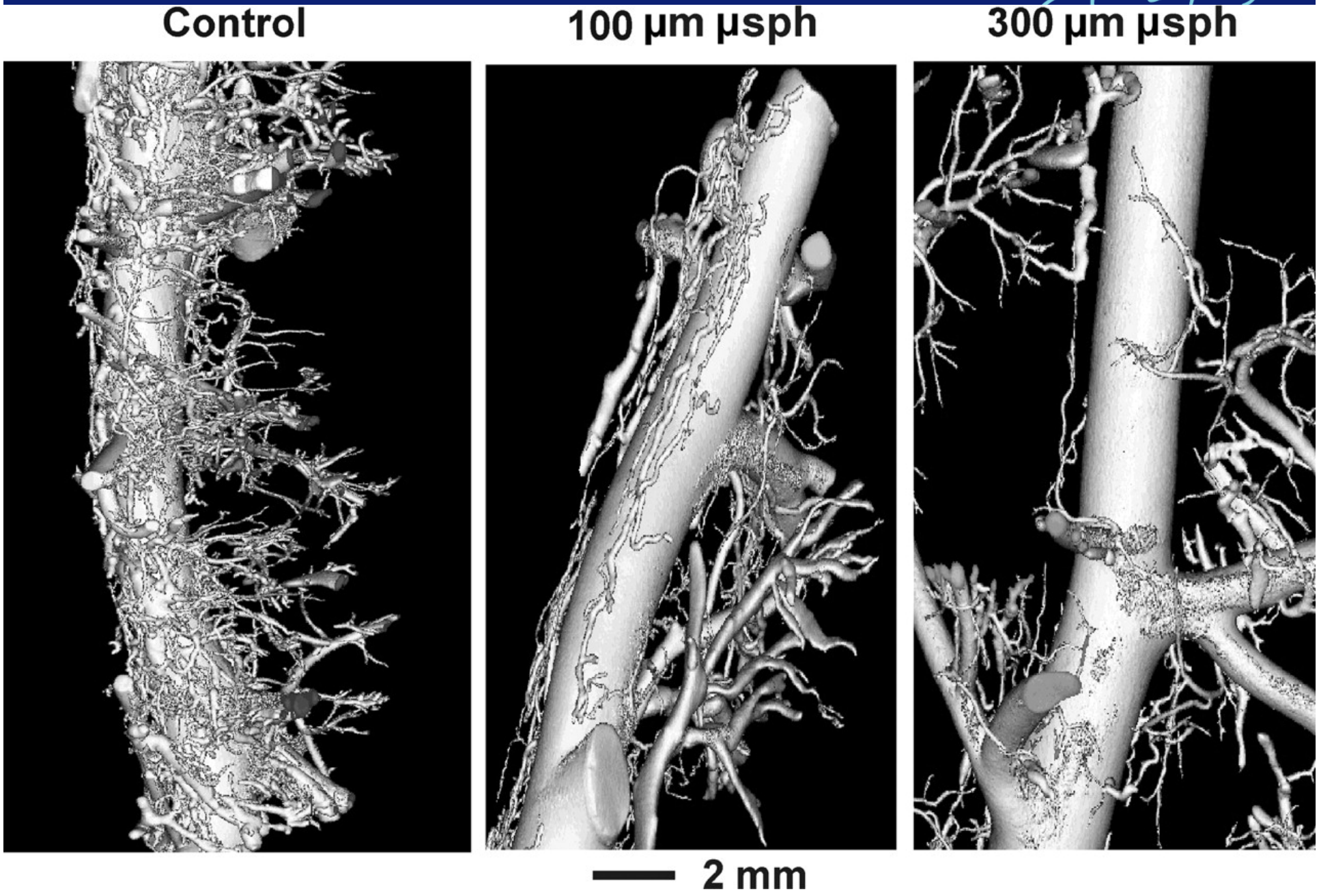


Strain

Hemodynamics Laboratory2003

Ritman et al.

Erasmus MC



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*

PCI and VP Therapy

- What are the "treatment imperatives"…

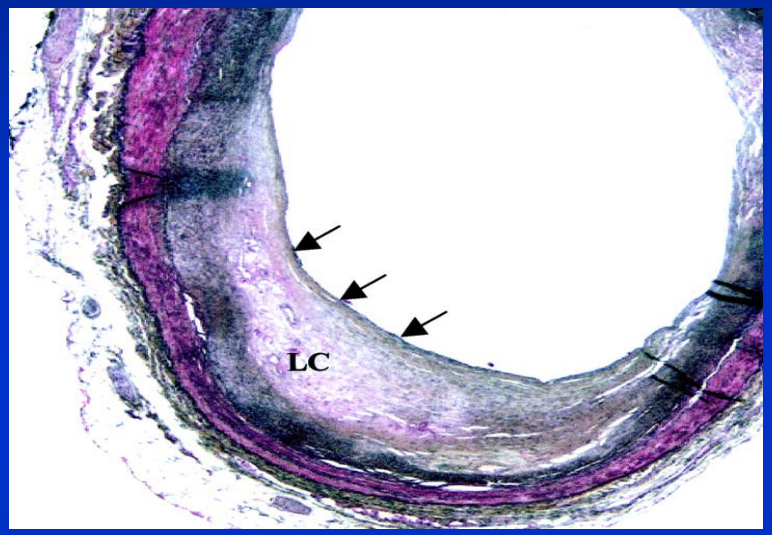
- Must address not merely the vulnerable plaque but also the vulnerable patient

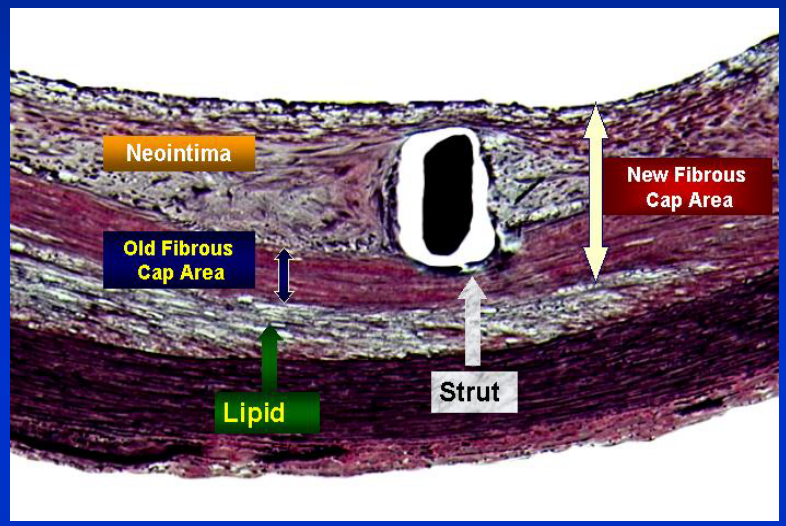
  PCI with Balloon or Stents therapy is focal or at most multi-focal can be used for plaque sealing but is obviously limited if a more regional or systemic therapy is required.

The Hypothesis Than 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

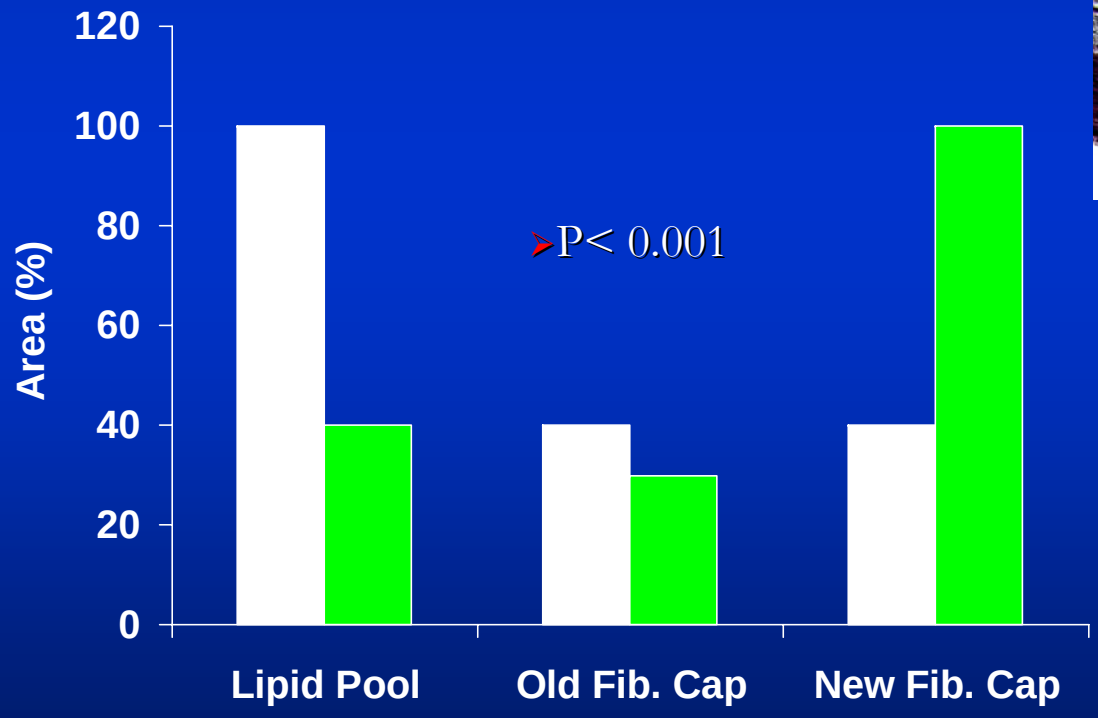


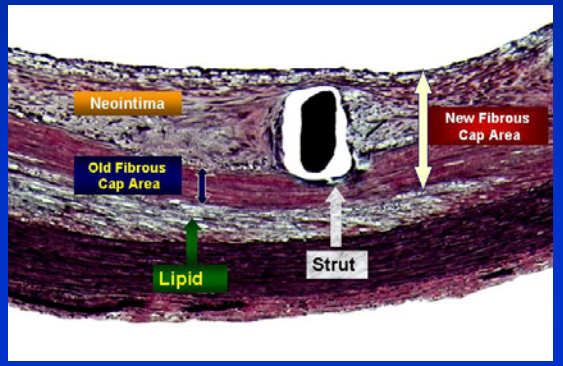


Plaque Features		Mechanical Stabilization
Soft Tissular Matrix	→	Mechanical Compression
Thin Fibrous Cap	→	New Thick “Fibrous Cap” Formation
Prominent Lipidic Core	→	Minimal Lipidic Core
Thin Plaque Shoulders	→	Stabilized by Healthy Thin Neointima

Mechanical Stabilization of Vulnerable Plaques with BMS

Experimental Data: Mechanical Stabilization of TCFA in Rabbits

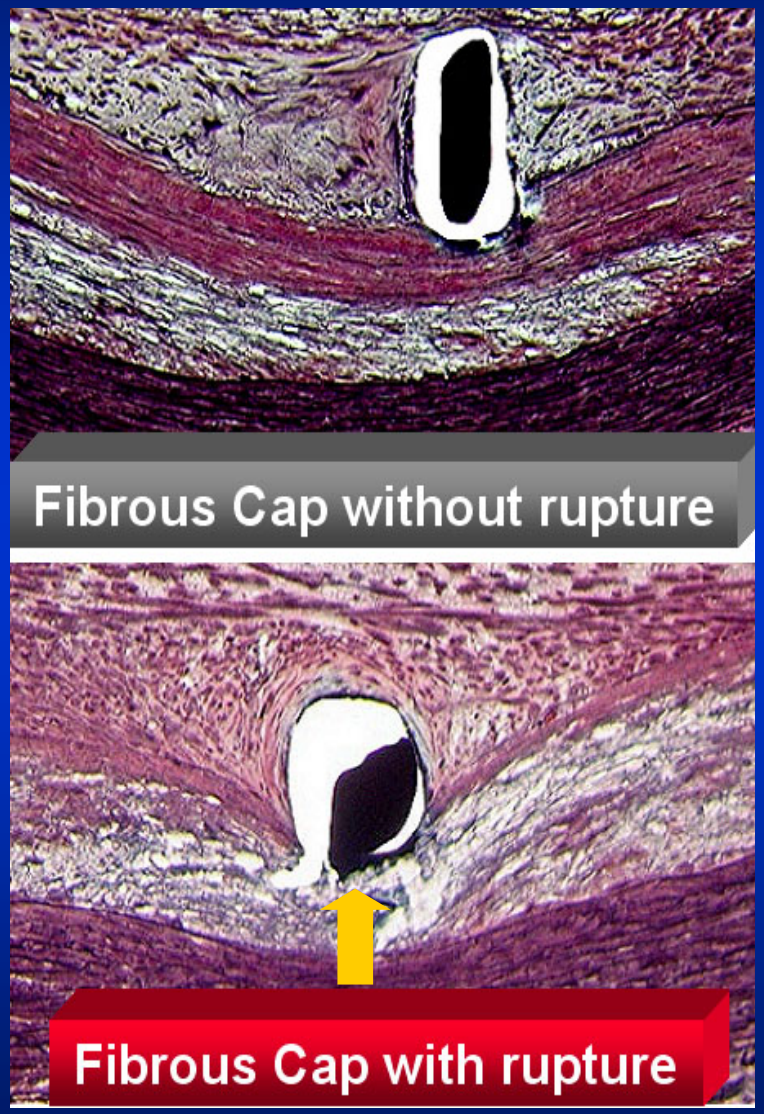




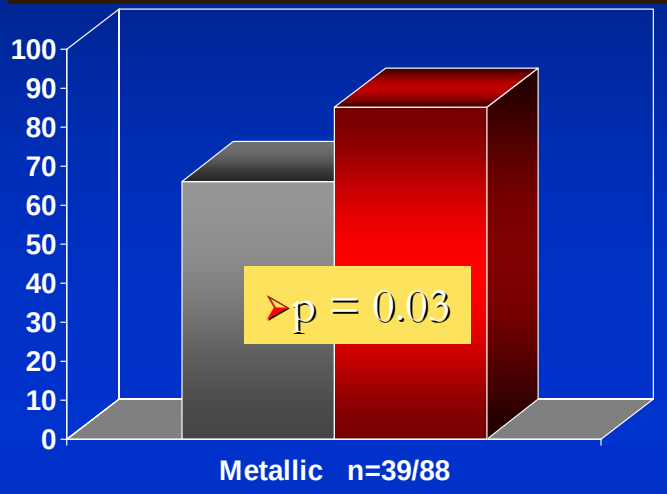
Echeverri D, Moreno P. ACC 2003

Workhorse Stents Rupture Fibrous Cap & Increase NIH

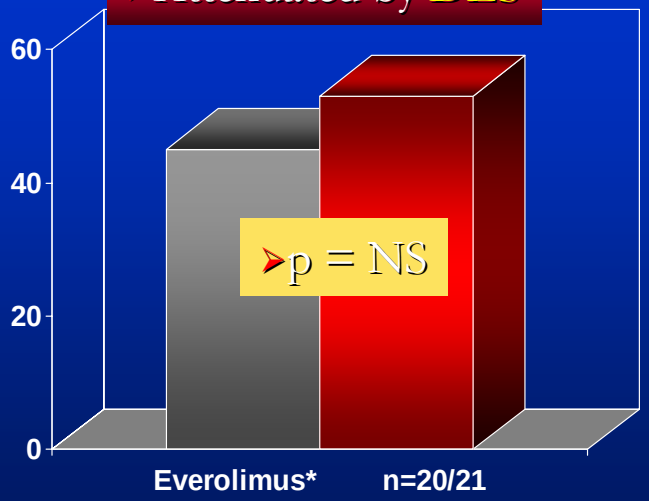
- 276 struts on TCFA; 188 ruptured the Cap (63%)



- NIH = Neointimal Hyperplasia



- Attenuated by DES



- Moreno et al. TCT 2004

DES and VP Therapy

- 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

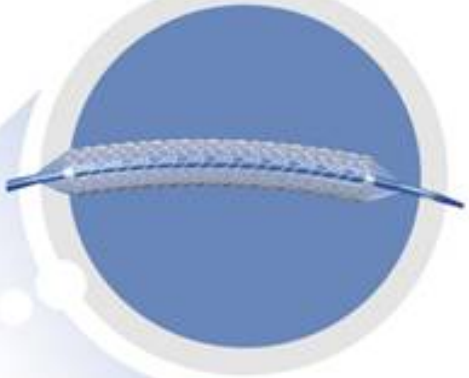
- reduced inflammation and giant cell formation
- reduced fibrin deposition, and hemorrhage
- increased endothelialization

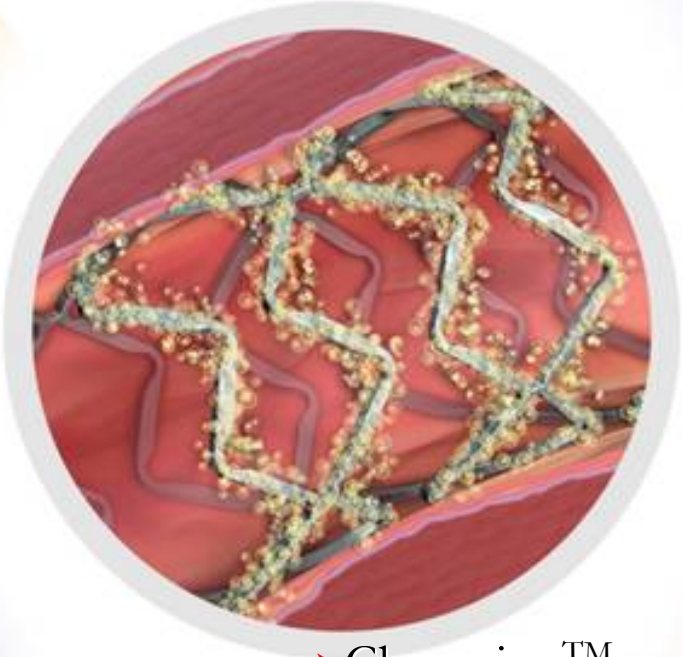
Very low incidence of strut-induced fibrous cap rupture

Self-expandable devices may be the future for invasive therapy of fibroatheroma.

BVS Fully Bioabsorbable Drug Eluting Stent

- BVS Bioabsorbable Stent Platform

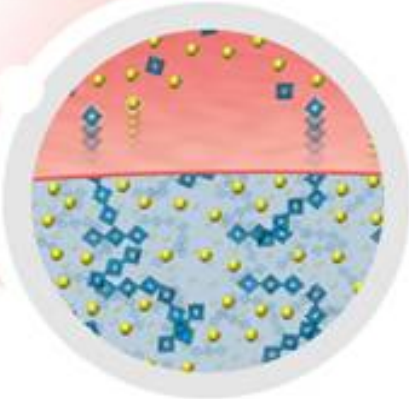




- ML VISION® Balloon SDS

- Everolimus

- Champion™ Bioabsorbable Polymeric Drug Release



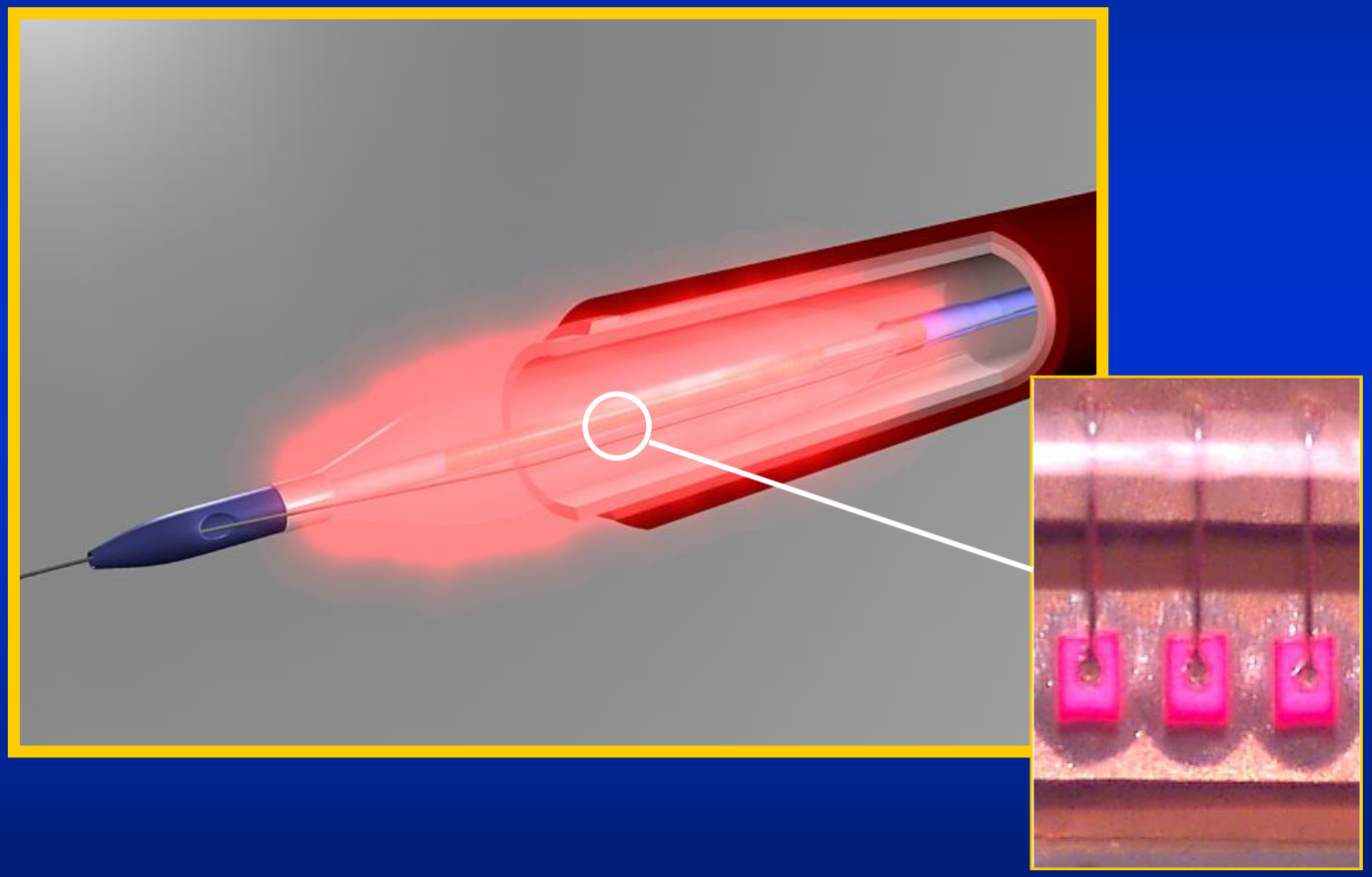
Photodynamic Therapy

What are the "treatment imperatives"…

- PDT involves the interaction of a photosensitizing drug, light and tissue oxygen.
- Photosensitizing agents, many of which are porpohyrins 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™

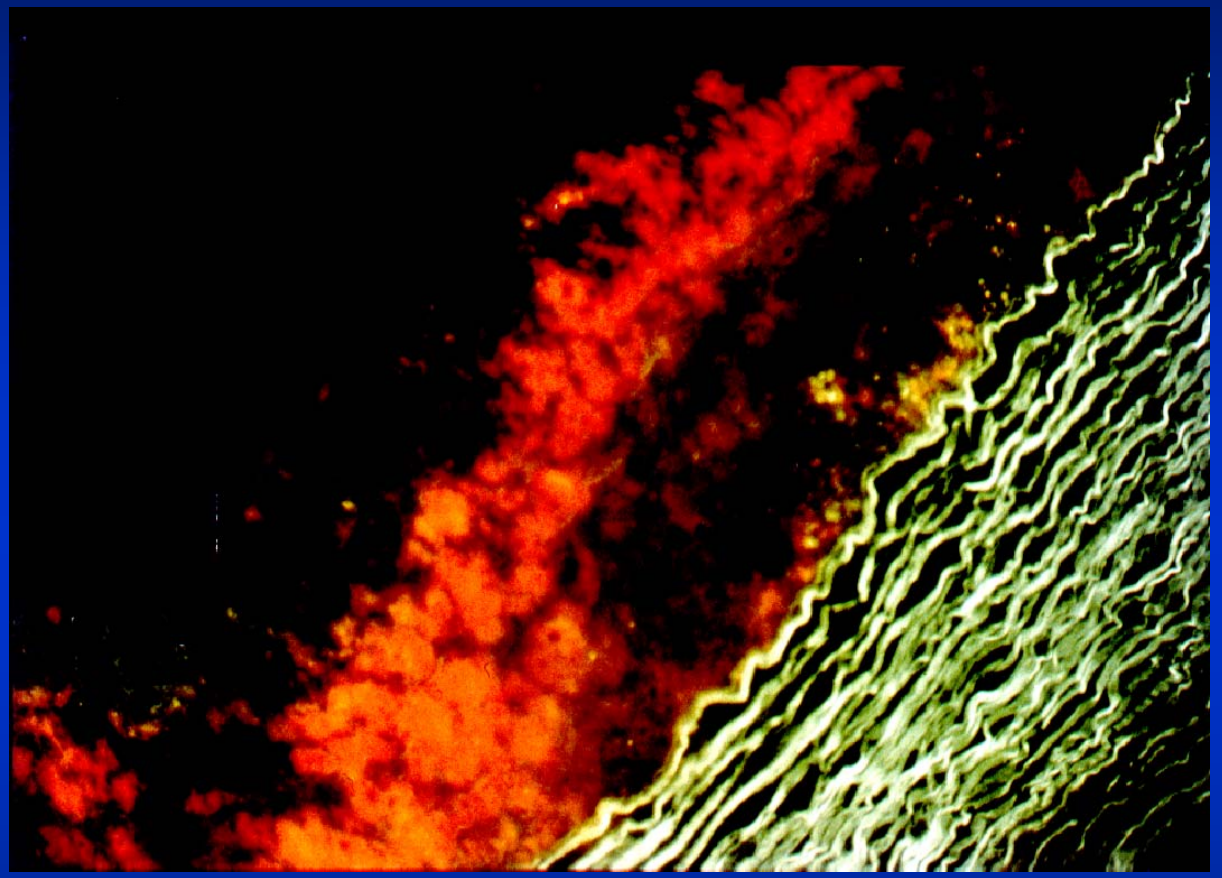
LS11 activated with endovascular LED
– no need for laser



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]

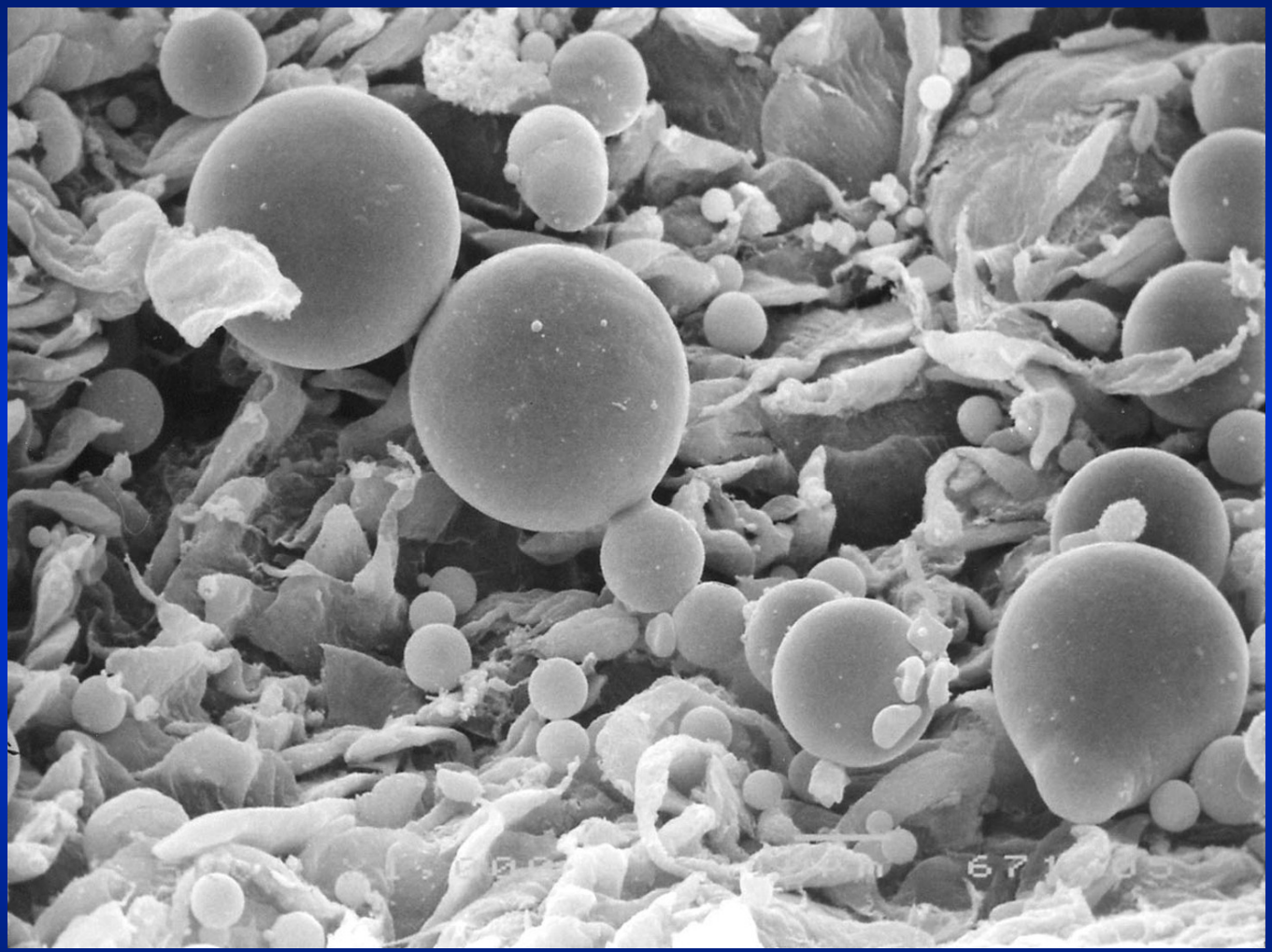
Selective Plaque Accumulation



LS11 revealed in atherosclerotic plaque in rabbit aorta using fluorescence microscopy

Image through courtesy of Dr K Aizawa, Tokyo Medical University

Photo-atherolysis?

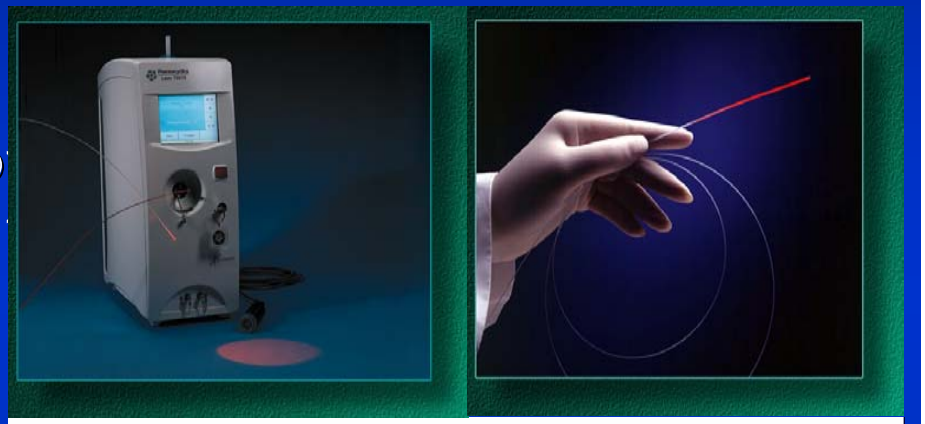


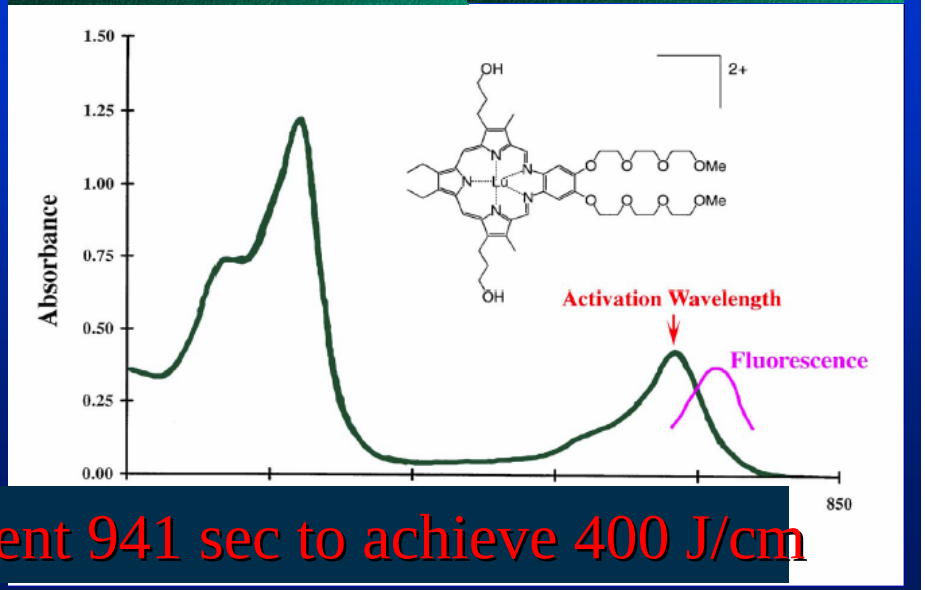
- Dissociation of plaque lipid after LS11 PDT treatment

(Saito T et al. Tokyo, J)

- Motexafin Lutetium (MLu) Phototherapy
- *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

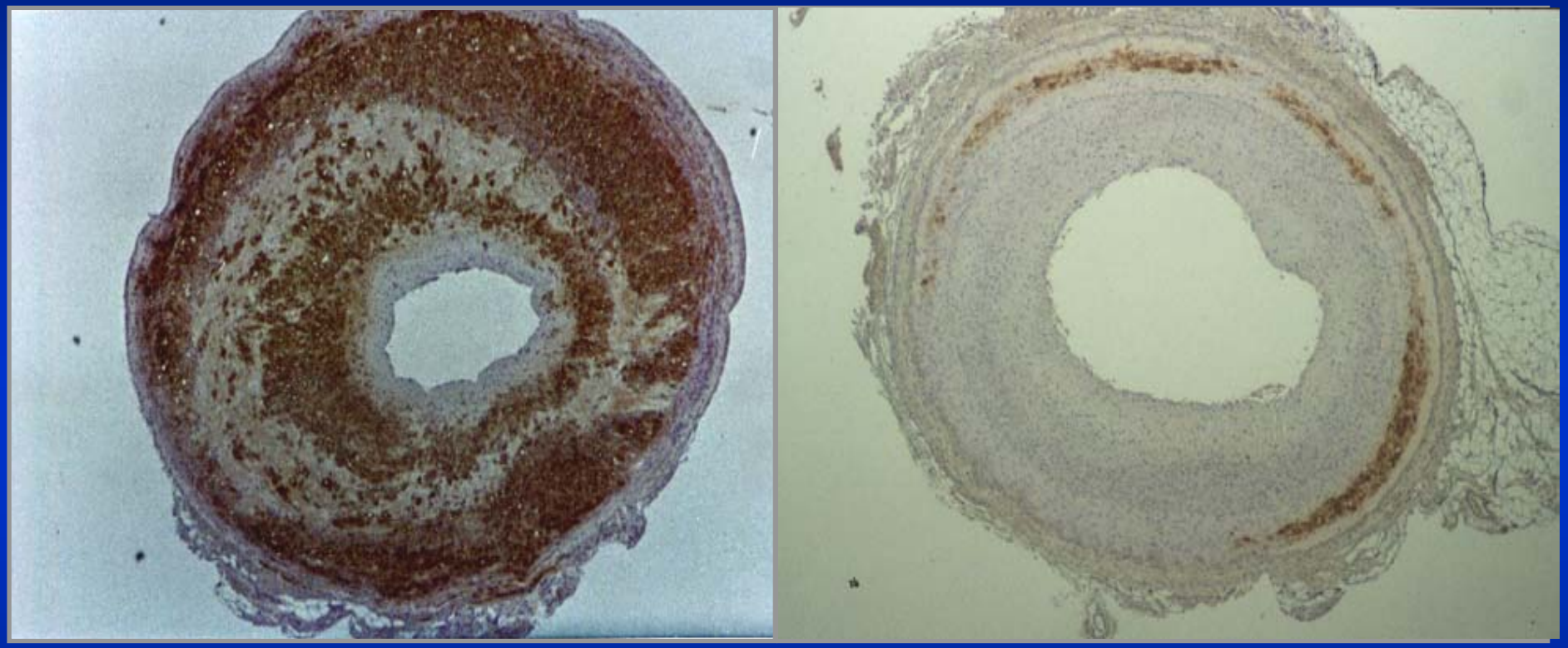




- Far red light ~730 nm light treatment 941 sec to achieve 400 J/cm

MLu Phototherapy:

Effect on Macrophages



Control

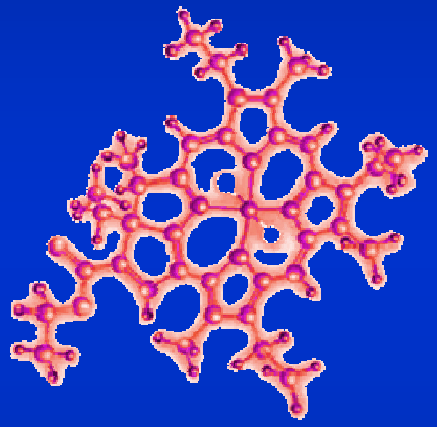
Treated

Immunoperoxidase staining with RAM11

Hayase M, et al. *Cardiovascular Res.* 2001;49:449-55

MIRVANT PROGRAM

+



O_2

$*O_2$

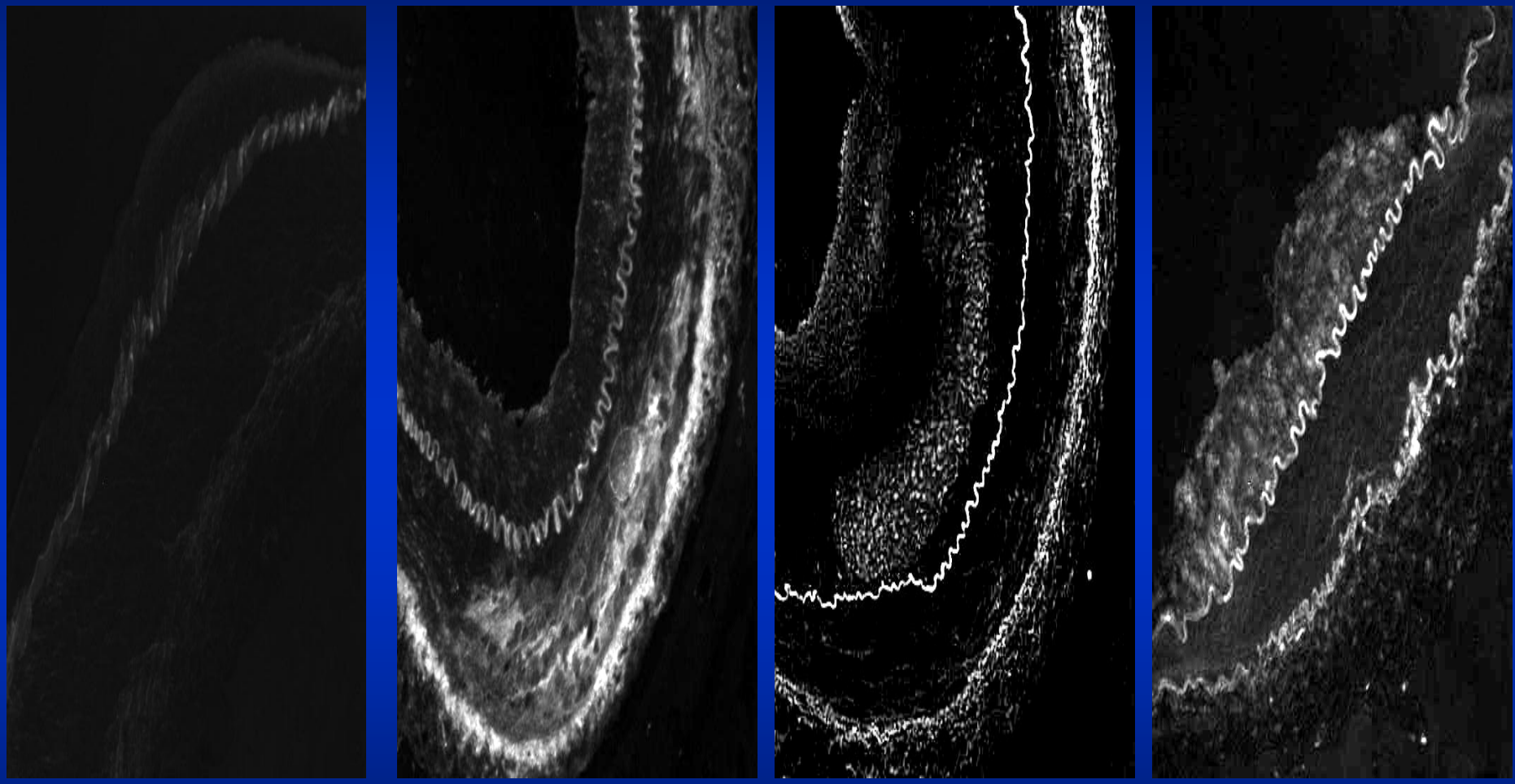
Cell Depletion

Miravant Light Catheter

Miravant Photosensitizer Compound (MV0611)

Biological Response

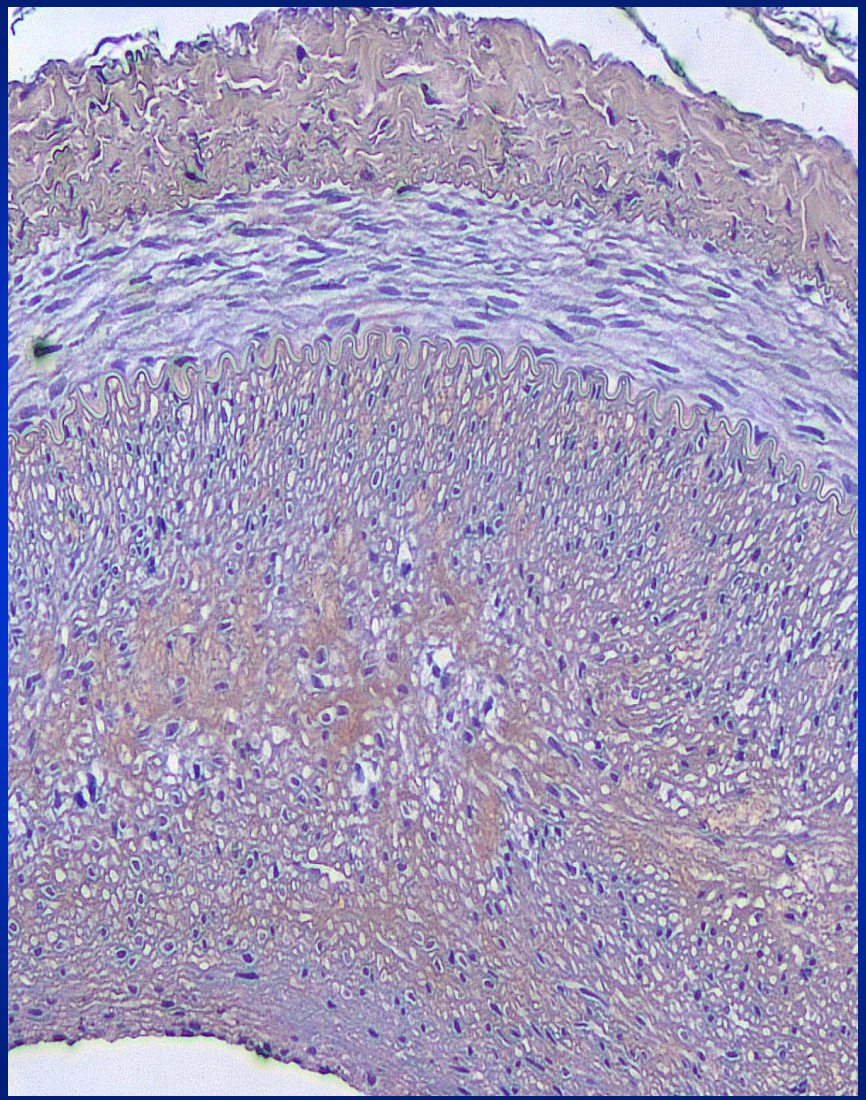
Tissue Distribution of MV0611

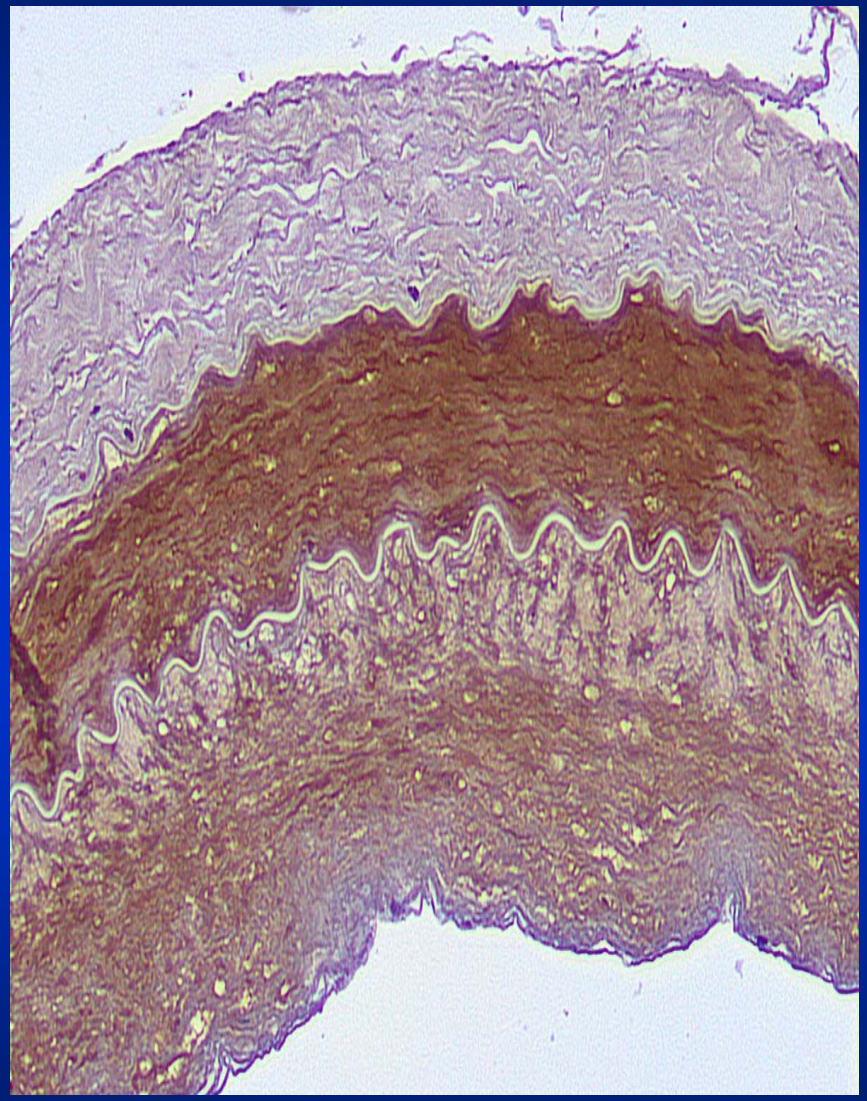


Control 4 hours 8 hours 24 hours

Autofluorescent Drug Localized in Plaques

Increased P53 Expression

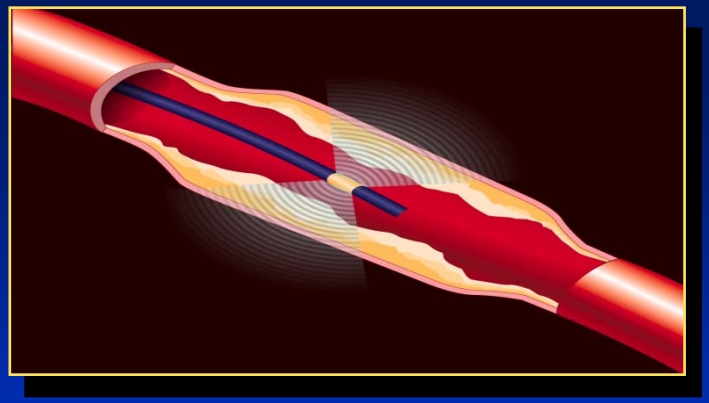




- C
P5

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