Real World Paradigm for the Identification of Vulnerable Plaque and Vulnerable Patients

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In the coronary arteries, things may not be as nice as they seem.

Mild lesions are not always what they appear to be:
Heart Disease is Still #1 Killer

• Over one million Americans die from cardiovascular each year, one/minute.
• Cardiovascular disease is the largest cause of hospitalization in the U.S., accounting for $26 billion in Medicare expenditures.
• Based on previous research, 80% of these attacks can be attributed to vulnerable plaque.
Vascular Events and Atherosclerosis

- Vascular events in AMI patients are determined by local pre-event lesion histopathology.
- Plaque ruptures usually occur in the proximal 1/3 of coronary arteries.
- 84% of MI’s are caused by lesions <70% occlusive.
- In acute MI, 20% of culprit arteries have multiple ruptured plaques.
  - 75% of plaques causing acute MI and Sudden Death have ruptured multiple times.
  - 50% of plaque ruptures are clinically unrecognized.
- 7% of IVUS based intermediate lesions lead to death within a year.
- Multiple complex plaques at the time of MI purport a bad prognosis.
  - 54% of patients have repeat catheterization within a year.
  - 19% of patients have a non-culprit artery related event in one year.
We are treating only the tip of the iceberg
PCI

- PCI is effective in treating symptomatic disease.
- Except in acute myocardial infarction, PCI has never been shown to reduce mortality.
- Lesions routinely treated with PCI are not the ones that cause most MI and sudden death.
- Vulnerable lesions can be suspected by angiography and IVUS.
- To date, we have not had the tools or vision to know which lesions to treat and how to treat them.
The Vulnerable Plaque
The “Vulnerable” Coronary Plaque
Thin cap fibroatheroma with necrotic core

Necrotic core
Lumen
Fibrous Cap
What if We Could…?

• Quickly and accurately predict the composition of an atherosclerotic artery?
  – Calcium
  – Fibrous tissue
  – Fibro-lipidic tissue
  – Lipid necrosis

• Risk stratify the treatment of intermediate lesions?

• Identify early stage disease and provide guidance for additional diagnostic needs and systemic therapy?
Virtual Histology

- IVUS-based tissue characterization merged with novel border detection and analysis software.
- 10 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

Post Processing Signals

IVUS Signal

Investigational Use Only
Teaching the Computer
Virtual Histology™ IVUS

Different frequencies correspond to different types of tissue.

- Dense Calcium
- Fibrous
- Fibro-fatty
- Necrotic Core
Progression of Atherosclerosis

Intimal Xanthoma, Lipidstreaks

Calcified Nodule

RUPTURE

Thrombosis → Healing

SUDDEN DEATH

Fibrous Cap Atheroma

Thin Fibrous Cap Atheroma = inflamed, lipid rich necrotic core

Fibrocalcific plaque

Supernicial erosion

Intimal thickening

Pathologic Intimal thickening

Healing → Thrombosis

SUDDEN DEATH
Progression of Atherosclerosis

Modified from Virmani et al. Arteriosclerosis Thromb Vasc Biol 2002:20;1262

Intimal Xanthoma, Lipid streaks

Fibrous Cap Atheroma

Intimal thickening

Pathologic intimal thickening

Thin Fibrous Cap Atheroma with inflamed, lipid-rich necrotic core

Calcified Nodule

Thrombosis → Healing

Rupture

Fibrocalcific plaque

Thrombosis → Healing

Superficial erosion

SUDDEN DEATH

SUDDEN DEATH

SUDDEN DEATH
Grey Scale
vs.
Virtual Histology
vs.
Histopathology
1b4 Grey scale
Ability of Gray Scale IVUS to Differentiate Plaque Morphologies
The Vulnerable Patient
Factors Connoting High-risk for Coronary Events

- Traditional risk factors
  - Hyperlipidemia
  - Hypertension
  - Diabetes
  - Obesity
  - Smoking
- Biomarkers
  - Metabolic syndrome
  - Insulin resistance
  - Certain lipid disorders (high LDL IVb, low HDL 2b)
  - Multiple risk factors for inflammation (CRP, elevations of multiple antibodies)
- Clinical Markers
  - Positive perfusion scans
  - Very high Calcium scores
- Previous events:
  - Several lesions at time of coronary event.
  - Intermediate lesions in proximal arteries.
Most MIs Arise From Smaller, Non flow-limiting Stenoses

How to Diagnose Coronary Atherosclerosis at a Pre-Clinical State?

Functional testing
- Stress-ECG
- Stress-Echocardiography
- Nuclear Perfusion Imaging
- Positron Emission Tomography

Non invasive
- Computed Tomography, Magnetic Resonance Imaging

Invasive
- Intravascular Ultrasound Imaging
- Coronary Angiography

Plaque Size:
- 20%
- 20%
- 45%
- 70%
- 90%

Normal
- Stary II - III
- IV
- V or VI a - c

Adapted from Erbel R et al. Deutsches Ärzteblatt 1999
Radiographic Calcium

- Fluoroscopic calcium predicts not only the presence of significant coronary artery disease, but also portends a poor prognosis.\(^1\)
  - Five year survival for patients with calcification only 58%.
- Calcium score by CT predicts presence of significant coronary artery disease with or without critical stenoses.
  - Calcium scores > 1,000 associated with 25% annualized rate of hard coronary events (MI and Death).\(^2\)
- Absence of calcium on CT portends an excellent prognosis even in the presence of serious risk factors.\(^3\)

\(^1\) Margolis JR; Chen JT; Kong Y; Peter RH; Behar VS; Kisslo JA: The diagnostic and prognostic significance of coronary artery calcification. A report of 800 cases. *Radiology* 1980 137:609-16


\(^3\) Raggi P; Shaw LJ; Berman DS; Callister TQ: Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *JACC* 2004;43:1663-9
Why Calcium Accumulates Into Plaques

• Inflammation
  – Inflamed cells (red) die and dump their calcium in the extracellular space leading to microcalcification.
  – Scattered calcification (white) accumulates in areas of lipid necrosis (red).
  – Microcalcification aggregates into larger, focal sites of dense calcium (red with Ca, +/- reverberations).

• Intramural hemorrhage leads to dense calcification.
CALCIUM IS A MARKER OF INFLAMMATION AND PLAQUE RUPTURE.
Virtual Histology Can Differentiate Between Low and High Risk Lesions in These Patients?
Stable Lesions
(Fibrotic Plaque)
Histopathology of Early and Intermediate Stage Lesions

- Lipid Streaking
- Pathological Intimal Thickening
Histopathology of Early and Intermediate Stage Lesions (Fibrocalcific Plaque)
Histopathology of Early Stage and Intermediate Lesions (Fibro-atheroma)
Acute Culprit Lesions (Prominent necrotic core)

RECENT MI

UNSTABLE ANGINA

Just proximal to stented lesion
How do we identify patients who are at high-risk for Myocardial Infarction and Sudden Death?

• Study high-risk patient populations
  – DM
  – Insulin resistance
  – Metabolic syndrome
  – High Framingham scores

• Do EBCT or MSCT
  – Study patients with high calcium scores

• Study high risk, INTERMEDIATE lesions.
  – Improve our understanding of atherosclerosis progression.
  – Try to identify therapeutic benefit of systemic medication.

• Correlate high-risk lipid profile and Virtual Histology
  – Try to understand effect of plaque composition on future events.
Paradigm for the Identification of Vulnerable Plaque and Vulnerable Patients

Positive Risk Factors

Multi-slice CT

High Calcium Score
Coronary Angiography

Low Calcium Score
IVUS and VH

Risk Factor Modification
We cannot always control the forces of Nature.

Satellite photo
Typhoon
Tokage
But identifying the problem in advance may mitigate adverse effects. . .

- Dense Calcium
- Fibrous
- Fibro-fatty
- Necrotic core
We may never be able to control typhoons, but there are many potential ways to prevent plaque rupture.

• **Systemic therapy:**
  – Statins
  – Drugs to raise HDL and change particle size
  – Anti-inflammatory medications
  – Antibiotics

• **Interventions:**
  – Plaque sealing with DES
  – Bioabsorbable stents
  – Intracoronary application of medication
Are We Justified in Stenting Intermediate Lesions?
Questions to Answer Before Stenting Intermediate Lesions

- Is intermediate plaque likely to rupture?
- Do we have effective RX
  - Is it safe?
  - Is it durable?
- What are the risks?

- Check biomarkers/tissue characteristics
- Drug Eluting Stents
  - Short-term yes
  - If deployed properly
- Late SAT
Future Paradigm for the Identification and Treatment of Vulnerable Plaque and Vulnerable Patients?

Positive Risk Factors

Multi-slice CT

High Calcium Score

Coronary Angiography

Low Calcium Score

IVUS and VH

Risk Factor Reduction

Plaque Sealing + Systemic Therapy