VH™ IVUS to Assess
Plaque Progression and Regression

M. Pauliina Margolis, MD PhD & James R. Margolis, MD
Volcano Therapeutics and Miami International Cardiology
Miami, Florida USA
2005

• The incidence of death and MI due to coronary artery disease has declined by an average of 20-30% due to:
  – Life style changes
  – Systemic medication
  – ? PCI and CABG

• Why is Coronary Artery Disease still the #1 killer worldwide?
The “Vulnerable” Coronary Plaque
Thin cap fibroatheroma with necrotic core

Necrotic core
Fibrous Cap
Lumen
Virtual Histology

- IVUS-based tissue characterization merged with novel border detection and analysis software.

- 13 year development effort: Collaboration between The Cleveland Clinic Foundation and Volcano Therapeutics.
Virtual Histology™ IVUS

Gray-scale IVUS uses only the envelope amplitude (echo intensity) in formation of the image.

Virtual Histology uses both echo Amplitude **AND** Frequency.

Frequency of echo signal can also vary, depending on the tissue...
Virtual Histology™ IVUS

Different frequencies correspond to different types of tissue.

- Dense Calcium
- Fibrous
- Fibro-fatty
- Necrotic Core
“Fibrous” – Plaque comprised of nearly all fibrous tissue. Generally not viewed by Dr. Virmani to be acutely dangerous.

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

“Pathological Intimal Thickening” – Mainly mixture of fibrous, fibrofatty, and some necrotic core (<5%) and calcified tissue.
Development of Human Thin Cap Fibroatheroma

- Intimal thickening
- Intimal xanthoma
- Pathologic intimal thickening
- Fibrous cap atheroma
- Thin-cap Fibroatheroma

Fig. 3-2

- Smooth muscle cells
- Macrophage foam cells
- Extracellular lipid
- Cholesterol clefts
- Necrotic core
- Calcified plaque
- Hemorrhage
- Thrombus
- Healed thrombus
- Collagen
“Fibro-Atheroma” – Fibrous and/or Fibro-Fatty plaques with significant Necrotic Core (NC greater than 10% of total plaque volume).

It will very likely be that the most important goal is to differentiate the Fibro-Atheroma plaque type from the other three plaque types during assessments of ambiguous lesions.
For purposes of risk-assessment, Fibro-Atheroma can be further differentiated into 3 sub-groups:

“Fibro-Atheroma with Dense Calcium” – Fibro-Atheroma with Dense Calcium present in plaque (generally viewed as being more dangerous than FA without DC)

“Fibro-Atheroma without Dense Calcium” – Fibro-Atheroma without presence of Dense Calcium.
Fibro Atheroma

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

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

a. “TICFA with significant narrowing” (significant narrowing defined as greater than 50% reduction in Cross Sectional Area (CSA) on IVUS, or stenosis of 25% or greater on angiogram). Dr. Virmani’s data suggest that TICFA with significant narrowing represents the highest risk of all plaques.

b. “TICFA without significant narrowing” (CSA reduction of less than 50% on IVUS, less than 25% narrowing on angiogram). Dr. Virmani’s data suggest that TICFA without significant narrowing purports a considerably lower risk TICFA.
Fibro Atheroma with Fibrous Cap
Multiple Plaque Ruptures and Healed Ruptures
Multiple Plaque Ruptures
One patient, one artery, different lesions
Serial Sections of a Thin-Cap Fibroatheroma

Dr R Virmani
Serial images of plaque composition and character with Volcano IVUS
VH™ IVUS
Plaque Progression and Regression

• Current and future studies are designed to provide information of the role of VH™ IVUS with regards to the four conundrums of plaque progression:
  – Correlation of clinical indices (risk factors, biomarkers, clinical presentation, MSCT and other technologies) with general plaque composition (FT, FF, NC, DC) at index and follow-up
  – Progression and regression of different plaque types (fibrotic, fibro-calcific, pathological intimal thickening, thick cap FA, and TCFA)
  – Role of thrombus in plaque progression in different clinical presentations (grayscale and VH IVUS)
  – Role of Calcium (fine, dense microcalcification, and calcified aggregates) in plaque stabilization
Plaque Progression/Regression
Expert opinions

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can lipo-necrotic tissue turn into fibrosis or fibro-lipidic tissue?</td>
<td>YES</td>
</tr>
<tr>
<td>Can fibrosis turn into fibro-lipidic?</td>
<td>YES/no</td>
</tr>
<tr>
<td>Can microcalcification disappear?</td>
<td>YES</td>
</tr>
<tr>
<td>Can larger calcified plaques disappear?</td>
<td>NO</td>
</tr>
<tr>
<td>How much can different plaque types regress?</td>
<td>Can regress lipid, but not fibrosis or large Ca lesions</td>
</tr>
<tr>
<td>What is effect of risk factors, medication?</td>
<td>Reduction of plasma lipids leads to lipid mobilization (extracellular versus intracellular lipid), intimal thickening remains</td>
</tr>
</tbody>
</table>

If we have the potential to do so much, why is CAD still number one killer in the world and why has systemic medication failed?
Of the following components of the Atherosclerotic plaque which ones can VH IVUS differentiate?

**HISTOLOGY**

- Proteoglycans
- Fibrous tissue
- Lipid pool/droplets
- Necrotic core
- Calcium
- Thin fibrous cap
- Hemorrhage
- Thrombus
- Macrophages/inflammation

**VIRTUAL HISTOLOGY**

- Fibrous tissue
- Fibrous tissue
- Fibrofatty
- Necrotic core
- Calcium
- >110 µm
- -
- -
- - non specific, part of NC
The Role of Plaque Calcification in Plaque Stability

- Coronary calcification correlates highly with plaque burden, but its effect on plaque instability is less obvious.
- Plaque calcification is enhanced significantly due to the presence of inflammation (NC) and intraplaque hemorrhage (plaque rupture, leakage of vasa vasorum)
- Over 50% of TCFAs (non-ruptured) show an absence or only speckled calcification. In the remaining segments, Ca is almost equally divided into fragmented or diffuse patterns, suggesting a large variation in the degree of calcification within these lesions.
- In contrast, 65% of acute ruptures show speckled calcification, with the remainder showing a fragmented or diffuse pattern.
The Role of Plaque Calcification in Plaque Stabilization

- Plaque erosions are almost devoid of calcification, or when present it is only speckled.
- Calcified nodules contain massive amounts of calcium relative to plaque area and in some instances even show bone formation.
  - Cause of sudden cardiac death in 5% of the cases.
- The amount of calcification within a coronary artery increases with age; however, women generally show a 10-year lag compared to men with equalization by the 8th decade.
Different Stages of Tissue Calcification

Microcalcification – Red on VH

FINE $\mu$CA

MORE EVIDENT $\mu$CA

DENSE $\mu$CA

Ca aggregates/chunk

Ca NODULE

Dense Calcium – White on VH
Plaque Calcification with VH IVUS

Fine microcalcification  Dense microcalcification  Aggregate of Ca
Progression Factoids

• Symptomatic CAD takes on average 65 years to develop.
• 18.6% progression of CAD in non-bypassed segment in 5 years (CASS 1980s).
• Of patients waiting for PTCA (Kaski 1995):
  – 24% had angiographic progression of CAD in eight months.
  – 57% had an acute coronary event.
  – 28% of lesions intended for angioplasty progressed.
  – 9% of non-culprit lesions progressed.
Progression Factoids

• After PCI, 20% of patients with multiple complex lesions will have an ACS the following year and 6% will die (Goldstein NEJM 2000).

• In a well medicated patient population (e.g. statins 66.3%) incidence of PCI for previously asymptomatic lesion is 5.8-10.8%. (Glaser, et al Circ. 2005)
  – 87% of these lesions are intermediate by angio at index.
  – Mean time for 2\textsuperscript{nd} PCI was 163±99 days.
  – in the non-PCI arm 25% increase in the use of long-acting nitrates.
  – After unstable AP, if 3-VD and prior PTCA, the risk for another event increases by 20% with each risk factor.
Progression Factoids

- Ruptured plaques are associated with positive remodeling.
- ~50% of sudden coronary deaths attributed to plaque rupture occur in lesions with <50% diameter stenosis.
- 75% of plaques which cause a sudden coronary death, have ruptured previously 2-5 times at the same site.
  - Repeated ruptures, which may or may not be silent, are likely responsible for more plaque progression.
- Necrotic core expansion may occur from intraplaque hemorrhage:
  - due to plaque rupture or leaking vasa vasorum.
  - through accumulation of free cholesterol derived from erythrocyte membranes and recruitment of macrophages.
Progression of Coronary Artery Lesions

- n=486 patients with 4 serial angiograms within a year
- One non-intervened major coronary artery was chosen for the follow up
- 7% (36 arteries), progressed significantly, 13/36 had ACS

Yokoyama, Suzuki et al Circulation 1999
Role of Thrombus in Plaque Progression

• Intramural thrombus serves as a nidus for development of the next thin cap atheroma.

• After a plaque rupture thrombus with its long tail attaches to the vessel wall, organizes within 14 days, and becomes part of the plaque (fast plaque progression).

• Thrombus may not be visible on angio due to compensatory positive remodeling.

• R. Virmani: lesions with hemorrhage and inflammation, characterized by large necrotic cores, macrophage infiltration and calcification are more likely to exhibit vessel expansion than plaques without these features. In addition, vessel enlargement is also dependent on the plaque morphology related to the underlying luminal thrombus such that plaque rupture is associated with severe IEL expansion.

• Organized thrombus can increase the risk of the progression/formation of other TCFA.
Case # 3 (SG)

- 65 years old male
- Clinical presentation: MI 6 days earlier
- Risk factors: smoker, alcohol abuse
- Angiogram: hazy, about 90 % lesion in the proximal RCA
- EF: 25 %
Baseline IVUS
Partly organized 6 Day old Thrombus by grayscale IVUS
Case # 3 (SG)
Procedural notes

- IVUS VH
- Cutting balloon
- Distal Driver stent
- IVUS VH
- Cutting Balloon
- Mid Driver stent
- IVUS VH
- Proximal Driver stent
- Final IVUS VH
Final Angio
Final Grayscale IVUS

Distal and Mid

Proximal
Final IVUS Grayscale pullback Single Frames

Distal to 3rd stent

In 3rd stent

Stent struts

thrombus

4mm

Stent
IVUS Grayscale pullback Single Frames

3rd and 2nd stent overlap

4mm

Mid 3rd stent

2nd stent

Proximal 3rd stent
Reduced Myocardial Blush?
Time to Re-focus

• With the advent of DES the risk for non-target lesion intervention has become the same or even higher than the risk for repeat revascularization of the target lesion.
• VH™ IVUS has the potential to assess the:
  – natural history of CAD,
  – role of thrombus on plaque progression,
  – impact of plaque calcification on plaque progression and stabilization,
  – effect of systemic medication on general plaque composition and different plaque types including high risk, vulnerable plaques,
  – effect of regional therapy on high risk lesions,
  – value of VH IVUS itself on the outcome of culprit lesion intervention.