VH (Virtual Histology): A Technical and Clinical Update

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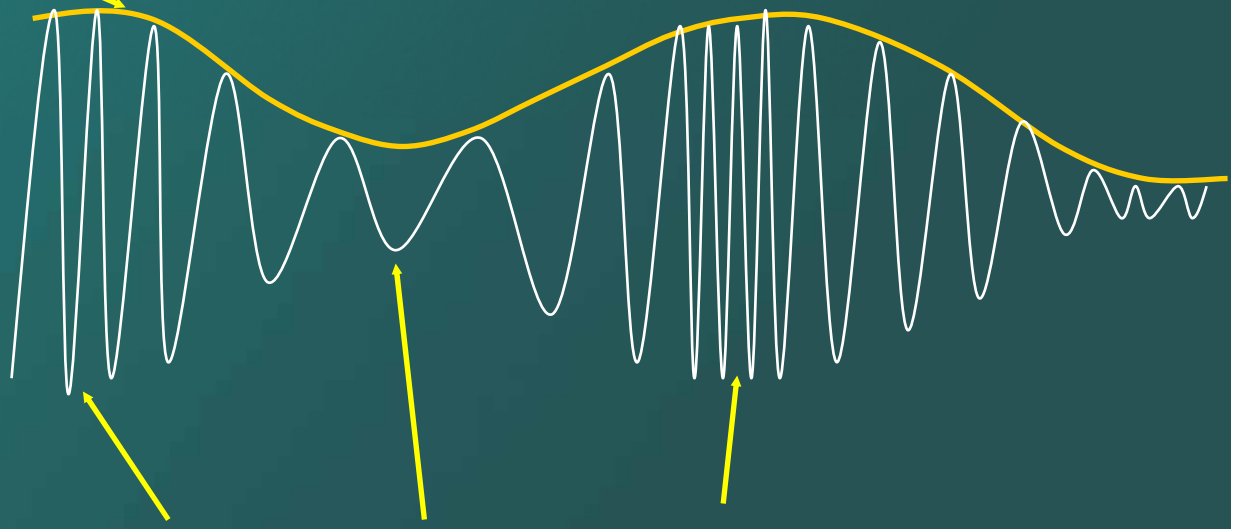
Cardiovascular Research Foundation

Virtual Histology™ IVUS

Only the envelope amplitude (echo intensity) is used in formation of the gray-scale IVUS image

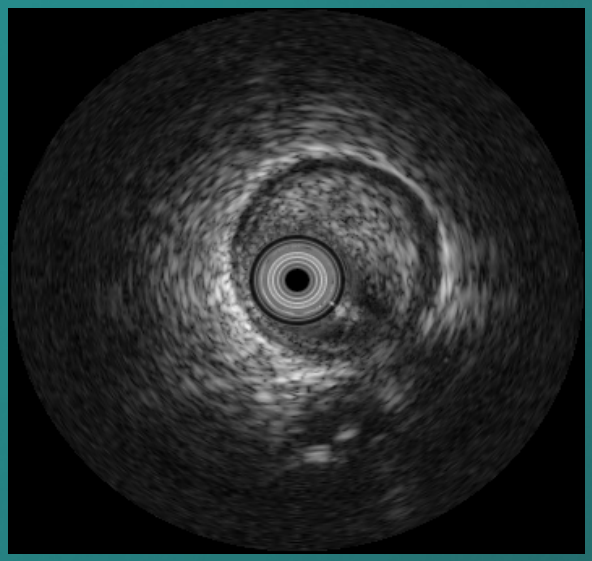
Amplitude *AND* Frequency are used to generate 8 parameters to create the look-up table



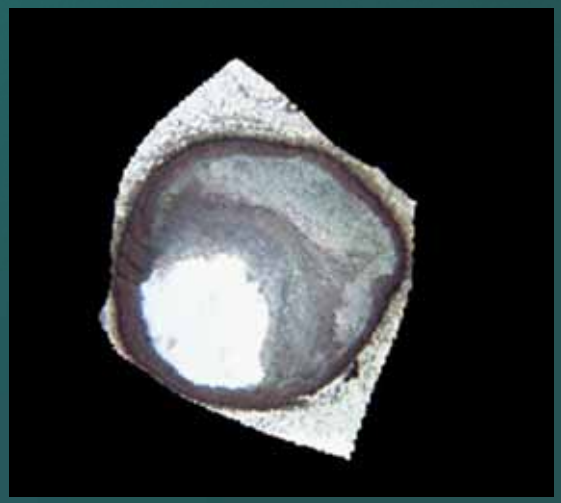
Frequency of echo signal can also vary, depending on the tissue

Thin Plate Spline Morphing

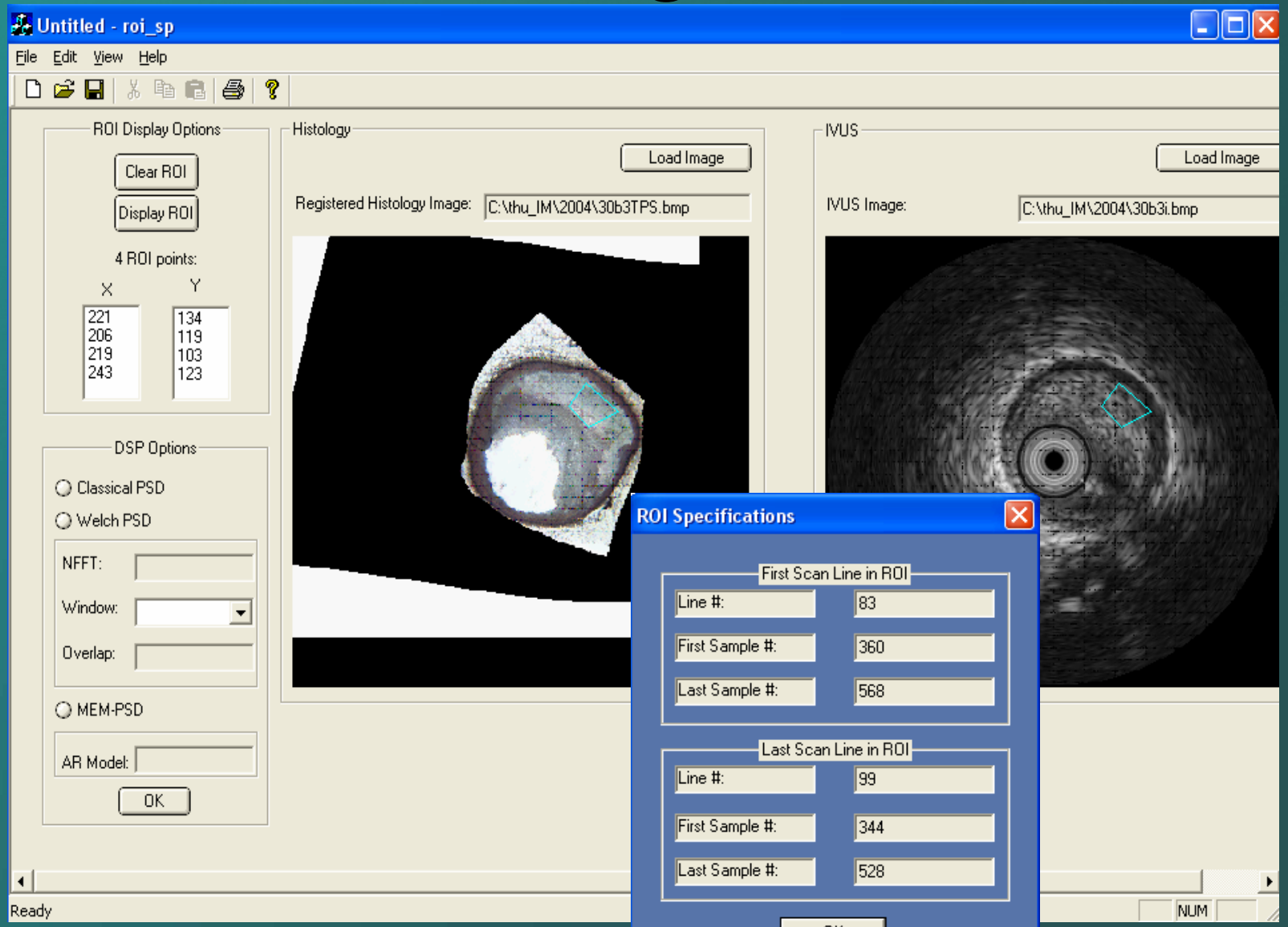
IVUS B scan



Movat pentachrome stain

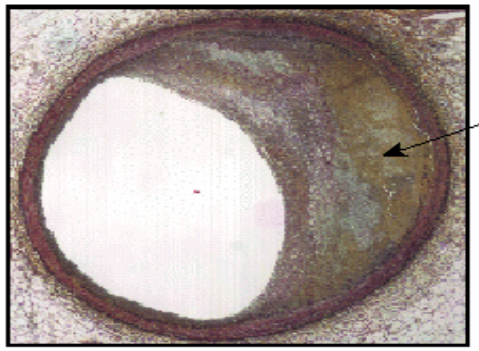


Selection of regions of interest



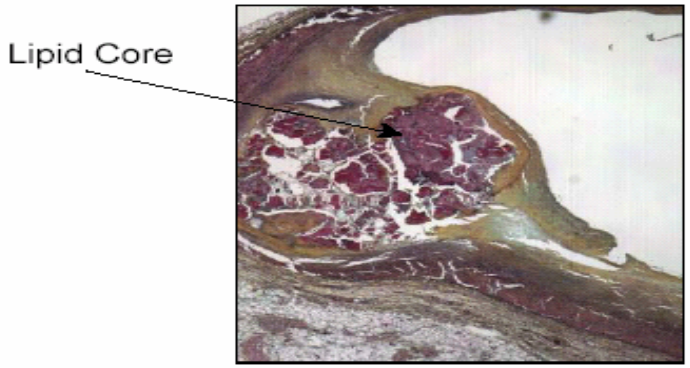
Fibrotic

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.



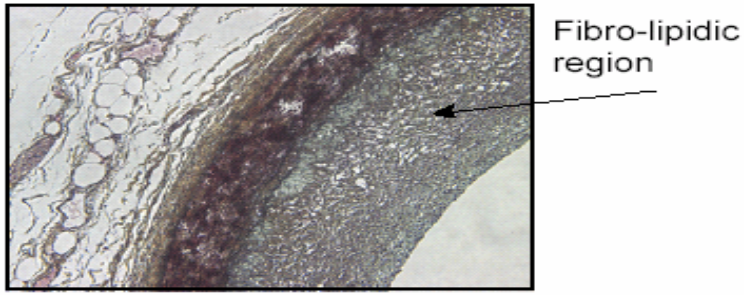
Necrotic core

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



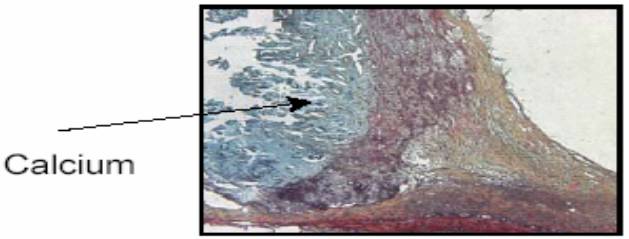
Fibro-Fatty

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.



Calcium

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



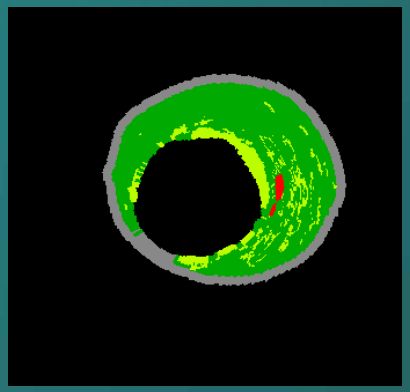
Correlation between In Vitro histology of DCA specimens vs In Vivo plaque composition

Courtesy of Dr. Antonio Colombo and Dr. Osamu Kato

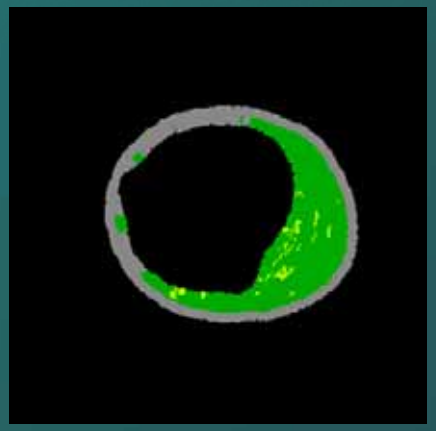
Milan Case #2

In vitro **histopathology showed mainly fibro-fatty tissue taken at the site of the culprit lesion in the left anterior descending (LAD).**

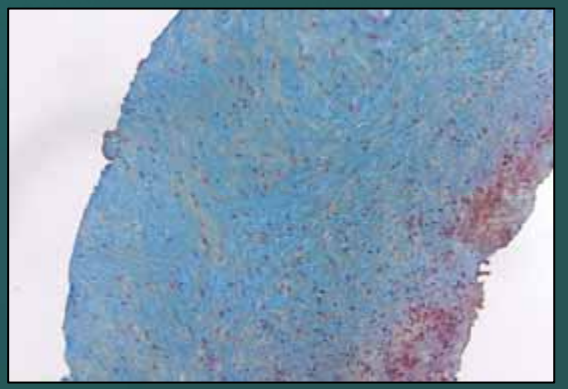
In vivo **VH from the site of the cut corresponded with the in-vivo plaque compostion showing greenish yellow fibro-fatty tissue.**



Pre DCA

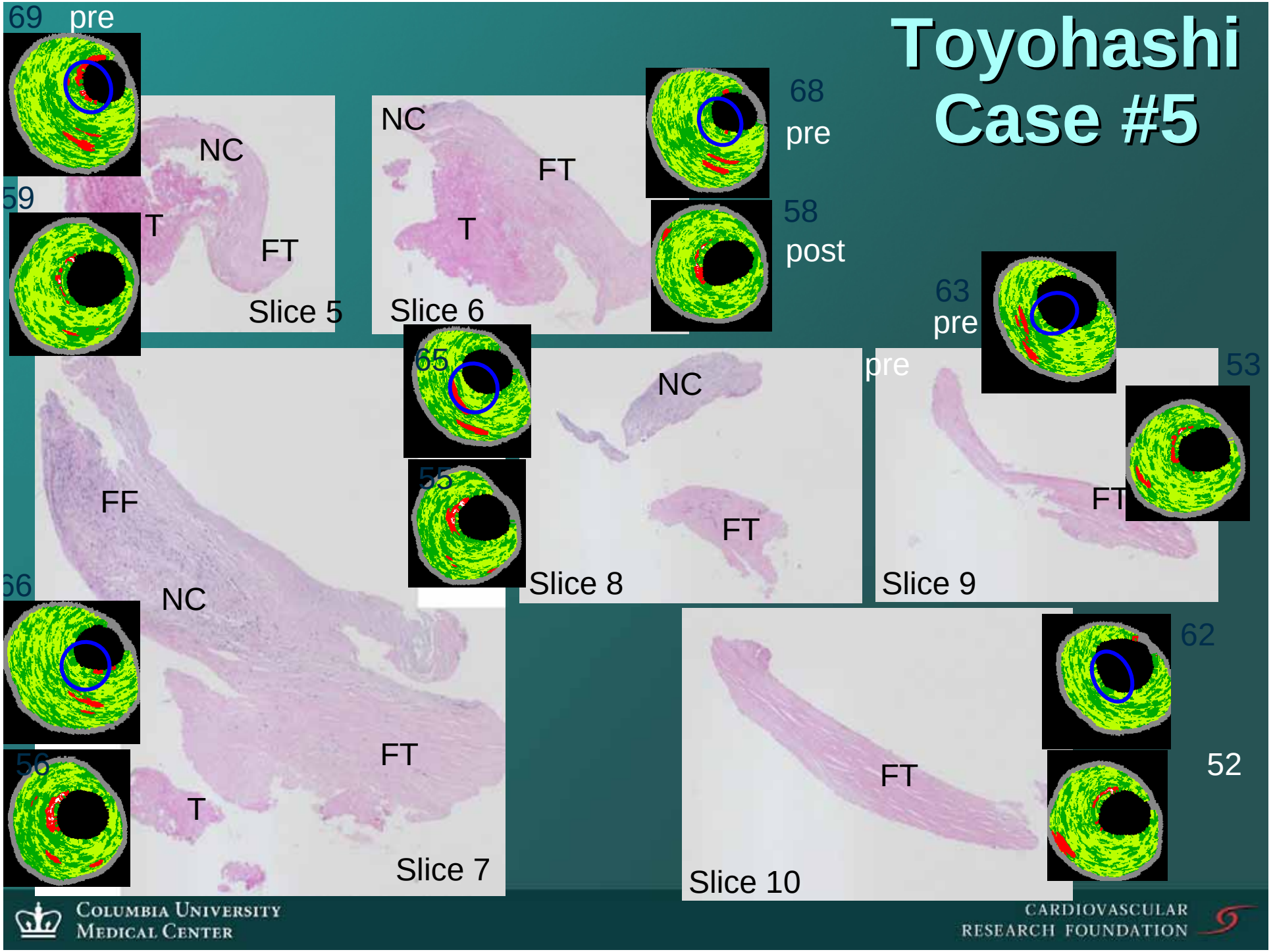


Post DCA cut



Histology

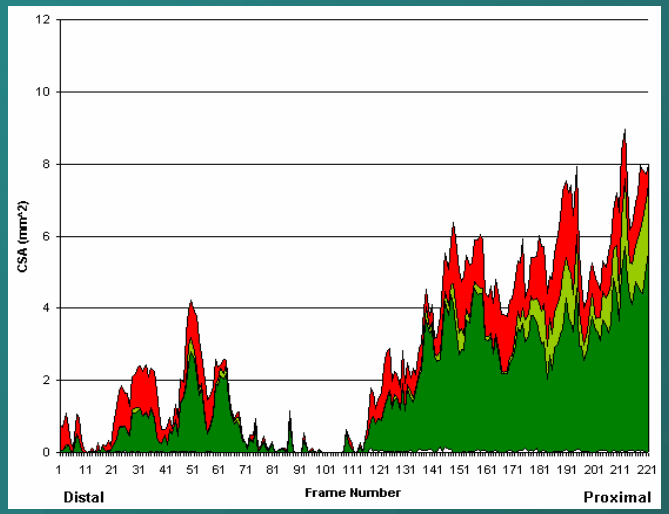
Toyohashi Case #5

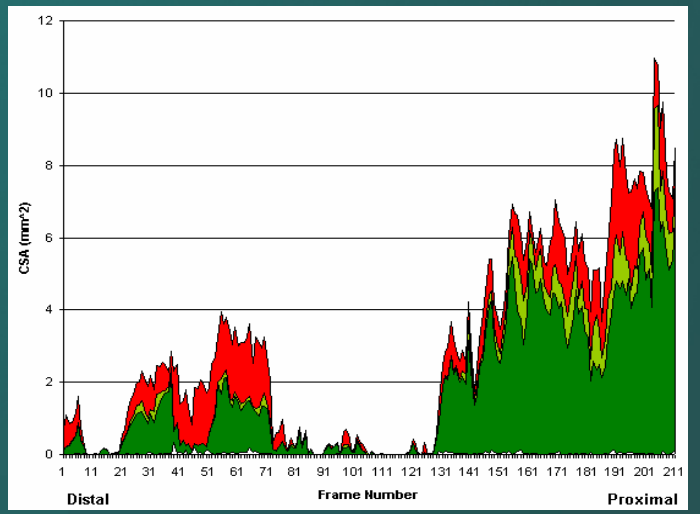


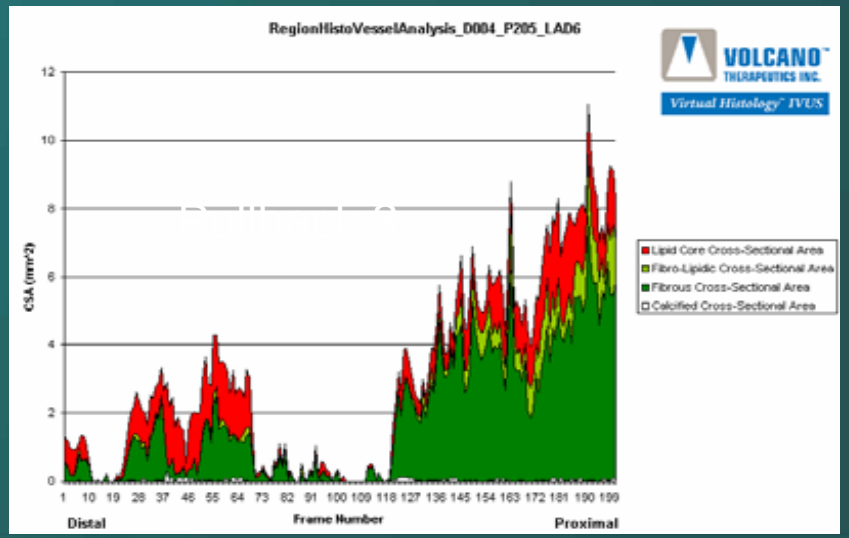
Reproducibility Data

Courtesy of Dr. James Margolis

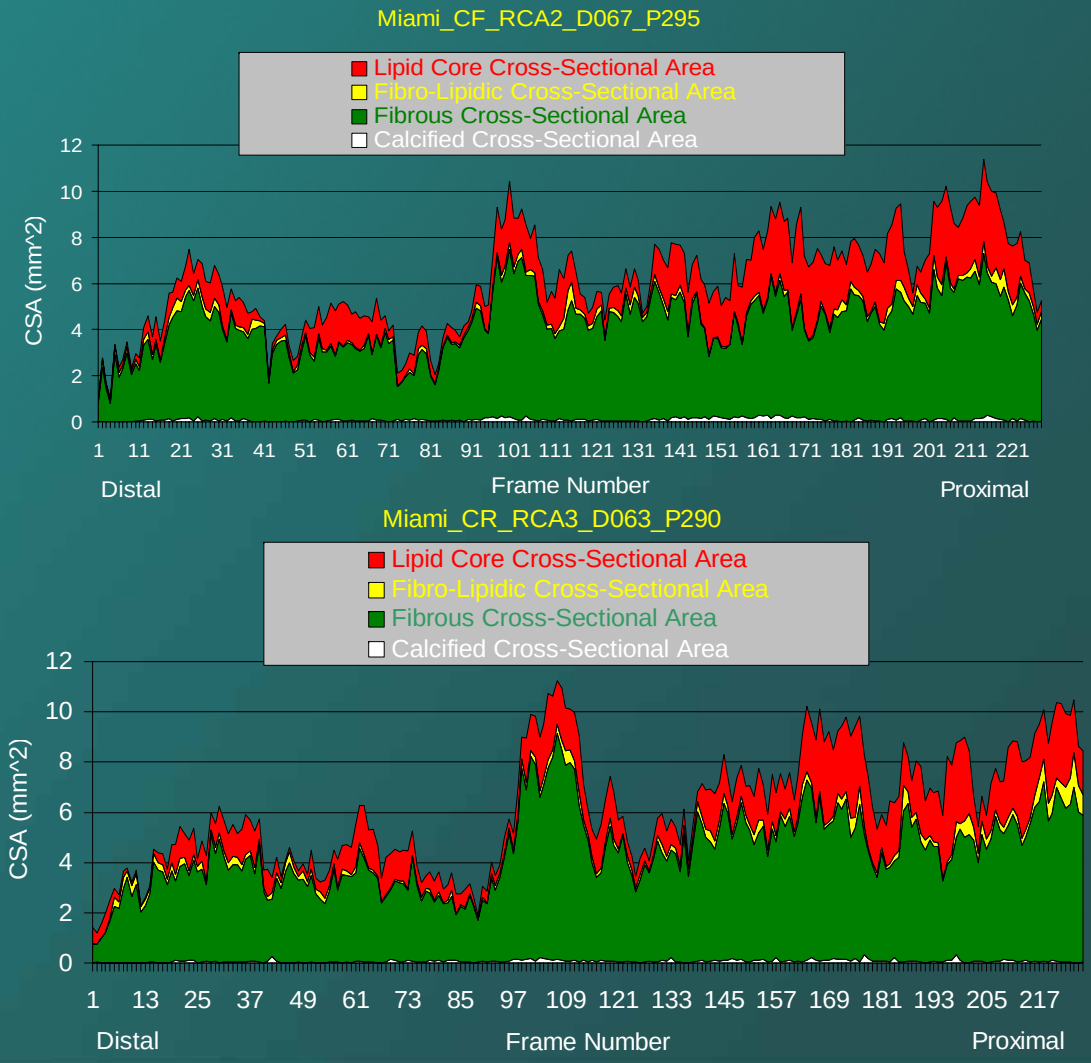
Three pullbacks done with the same 30MHz catheter



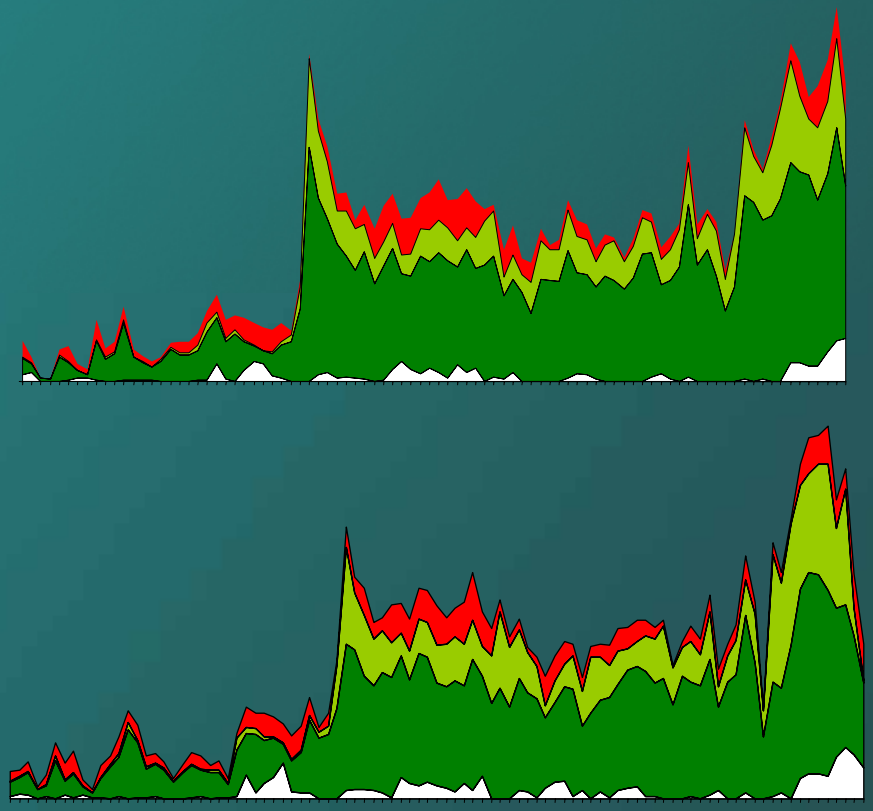




Two pullbacks done with different 30MHz catheters



Two pullbacks done with different 20MHz catheters



Additional technical development that is needed

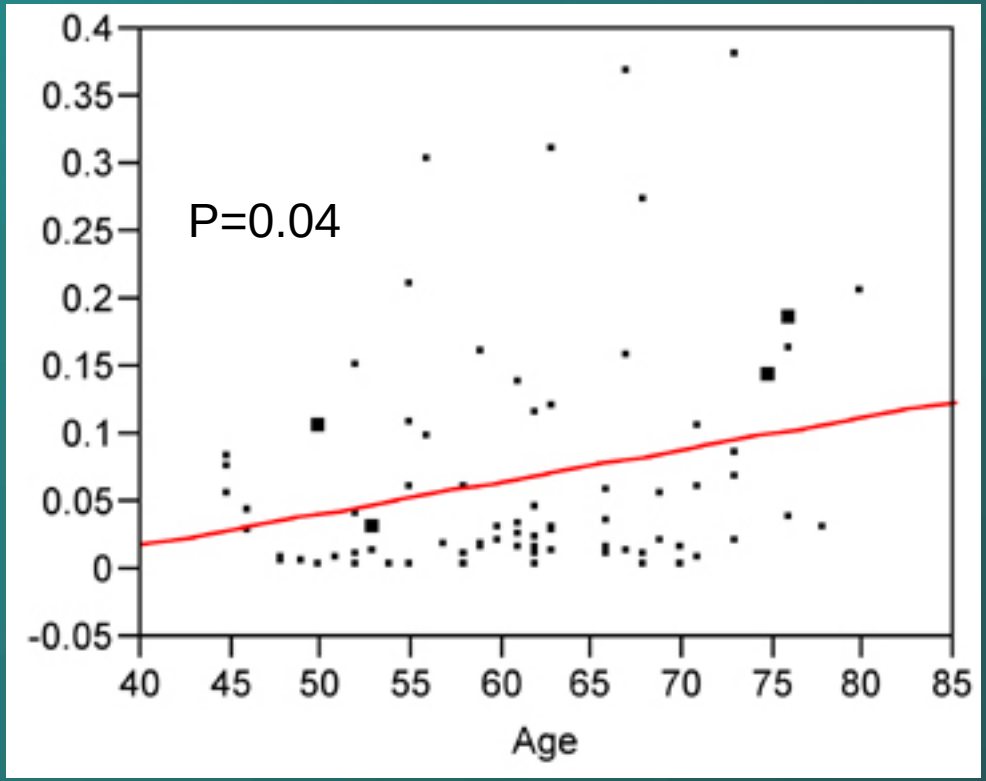
- Classification for
  - Blood
  - Thrombus
  - Stent metal
- Approach to “plaque behind calcium”
- Classification tree for other catheters
  - 40MHz BostonScientific catheter
- Reproducibility
  - IVUS plaque composition with different catheters of different types

Essen Data With Blinded Deconvolution
(courtesy of Raimund Erbel)

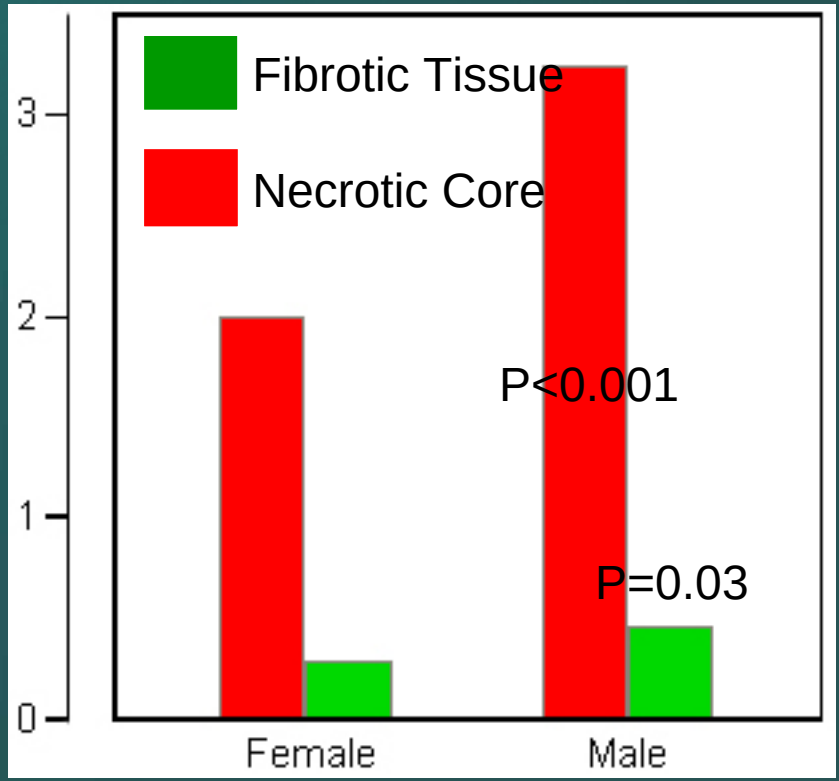
- Total (n=75)
  - Culprit artery pre-intervention (n=67)
  - Culprit artery after pre-dilation (n=3)
  - Culprit artery post-intervention (n=1)
  - Diagnostic (n=2)
  - Unknown (n=2)

Effect of age and gender on plaque composition

Dense calcium correlated with patient age

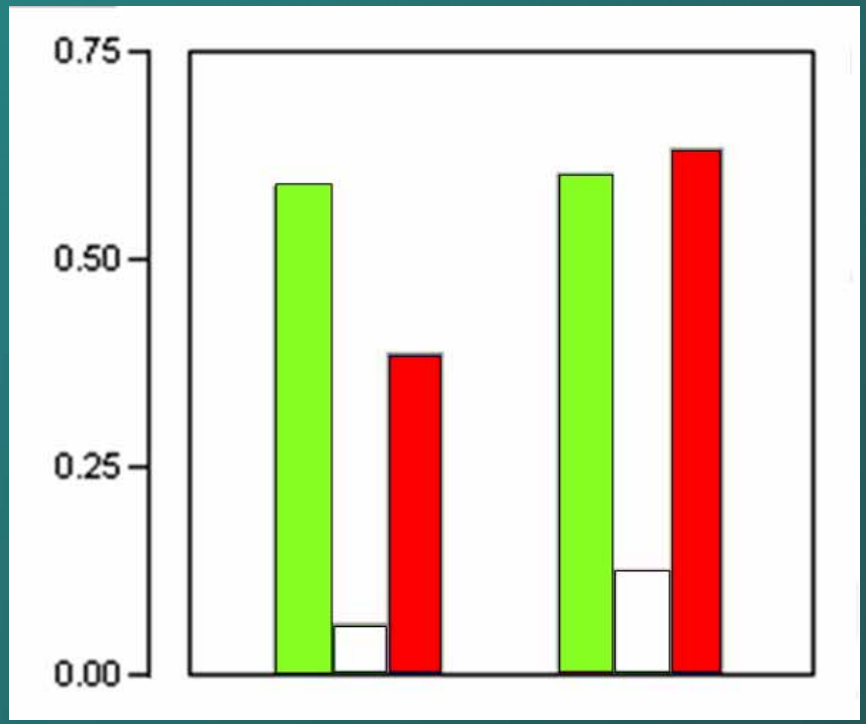


Males had significantly more fibrotic plaque and a larger a necrotic core

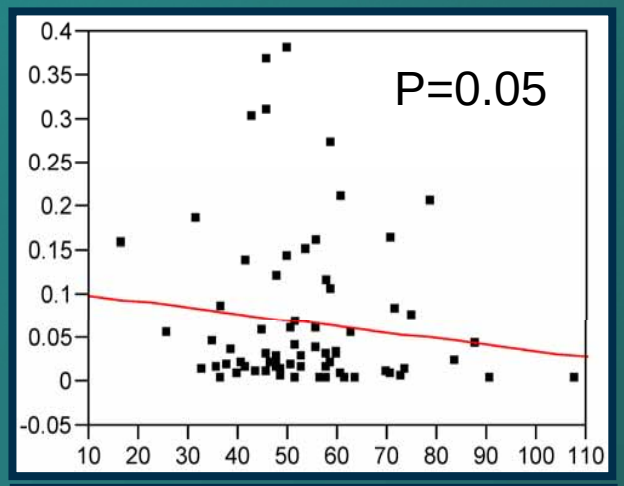


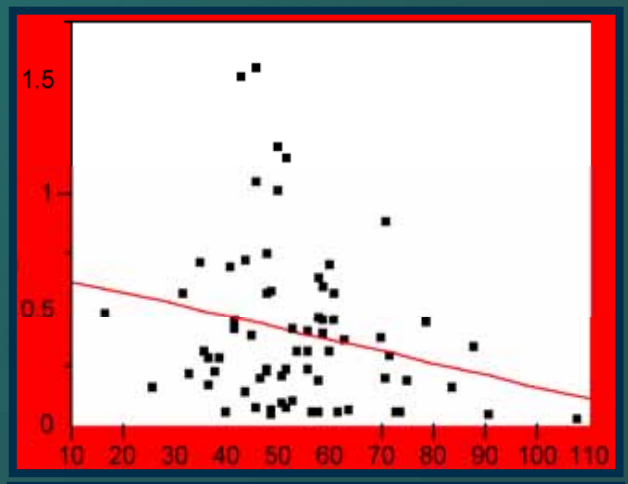
Plaque Composition in Diabetes

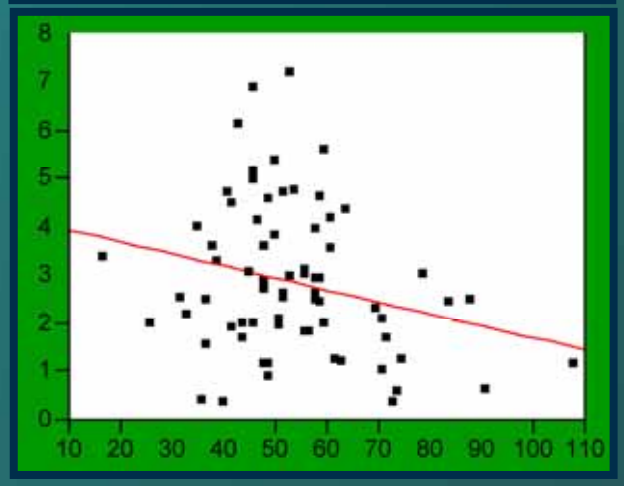
Significantly more Dense Calcium (P=0.04) and Necrotic Core (P=0.05) in Diabetic patients, but no difference in fibrofatty plaque

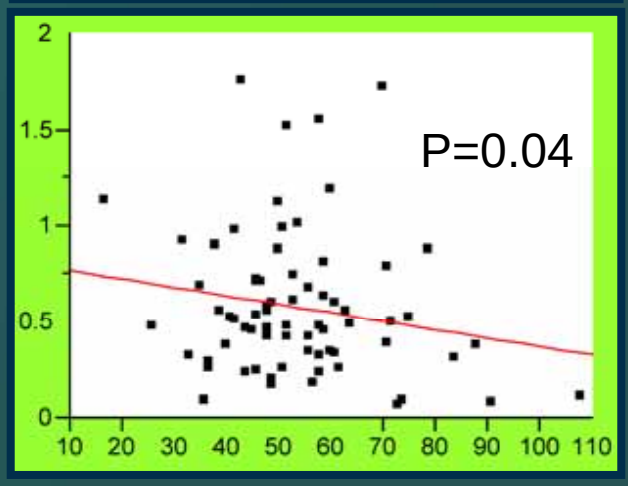


Relationship between HDL and plaque composition



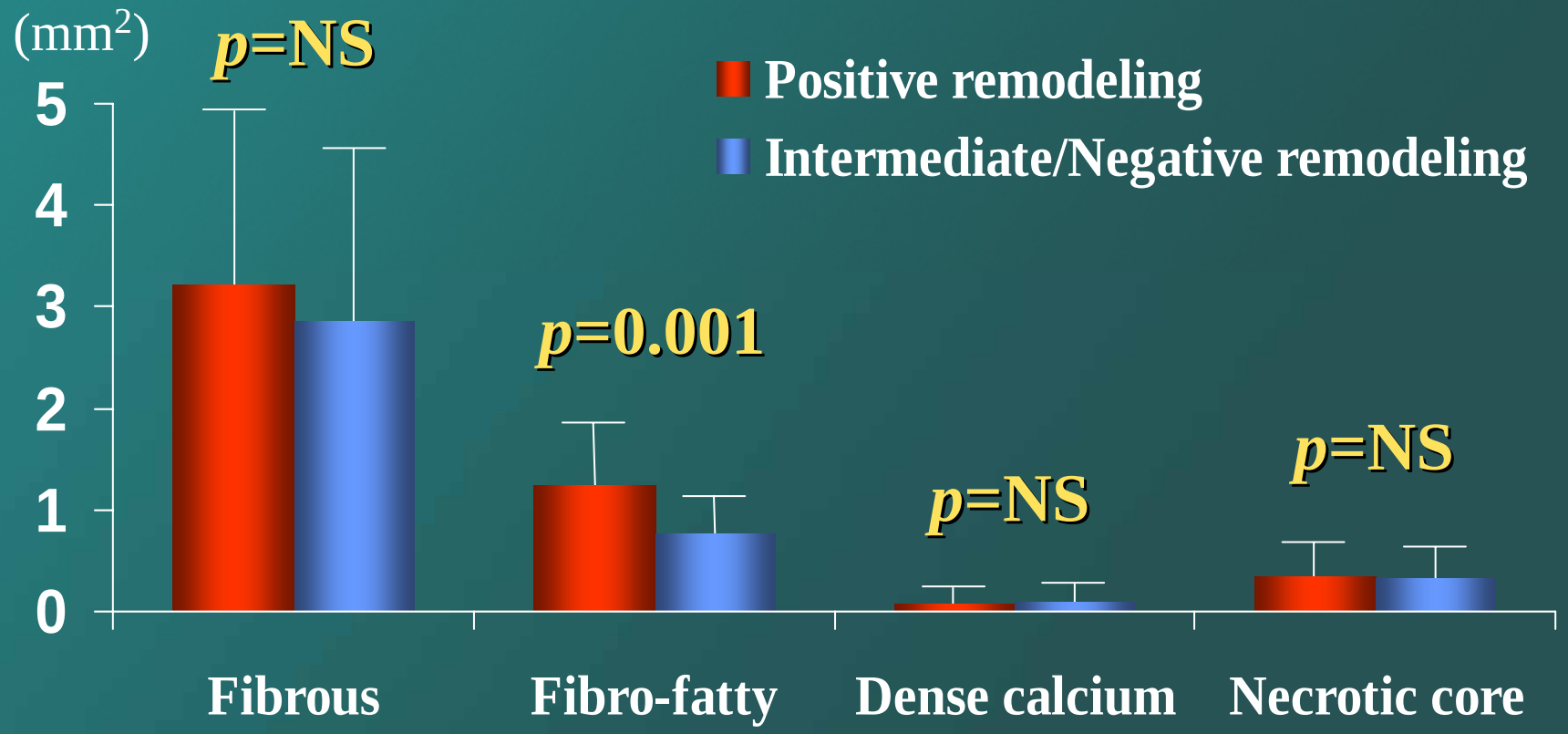






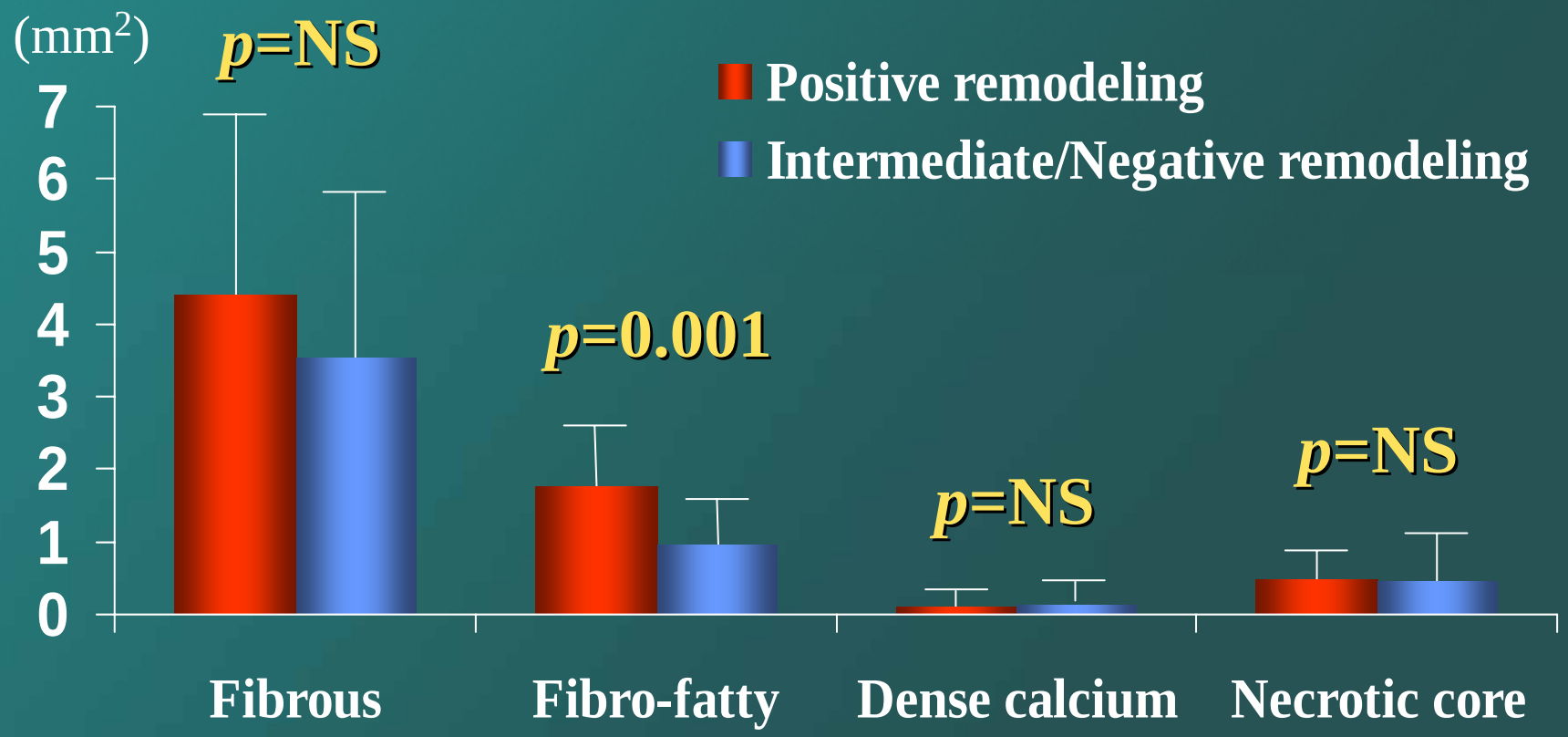
CRF: Plaque composition vs Remodeling (1)

Average of entire lesion segment analysis



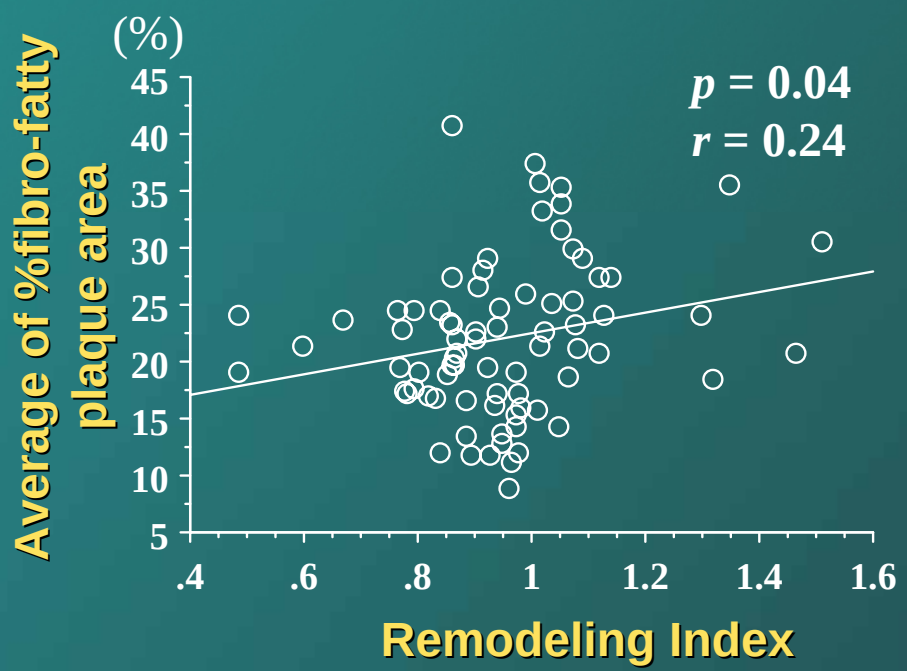
CRF: Plaque composition vs Remodeling (2)

Minimum lumen site analysis

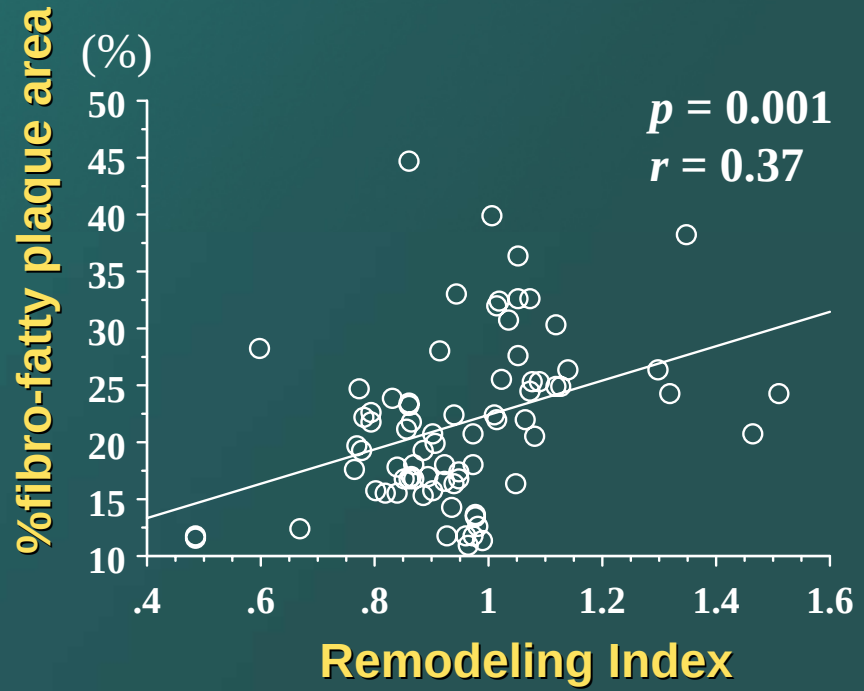


CRF: Plaque composition vs Remodeling (3)

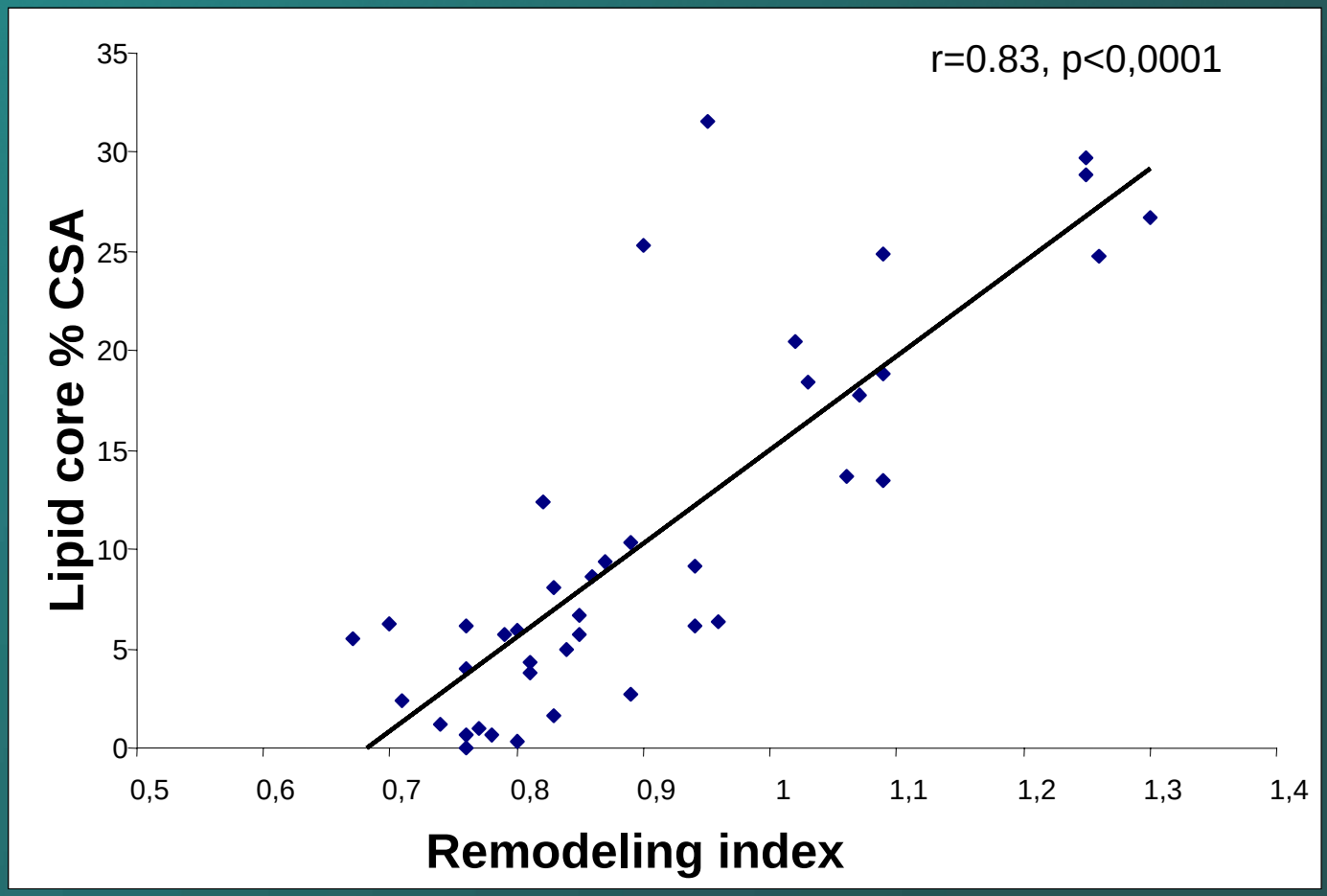
Average of entire lesion segment



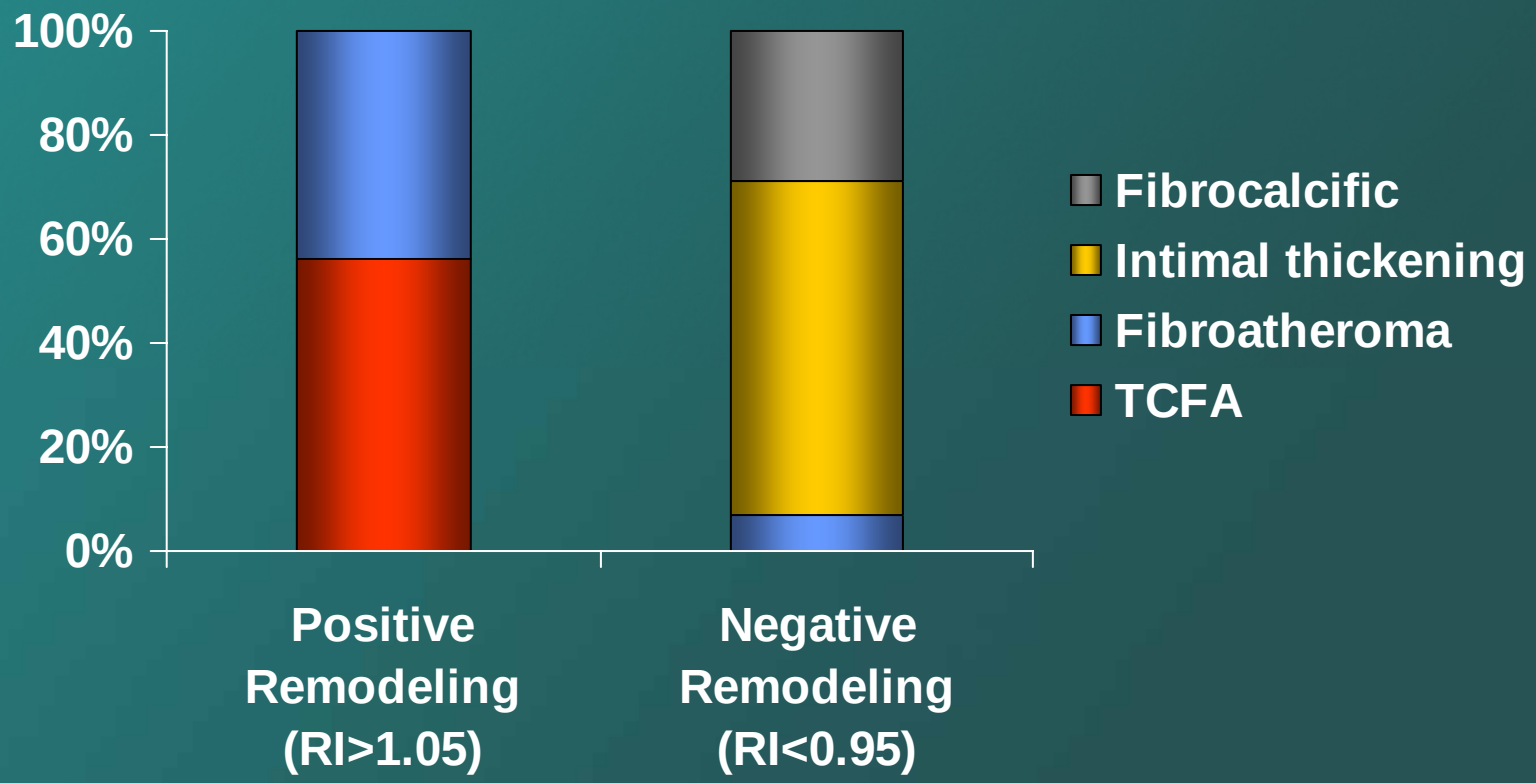
Minimum lumen site



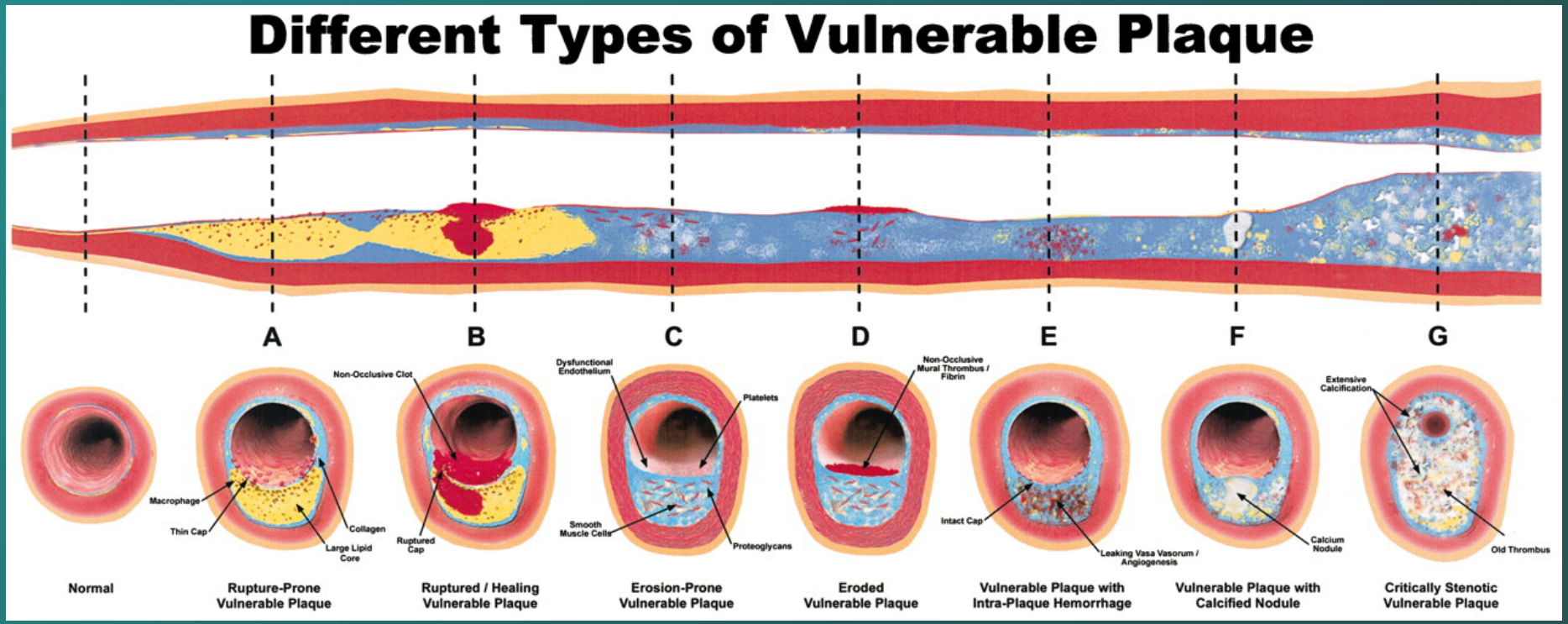
IBIS 1: Positive correlation between lipid core and remodeling



IBIS 1: Lesion types and remodeling



"Vulnerable Plaque" = thrombosis-prone plaque and plaque with a high probability of undergoing rapid progression



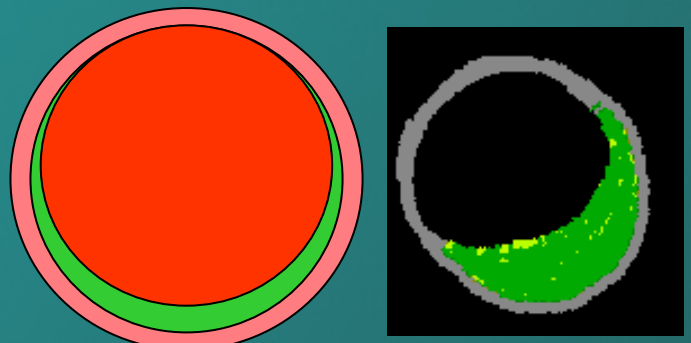
70% of ACS culprit lesions

30% of ACS culprit lesions

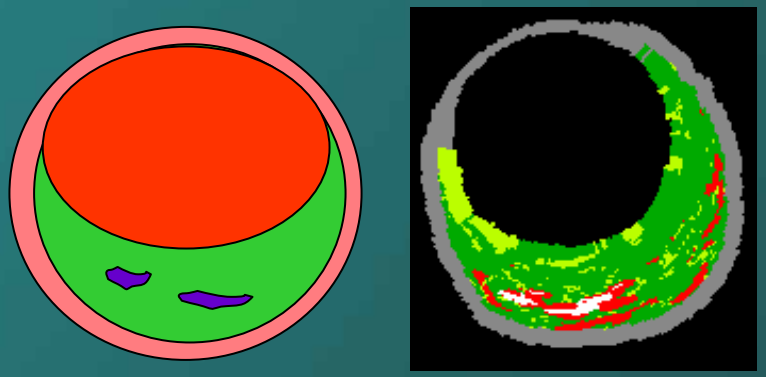
Naghavi et al. Circulation 2003;108:1664-72

Generally Stable Plaque Types*

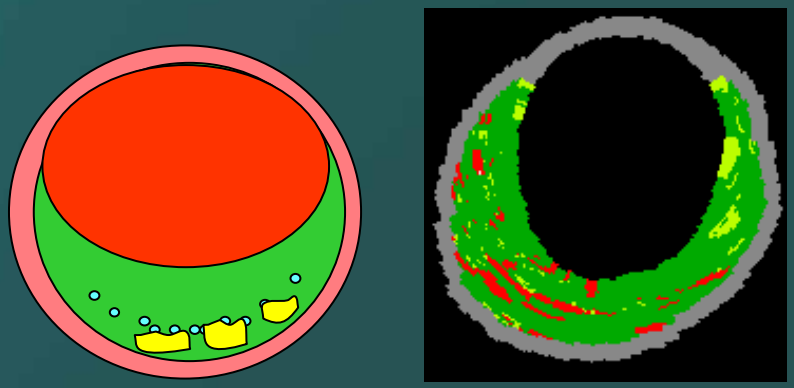
"Fibrous" – Plaque comprised of nearly all fibrous tissue.



"Fibro-Calcific" – Mainly fibrous plaques, with some Dense Calcium. Presence of Necrotic Core between 3-10% of plaque volume.



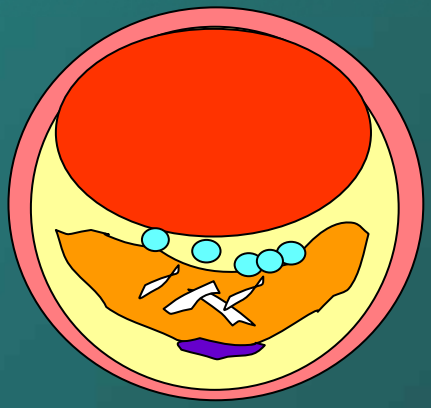
"Pathological Intimal Thickening" – Plaque comprising mainly Fibro-Fatty and Fibrous tissue, with Necrotic Core comprising from 0-3% (to account for specks of Necrotic Core which occasionally appear on VH, due largely to micro-calcifications within the Fibro-Fatty tissue). Indicative of disease and possible future progression to risky atheroma.

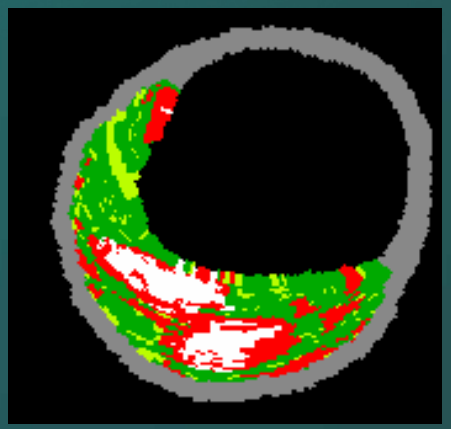


*Courtesy of Renu Virmani

The FibroAtheroma

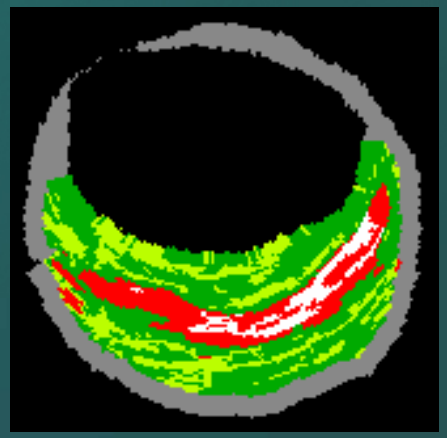
Fibrous and/or Fibro-Fatty plaques with significant Necrotic Core (>10% of total plaque volume). Goal of using VH to increase the value of IVUS will very likely be in differentiating the Fibro-Atheroma from the other three plaque types.



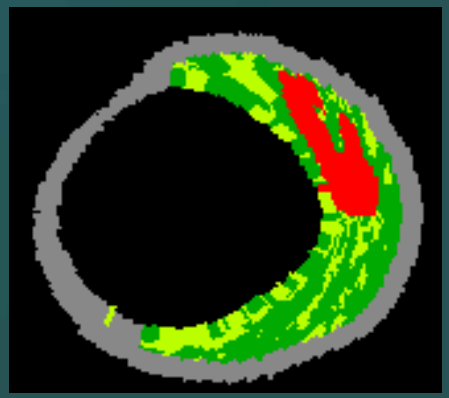


For the purpose of risk assessment the FibroAtheroma can be subdivided into 3 types

“Fibro-Atheroma with Dense Calcium” – (*Note that here Necrotic Core is not displayed as “on” or near the lumen on VH.)*

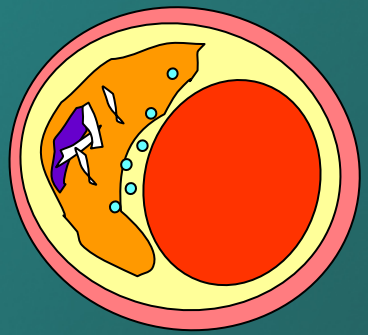


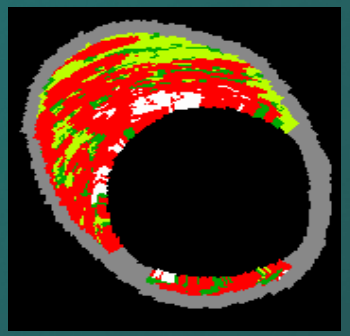
“Fibro-Atheroma without Dense Calcium” – (*Note that here Necrotic Core is also not displayed as “on” or near the lumen on VH.)*



Thin-Cap FibroAtheroma (TICFA)

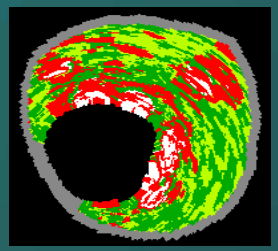
"Thin Cap Fibro-Atheroma (TICFA)" or **"Vulnerable Plaque"** -- Necrotic Core is significant (>10% of total plaque volume) ***and located at or near the lumen***.

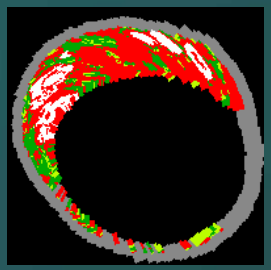




Further sub-classification based on presence of luminal narrowing may yield further prognostic value in assessing TICFA risk.

"TICFA with significant narrowing" (significant narrowing defined as ≥50% reduction in Cross Sectional Area on IVUS or DS≥25% on angiogram) - Dr. Virmani's data suggests that TICFA with significant narrowing represents the highest risk of all plaques.



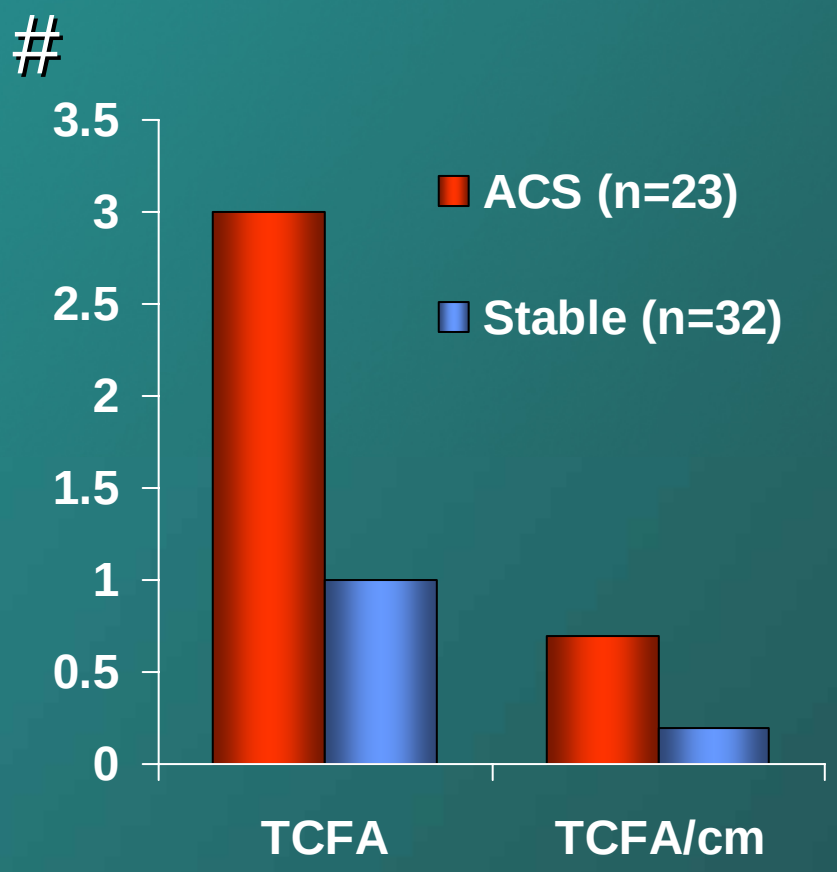


"TICFA without significant narrowing" (<50% area reduction on IVUS or <25% DS on angiogram - Dr. Virmani's data suggests that TICFA without significant narrowing is at a considerably lower risk.

In Vivo Resolution Limits of VH

- Longitudinal resolution
  - 240 μm = ability to accurately discriminate different tissues types along the axis of the vessel wall
- Axial resolution
  - 100-150 μm = ability to identify different structures from lumen towards adventitia
  - If the thickness of fibrotic cap is <100 μm, no fibrotic cap will be displayed
  - Therefore, a thin fibrotic cap (<65 μm) is inferred if the necrotic core lies at the intimal surface

IBIS 1: 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

- Clinical VH-IVUS is in its infancy.
- Agreement must be reached as to how VH-IVUS is analyzed.
- Additional clinical and core laboratory studies are needed and must be correlated with acute presentation and acute and late patient outcomes

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)

Meds Rx
Aspirin
Plavix 1yr
Statin

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

Repeat imaging in pts with events