

# **VH (Virtual Histology): A Technical and Clinical Update**

***Gary S. Mintz, MD***

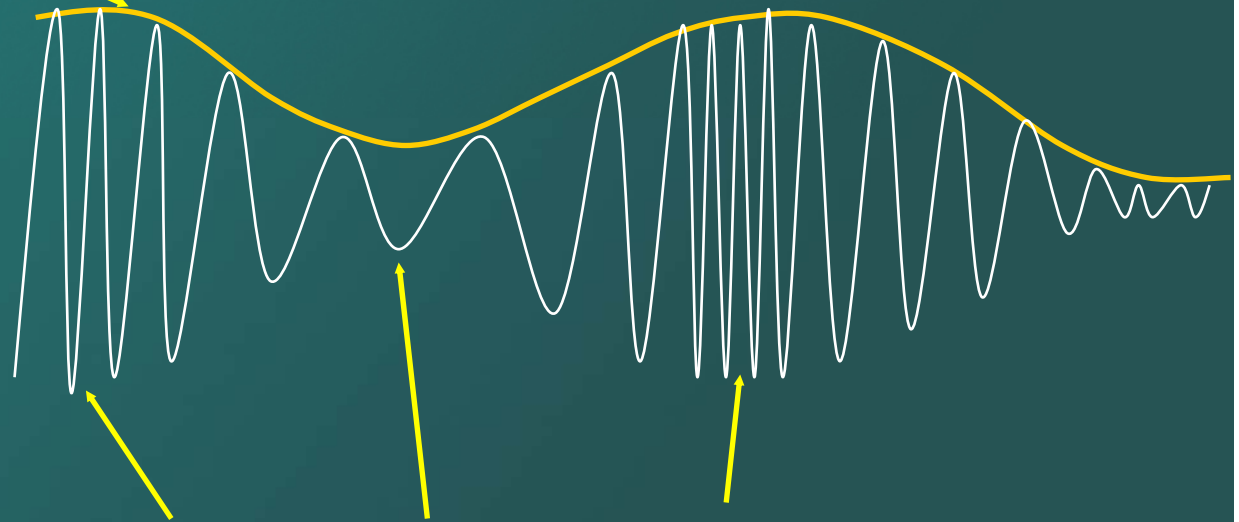
***Cardiovascular Research Foundation***



# Virtual Histology™ IVUS

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

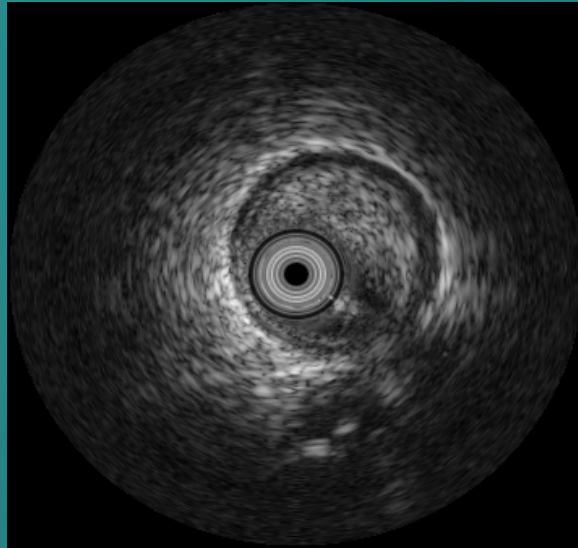
Amplitude AND  
Frequency are  
used to generate  
8 parameters to  
create the look-  
up table



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



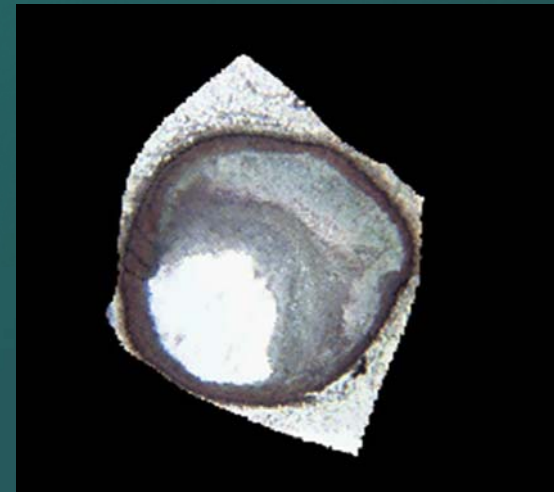
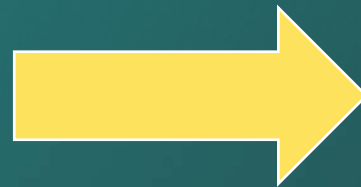
IVUS B scan



Movat pentachrome stain



# Thin Plate Spline Morphing



# Selection of regions of interest

The screenshot shows a software application window titled "Untitled - roi\_sp". The interface includes a menu bar (File, Edit, View, Help) and a toolbar with icons for file operations. The main workspace is divided into three panels:

- ROI Display Options:** Contains buttons for "Clear ROI" and "Display ROI". Below these are "4 ROI points:" with a table of X and Y coordinates:

X	Y
221	134
206	119
219	103
243	123
- DSP Options:** Includes radio buttons for "Classical PSD" and "Welch PSD", a "MEM-PSD" section with an "AR Model:" field, and an "OK" button.
- Histology:** Features a "Load Image" button and a text field for the "Registered Histology Image:" path: "C:\thu\_IM\2004\30b3TPS.bmp". It displays a histology image with a cyan ROI polygon overlaid.
- IVUS:** Features a "Load Image" button and a text field for the "IVUS Image:" path: "C:\thu\_IM\2004\30b3i.bmp". It displays an IVUS image with a cyan ROI polygon overlaid.

A modal dialog box titled "ROI Specifications" is overlaid on the main window. It contains two sections for defining the ROI boundaries:

- First Scan Line in ROI:**

Line #:	83
First Sample #:	360
Last Sample #:	568
- Last Scan Line in ROI:**

Line #:	99
First Sample #:	344
Last Sample #:	528

The dialog also includes an "OK" button at the bottom.

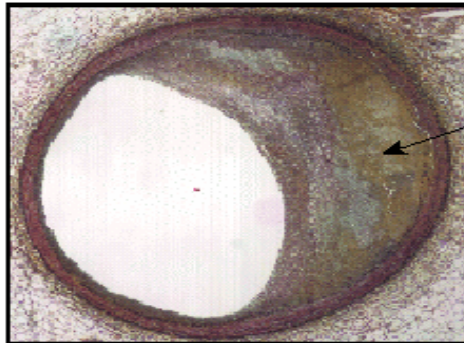
# Plaque Composition

- **Dense Calcium** – Focal areas of dense calcium – Shown in WHITE on VH
- **Necrotic Core** - Localized area of loss of matrix, presence of lipid (typically with micro-calcifications) Shown in RED on VH
- **Fibrous** – Densely packed collagen fibers with no evidence of intra-fiber lipid accumulation – Shown in DARK GREEN on VH
- **Fibro-Fatty** – Loosely packed collagen fibers with regions of fatty deposits present – Shown in YELLOW on VH



## Fibrotic

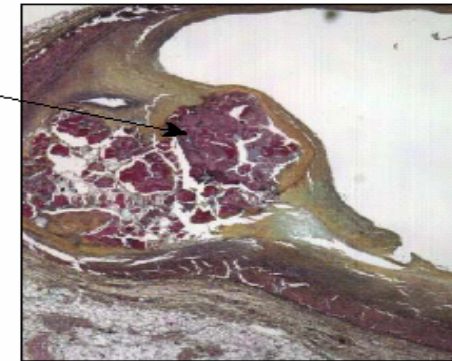
Densely packed bundles of collagen fibers with no evidence of intra-fiber lipid accumulation. No evidence of macrophage infiltration. Appears dark yellow on Movat stained section.



Fibrous tissue

## Necrotic core

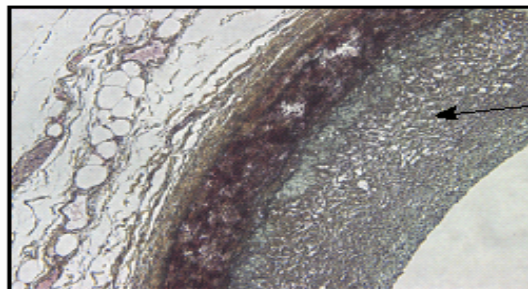
Highly lipidic necrotic region with remnants of foam cells and dead lymphocytes present. No collagen fibers are visible and mechanical integrity is poor. Cholesterol clefts and micro calcifications are visible.



Lipid Core

## Fibro-Fatty

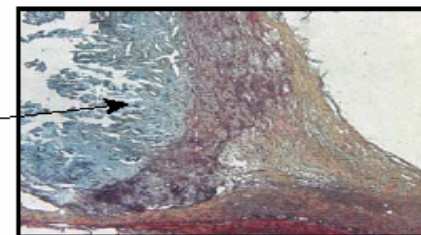
Loosely packed bundles of collagen fibers with regions of lipid deposition present. These areas are cellular and no cholesterol clefts or necrosis are present. Some macrophage infiltration. Increase in extracellular matrix. Appears turquoise on Movat stained section.



Fibro-lipidic region

## Calcium

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



Calcium

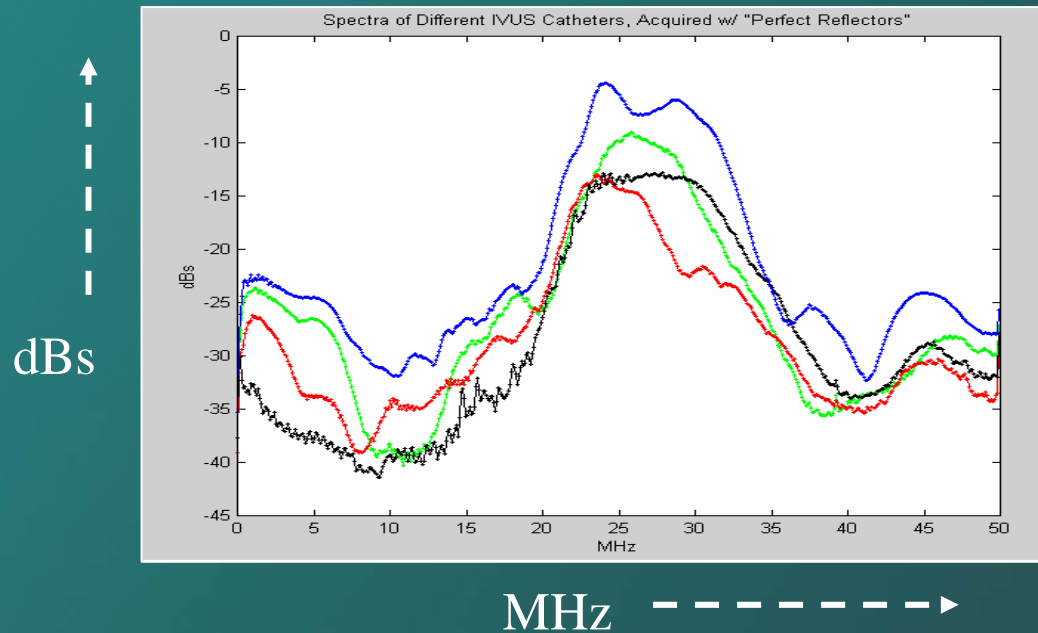


# Predictive Accuracies of Training and Test Datasets

	Fibrous (n=101)		Fibro-Fatty (n=56)		Calcified (n=50)		Necrotic Core (n=70)	
	Training	Test	Training	Test	Training	Test	Training	Test
<b>FFT<sup>2</sup></b>	<b>90.4</b>	<b>69.6</b>	<b>92.3</b>	<b>81.2</b>	<b>92.8</b>	<b>82.6</b>	<b>90.9</b>	<b>71.0</b>
<b>Welch</b>	<b>88.9</b>	<b>66.7</b>	<b>92.3</b>	<b>76.8</b>	<b>91.8</b>	<b>86.5</b>	<b>82.6</b>	<b>72.5</b>
<b>AR</b>	<b>90.4</b>	<b>79.7</b>	<b>92.8</b>	<b>81.2</b>	<b>90.9</b>	<b>89.5</b>	<b>92.8</b>	<b>85.5</b>

*Nair et al. Circulation 2002;106;2200-6*

However, there is significant (6 dB or  $33 \pm 6\%$ ) catheter-to-catheter variability in 30 MHz Boston Scientific Catheters and the signal changes over time (even during the same imaging run)



And post-imaging manual calibration was time consuming, introduced significant variability in the VH results, and had to be performed after every imaging run. This led to the 6 month development of Blinded Deconvolution (BD) - or automatic and continuous calibration during in vivo imaging.



# Back to the beginning and back to the future

- Validation
- Reproducibility: in vitro and in vivo
- Clinical verification
- Clinical correlation
  - Retrospective VH registries
  - Prospective studies
    - Natural History
    - Progression/ Regression

# Validation of Blinded Deconvolution in 30MHz Catheters

61LADs, 104 sections

Tissue Type	Predictive Accuracies	
	Training Set – 75%	Test Set – 25%
<b>Fibrous Tissue</b> ( <i>n</i> = 115)	<b>90</b>	<b>80 (80)</b>
<b>Fibrofatty</b> ( <i>n</i> = 63)	<b>93</b>	<b>81 (81)</b>
<b>Necrotic Core</b> ( <i>n</i> = 88)	<b>89</b>	<b>85 (86)</b>
<b>Dense Calcium</b> ( <i>n</i> = 56)	<b>91</b>	<b>93 (93)</b>

In parenthesis are the previously reported the accuracies with manual calibration in a highly controlled setting. Data highlights the reproducibility of the accuracy with different techniques



# EAGLE EYE CLASSIFICATION TREE

## Accuracy Data

Slice by Slice VH & Histology Comparison

- 30 LADs, 68 Artery Sites, 228 Total ROIs
- Overall accuracy for ROIs - 84.5%

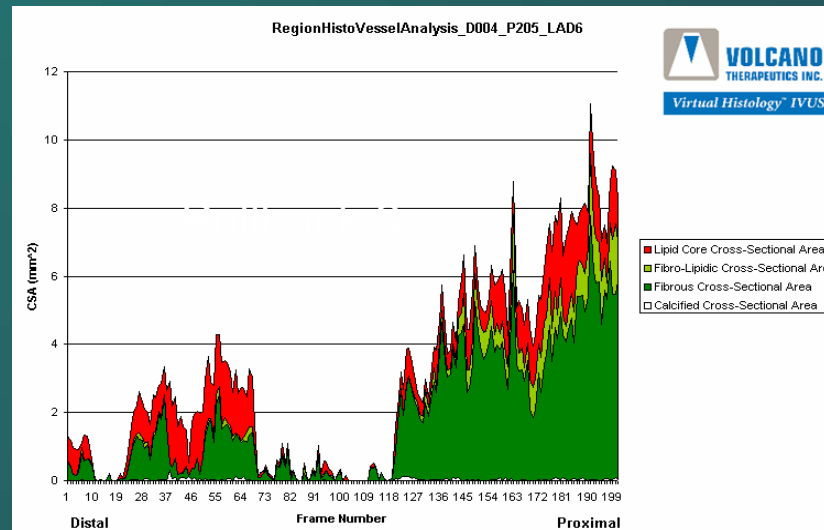
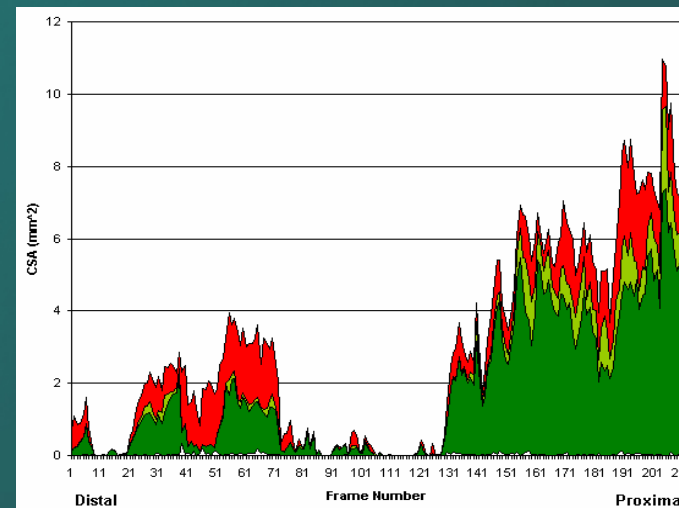
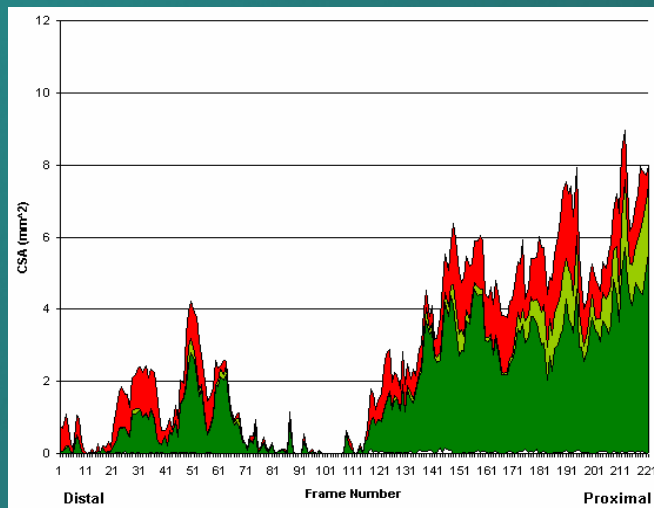
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	Sensitivity (%)	Specificity (%)	Predictive Accuracy (%)
Fibrous Tissue ( <i>n</i> = 97)	84.5	97.7	92.1
Fibro Fatty ( <i>n</i> = 58)	77.6	93.5	89.5
Necrotic Core ( <i>n</i> = 36)	83.3	92.2	90.8
Dense Calcium ( <i>n</i> = 37)	97.3	96.9	96.9

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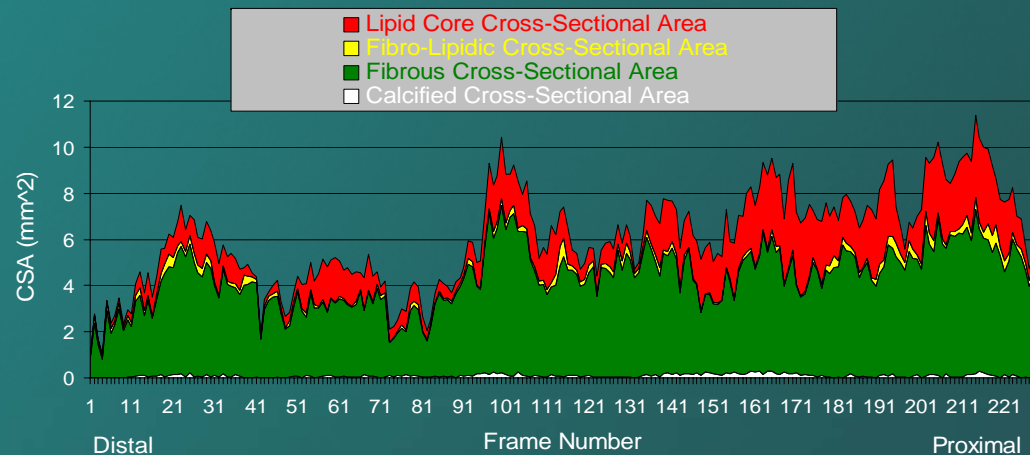


# Three pullbacks done with the same 30MHz catheter

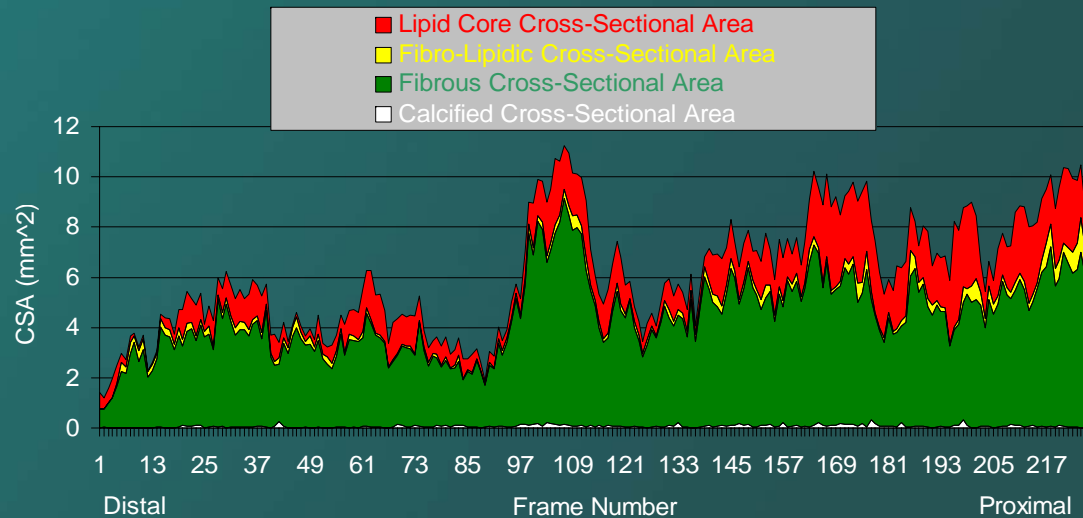


# Two pullbacks done with different 30MHz catheters

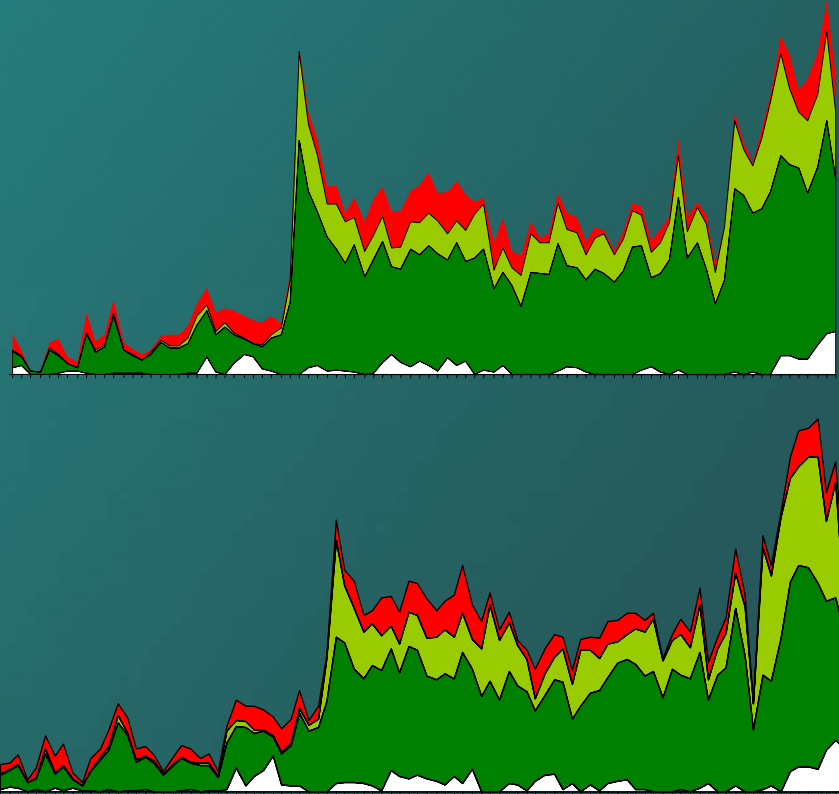
Miami\_CF\_RCA2\_D067\_P295



Miami\_CR\_RCA3\_D063\_P290



# Two pullbacks done with different 20MHz catheters

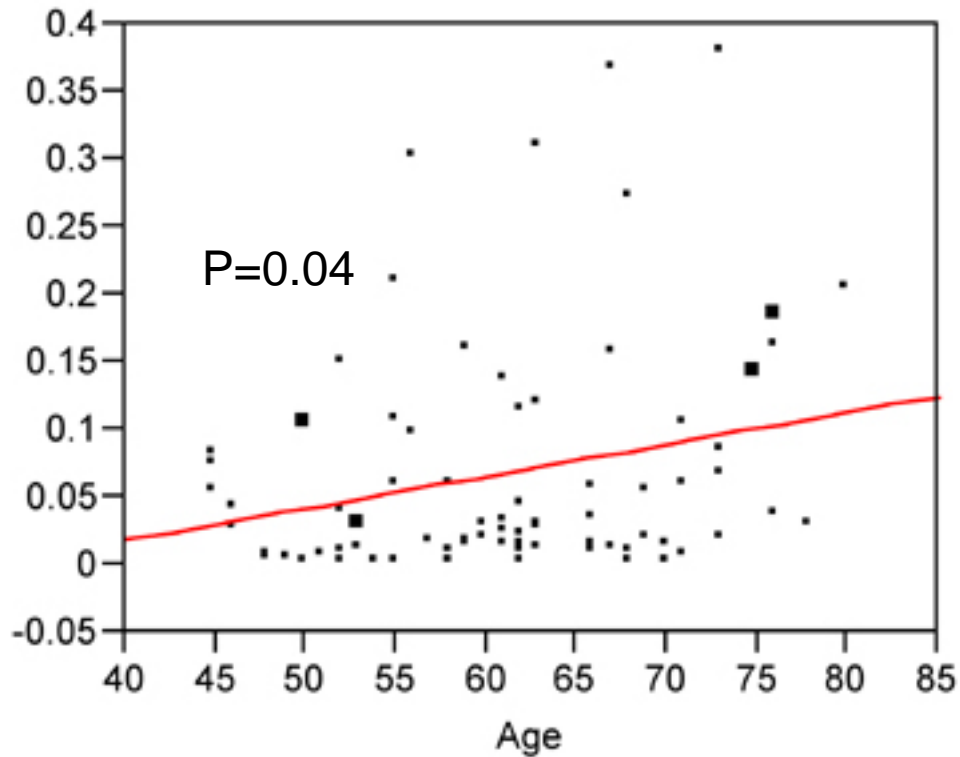


# Additional technical development that is needed

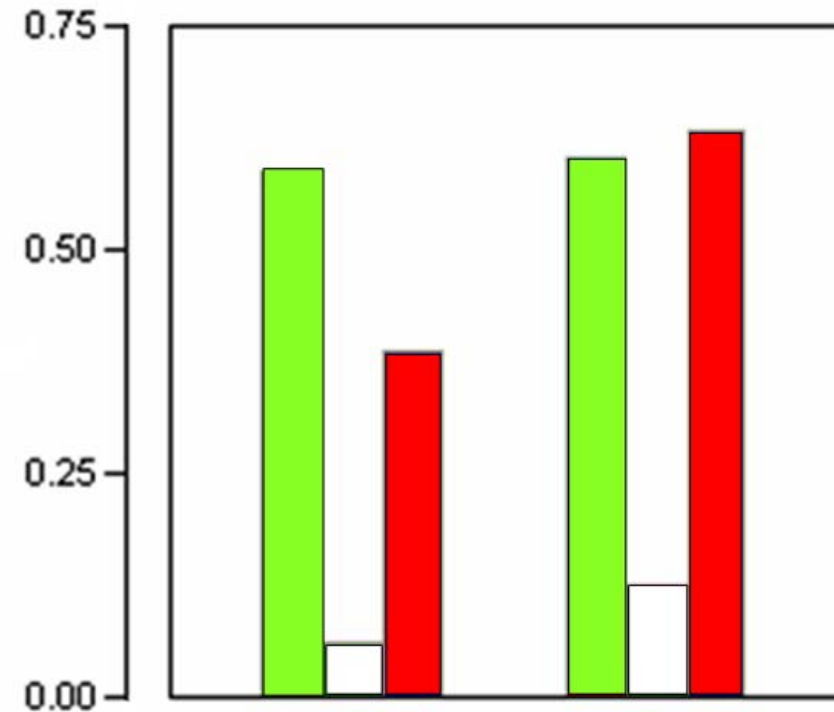
- **Classification for**
  - **Blood**
  - **Thrombus**
  - **Stent metal**
- **Approach to “plaque behind calcium”**
- **Classification tree for other catheters**
  - **40MHz BostonScientific catheter**
- **Reproducibility**
  - **IVUS plaque composition with different catheters of different types**

# Clinical correlates of plaque composition




Dense calcium correlated with patient age



Significantly more Dense Calcium ( $P=0.04$ ) and Necrotic Core ( $P=0.05$ ) in Diabetic patients



Courtesy of R. Erbel

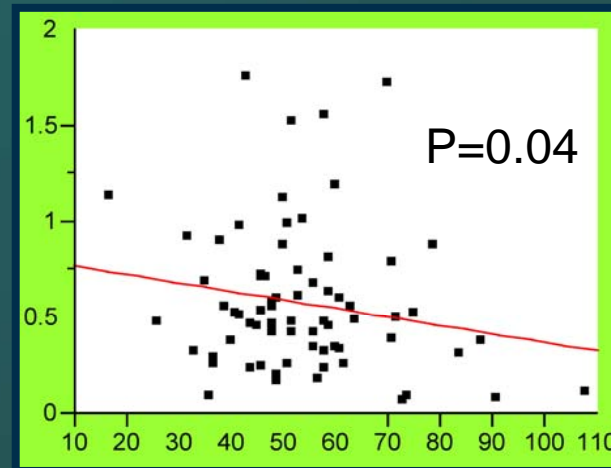
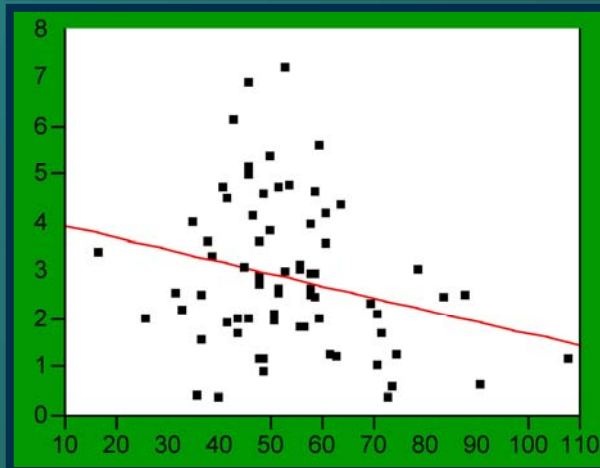
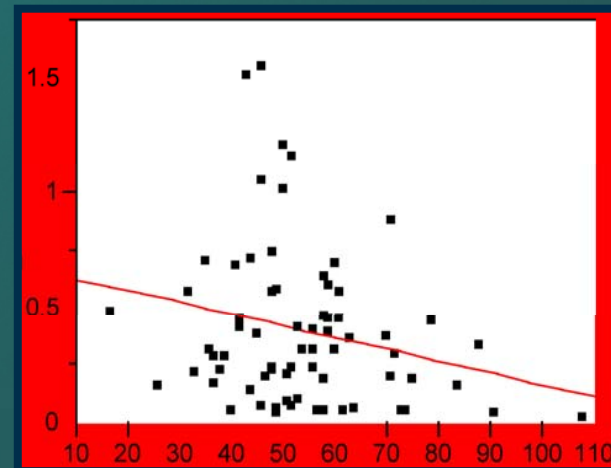
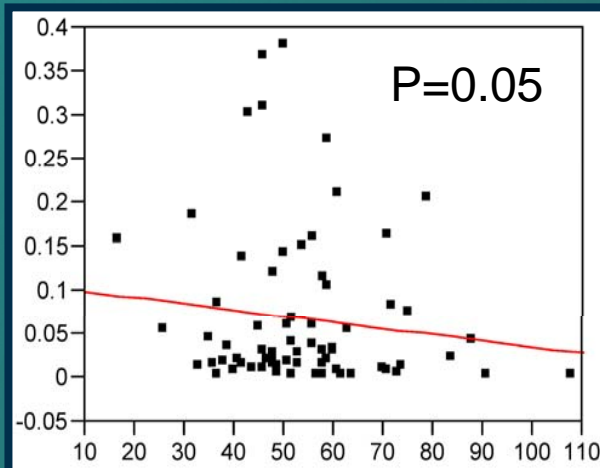
 Fibrofatty  
 Dense Calcium  
 Necrotic Core

No diabetes

Diabetes



# Relationship between HDL and plaque composition

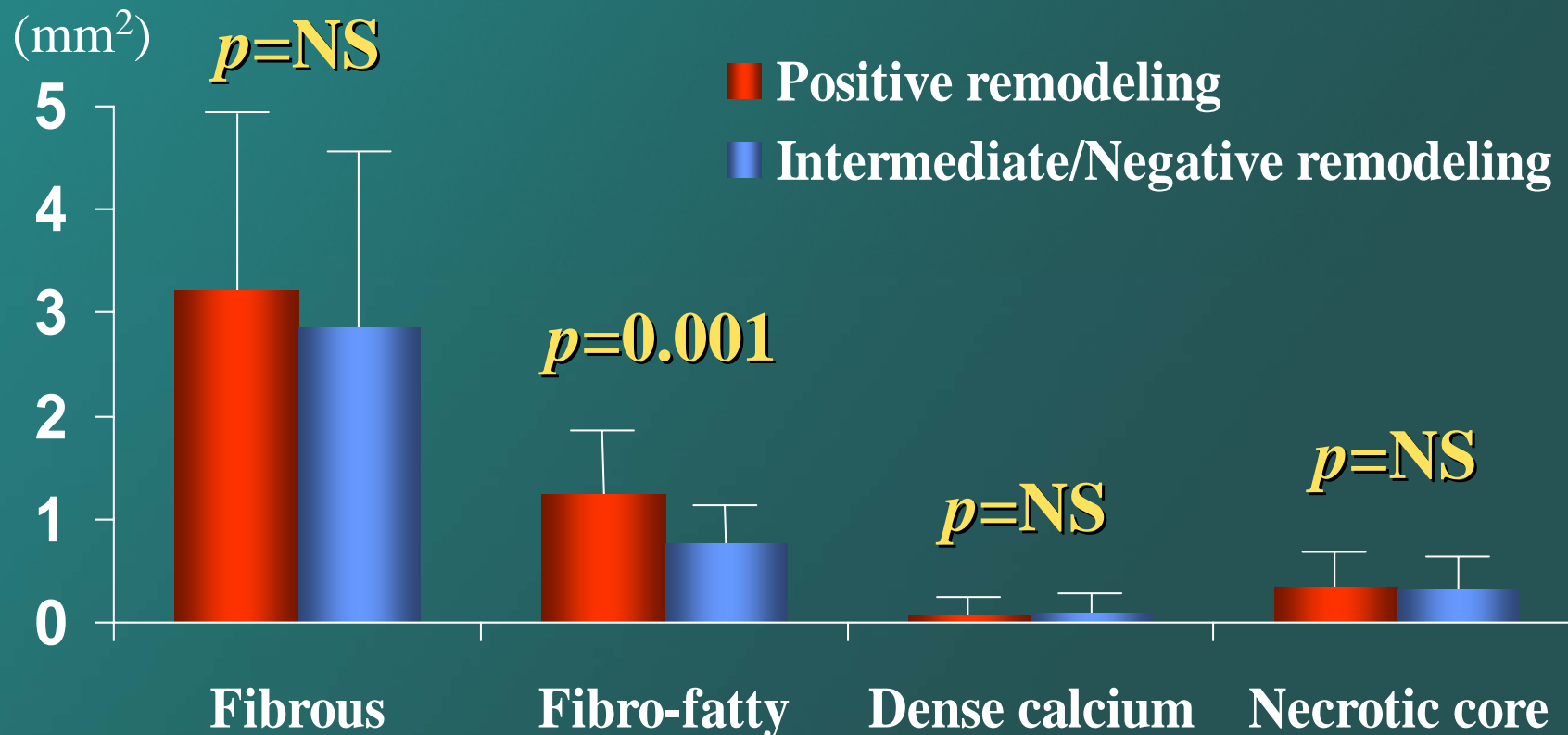


Courtesy of R. Erbel



# CRF: Plaque composition vs Remodeling

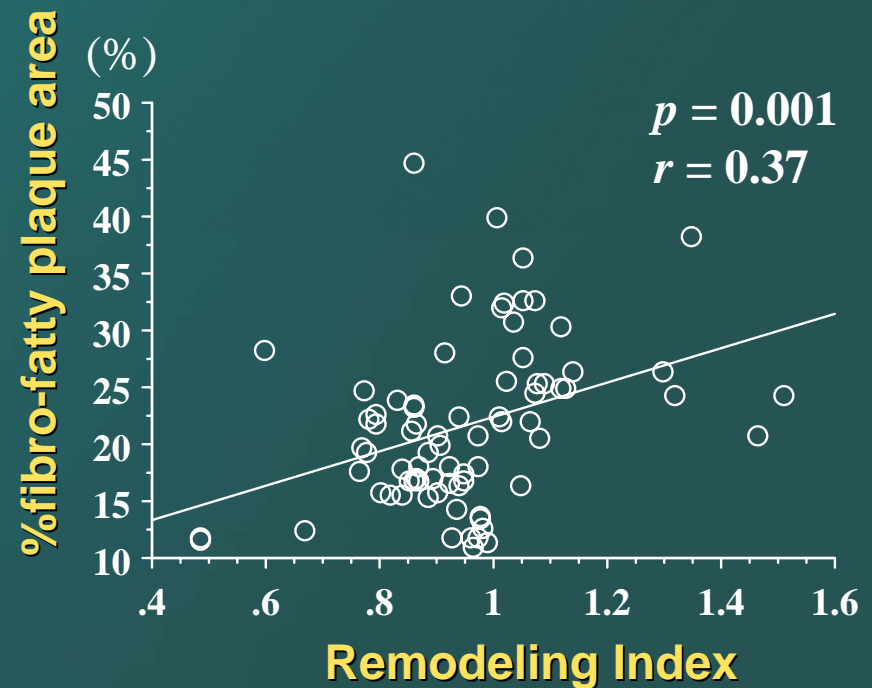
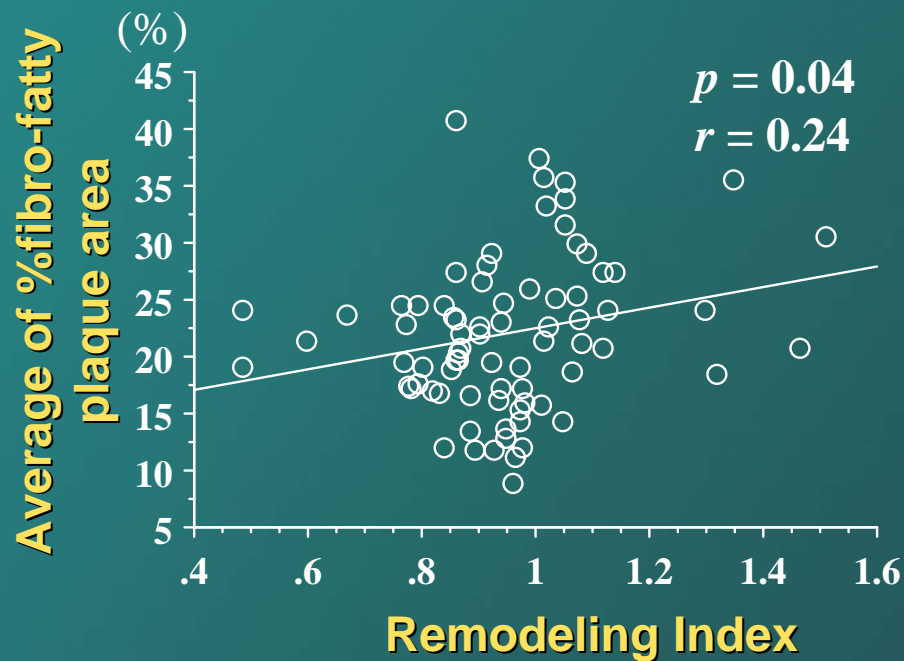
Average of entire lesion segment analysis



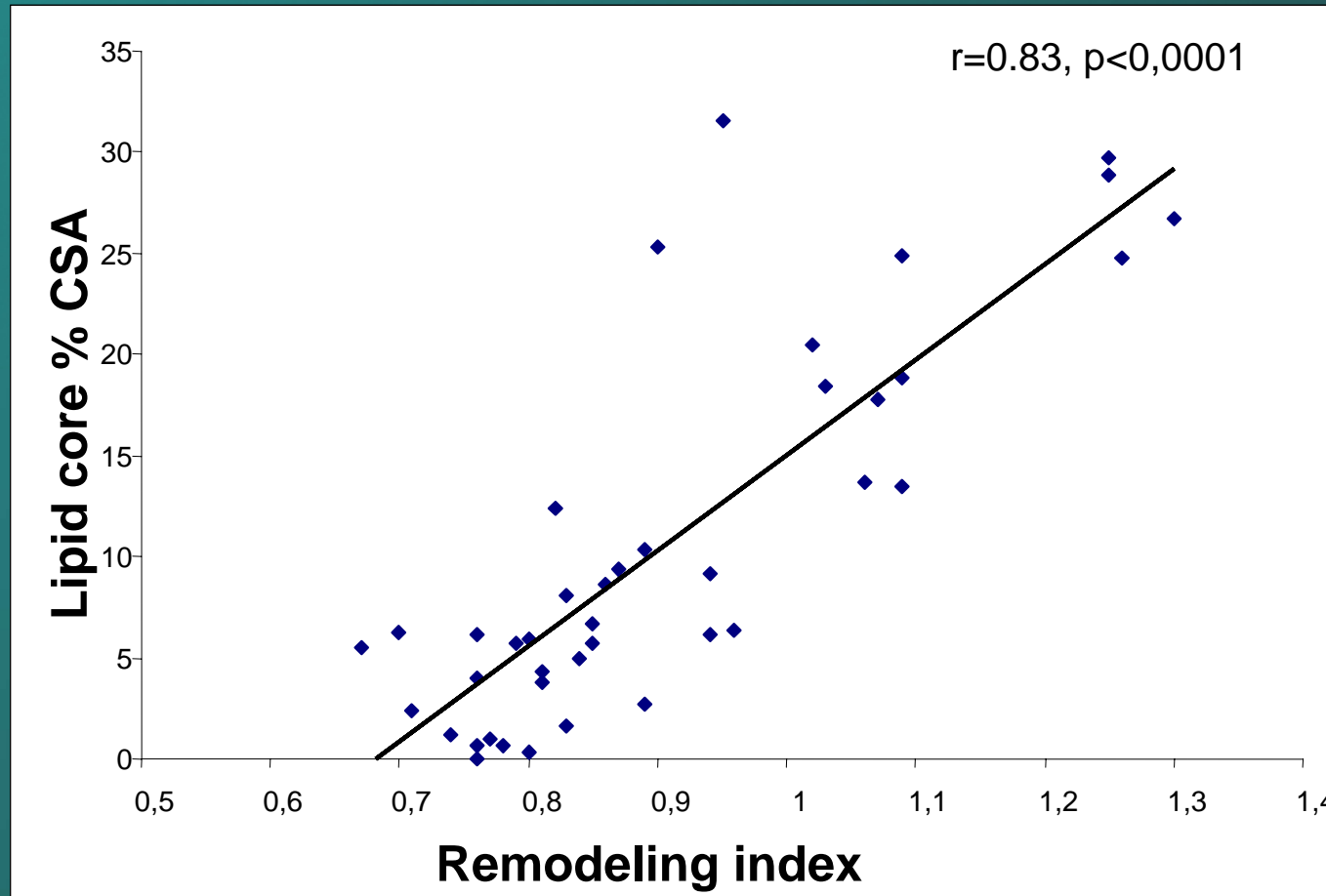
# CRF: Plaque composition vs Remodeling index

Average of entire lesion segment

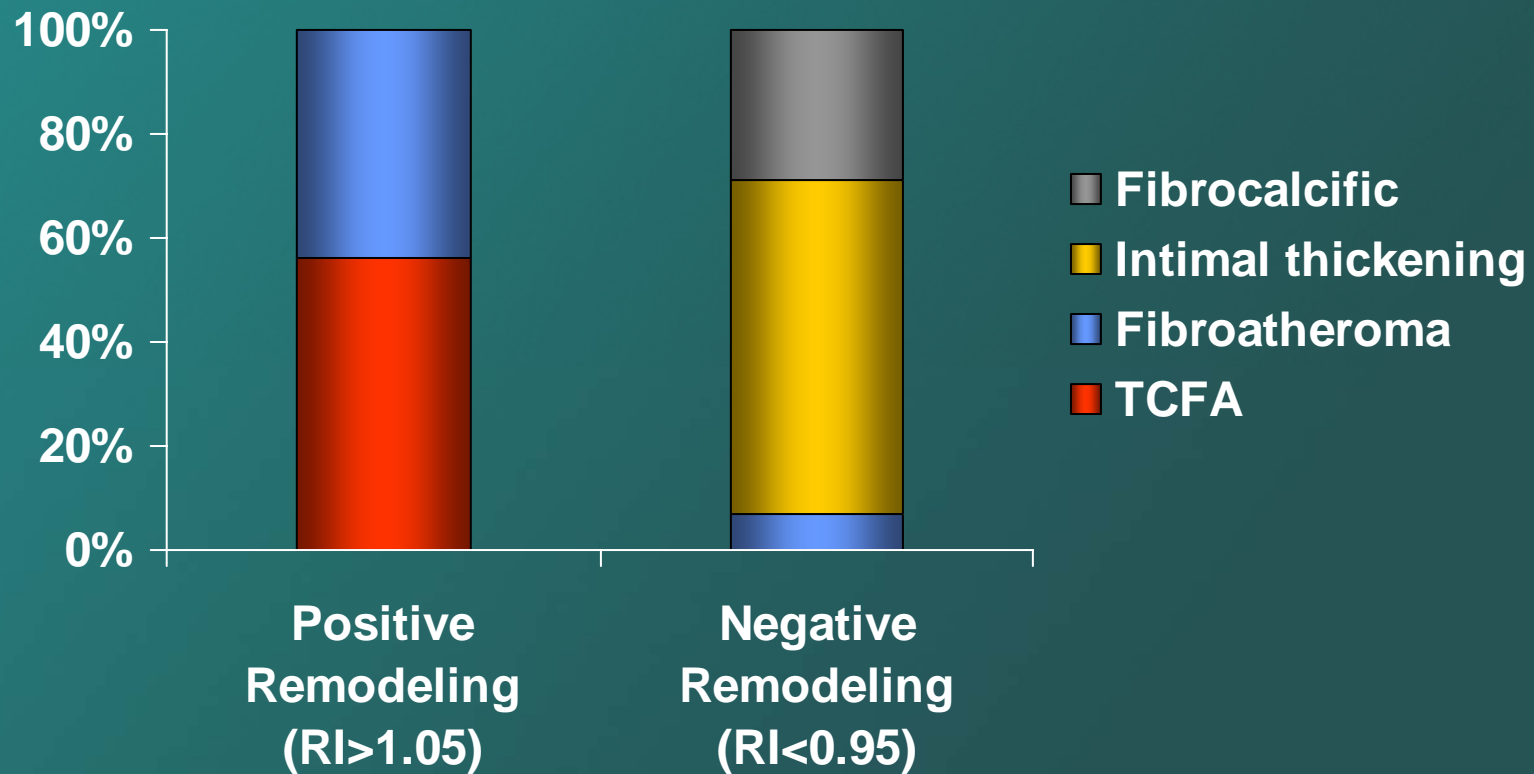
Minimum lumen site



# IBIS 1: Positive correlation between lipid core and remodeling

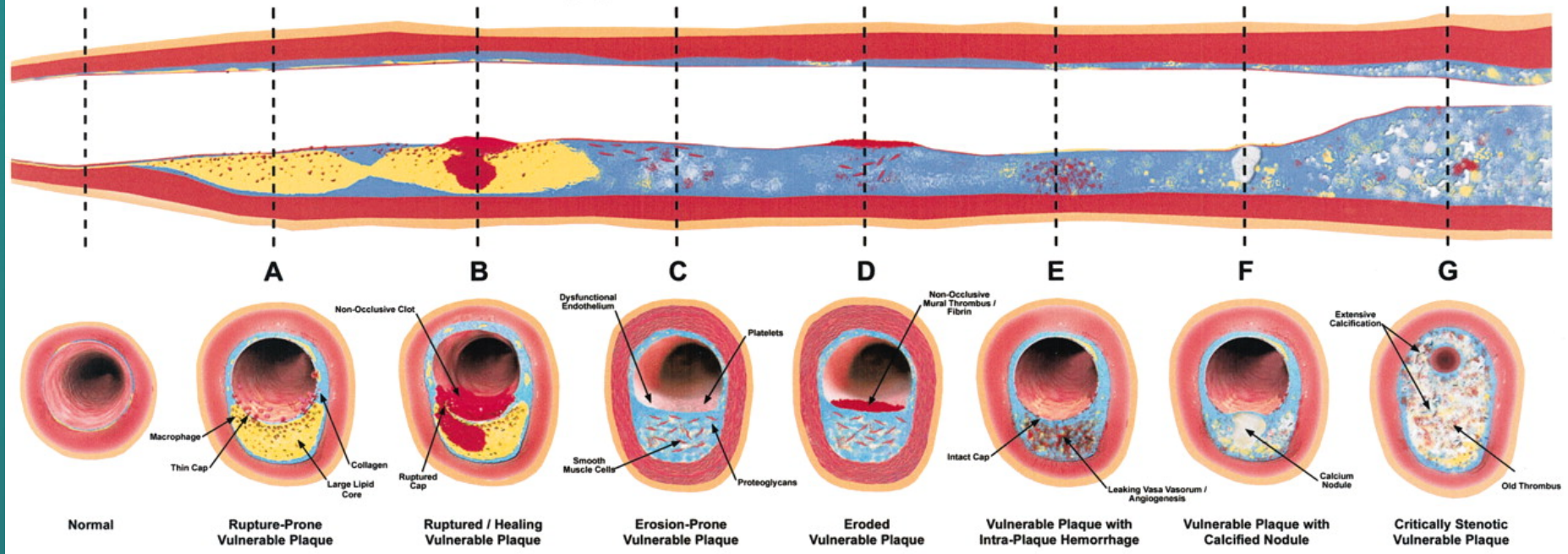


# IBIS 1: Lesion types and remodeling



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

## Different Types of Vulnerable Plaque



70% of ACS culprit lesions

30% of ACS culprit lesions

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

	Angiography	IVUS+VH+palpography
<b>Major criteria</b>		
Active inflammation		+
Thin cap with large lipid core		+
Endothelial denudation		
Fissured plaque		±
Stenosis >90%	+	+
<b>Minor criteria</b>		
Superficial calcified nodule		+
Glistening yellow		
Intraplaque hemorrhage		+
Endothelial dysfunction		
Positive remodeling		+
Three vessel imaging	+	±



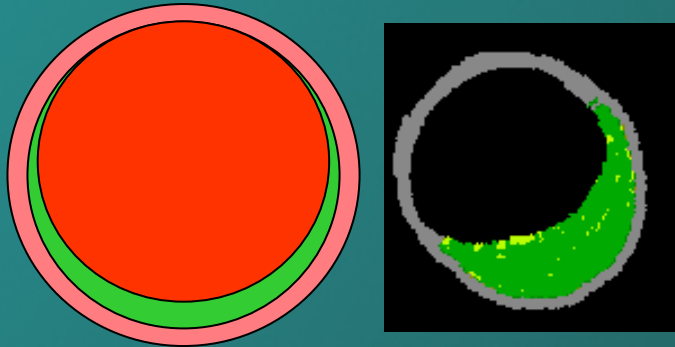
# In Vivo Resolution Limits of VH

- **Longitudinal resolution**
  - **240  $\mu\text{m}$  = ability to accurately discriminate different tissues types along the axis of the vessel wall**
- **Axial resolution**
  - **100-150  $\mu\text{m}$  = ability to identify different structures from lumen towards adventitia**
  - **If the thickness of fibrotic cap is  $<100 \mu\text{m}$ , no fibrotic cap will be displayed**



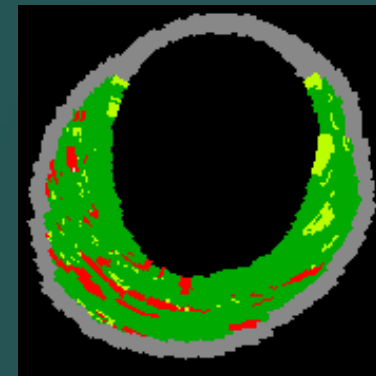
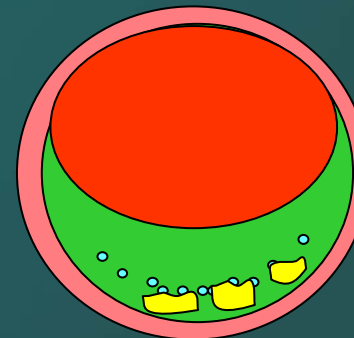
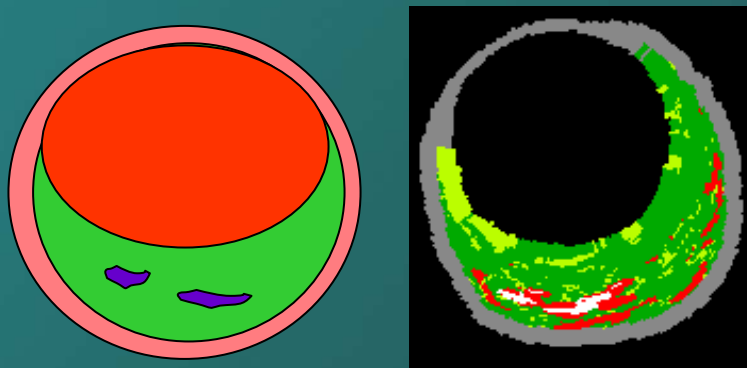
# Generally Stable Plaque Types\*

“Fibrous” – Plaque comprised of nearly all fibrous tissue.



“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.

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

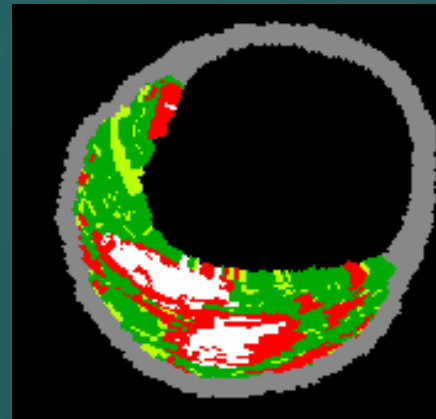


*\*Courtesy of Renu Virmani*



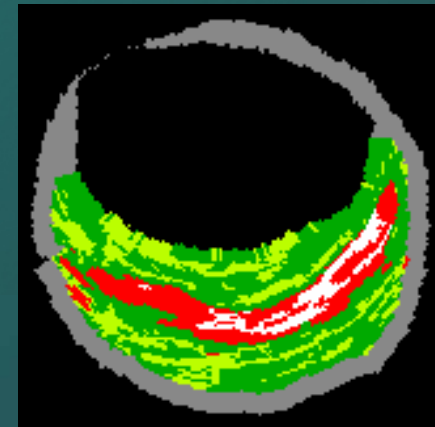
# The FibroAtheroma

*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.*

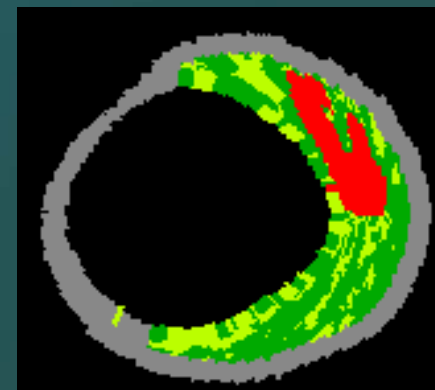


# For the purpose of risk assessment the FibroAtheroma can be subdivided into 3 types

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

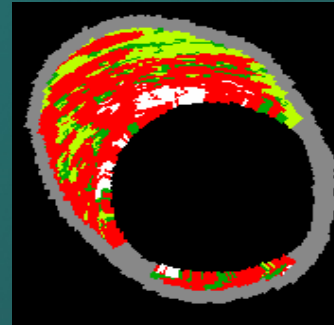
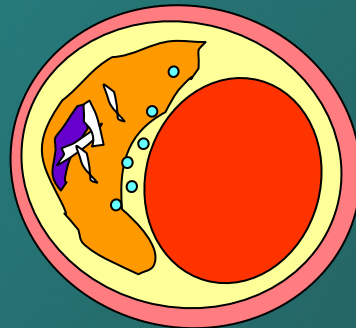


“Fibro-Atheroma without Dense Calcium”  
– (Note that here Necrotic Core is also not  
displayed as “on” or near the lumen on VH.)



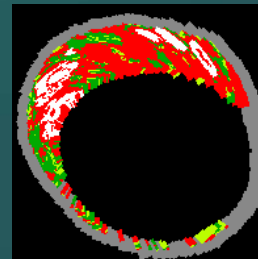
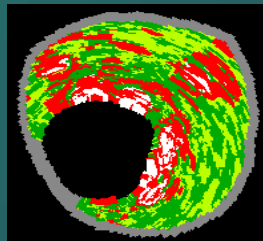
# Thin-Cap FibroAtheroma (TCFA)

“Thin Cap Fibro-Atheroma (TCFA)” or “Vulnerable Plaque” -- **Necrotic Core >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 TCFA risk.*

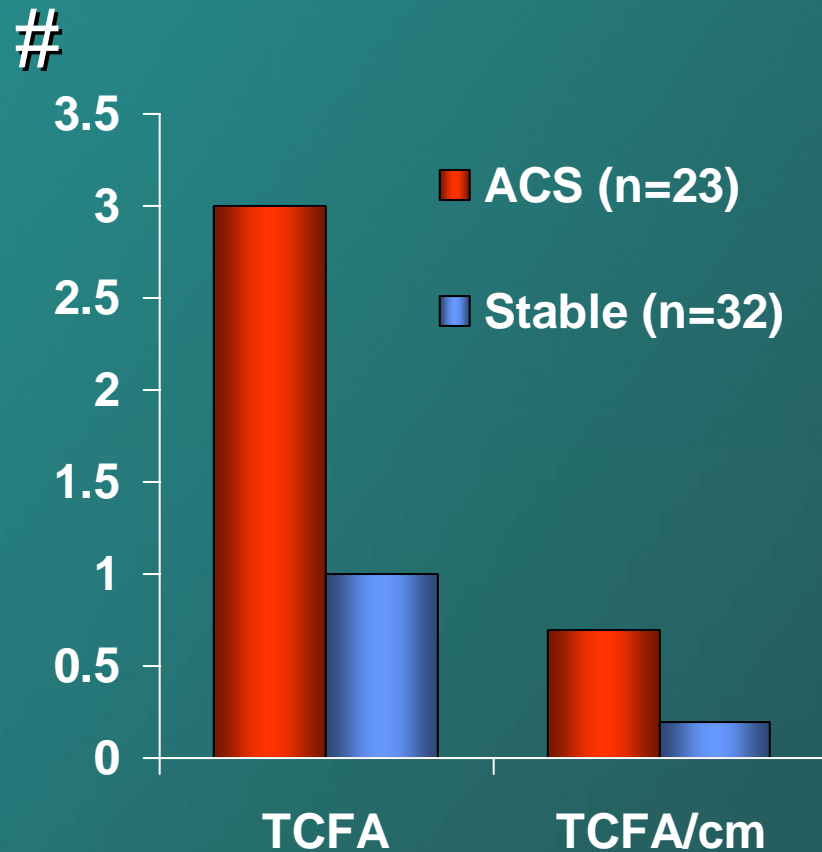
“TCFA with significant narrowing” (significant narrowing defined as  $\geq 50\%$  reduction in Cross Sectional Area on IVUS or  $DS \geq 25\%$  on angiogram) - Dr. Virmani’s data suggests that TICFA with significant narrowing represents the highest risk of all plaques.



“TCFA 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.



# 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
  - 1<sup>st</sup> 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, 3<sup>rd</sup>



**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**

