«Απεικόνιση και φυσιολογία στο αιμοδυναμικό εργαστήριο».

Ευάλωτη αθηρωματική πλάκα. Πού βρισκόμαστε?

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Επεμβατικός Καρδιολόγος
Επιμελητής, Καρδιολογικού Τμήματος Γ.Ν.Α. «Λαϊκό»
DISCLOSURES

• NONE
Vulnerable plaque. Where are we?

Baseline diagnostic angio

2 months later - ACS
No Improvement of Non-culprit related Events

Enrollment completed in 2006

COLOR Registry 2 Year

Enrollment completed in 2014
Vulnerable plaque. Where are we?

Continued Search for the Vulnerable Plaque: Are We Any Closer?

What makes a plaque vulnerable - morphology, chemistry, biologic activity or ischemia?

Criticisms:
- “Not possible to predict plaque events accurately”
- “Focus should be on vulnerable patients and systemic Rx”
- “Not worthwhile to ever pre-emptively stent a high-risk lesion”
Natural History of Coronary Plaque

Initial Development of Plaque
In areas of local flow disturbance in individual with genetic/lifestyle risk factors (IVUS/OCT)

Progression of Plaque
Invasive or Noninvasive Vascular Imaging (IVUS/OCT/CT)

Development of TCFA/Large PB (IVUS/VH/OCT/NIRS)
- Plaque morphology
- Plaque constituents/characteristics
- Arterial wall remodeling
- Local ESS environment

Disruption of TCFA ➔ New CV Event
- **Ongoing** pro-inflammatory/pro-atherogenic activity/stimulus. Imaging of:
  - Molecular markers of inflammation
  - Local Low ESS as ongoing stimulus

Toutouzas et al, Eur Heart J 2015
Plaque Progression: From PIT (LP) to Fibroatheroma (NC)

- Pathological intimal thickening without macrophage
- Pathological intimal thickening with macrophage
- Early fibroatheroma
- Late fibroatheroma

Joner M at CRT 2015
**Definition**

**TCFA**

![Graph showing rate of major adverse cardiovascular events for different conditions involving TCFA.](image)

<table>
<thead>
<tr>
<th>Lesion hazard ratio (95% CI)</th>
<th>TCFA (all)</th>
<th>TCFA + MLA ≤4 mm²</th>
<th>TCFA + PB ≥70%</th>
<th>TCFA + PB ≥70% + MLA ≤4 mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>46.7</td>
<td>15.9</td>
<td>10.1</td>
<td>4.2</td>
</tr>
</tbody>
</table>
Three Different Types of Vulnerable Plaque

**Vulnerable Plaque = Causing Thrombosis**
- Rupture
- Erosion
- Calcified Nodule

**Stable Plaque = Not Causing Thrombosis**
- Fibrocalcific Plaque
- Healed Rupture
- Pathological Intimal Thickening

Images Courtesy of Renu Virmani
OCT Defined Underlying Plaque in ACS

Prevalence (%)

Plaque Rupture

No Rupture

Calcified Nodule

Jia et al. JACC 2013;62:1748-58
Niccoli et al. EHJ 2015; 36:1377-84
Wang et al. EHJI 2015
Higuma et al. JACC Interv 2015;8:1166-76
Rupture

Description:
- Intimal tearing, disruption, or dissection of the cap
- Cavity may be present

Rupture/Thrombus

Tearney et al, ACC 2014
Erosion - Thrombus in the Absence of Rupture
Presence of Necrotic Core?

Definite OCT-Erosion

Probable OCT-Erosion

1) Luminal surface irregularity without thrombus
2) Attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal site

Presence of attached thrombus overlying an intact and visualized plaque

Younger females with smoking history

Jia H, et al. JACC 2013
Rupture vs Erosion

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Rupture (n=65)</th>
<th>Erosion (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disruption of fibrous cap</td>
<td></td>
<td>Deficiency of endothelium</td>
</tr>
<tr>
<td>Age</td>
<td>52±10</td>
<td>43±9</td>
</tr>
<tr>
<td>Male</td>
<td>89%</td>
<td>74%</td>
</tr>
<tr>
<td>Presentation</td>
<td>STEMI 70%</td>
<td>NSTEMI 60%</td>
</tr>
<tr>
<td>Plaque burden (%)</td>
<td>77±14</td>
<td>71±15</td>
</tr>
<tr>
<td>% Necrotic core</td>
<td>38±23</td>
<td>18±24</td>
</tr>
<tr>
<td>% Macrophage</td>
<td>3.4±2.8</td>
<td>2.5±2.7</td>
</tr>
</tbody>
</table>

Calcified Nodule

Prevalence of calcified nodules in ACS lesions

Clinical and Morphological Differences

<table>
<thead>
<tr>
<th></th>
<th>Calcified Nodule (n=37)</th>
<th>No Calcified Nodule (n=852)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>73 (65, 79)</td>
<td>66 (58, 73)</td>
<td>0.001</td>
</tr>
<tr>
<td>ACS presentation</td>
<td>45.9%</td>
<td>48.2%</td>
<td>0.79</td>
</tr>
<tr>
<td>DM</td>
<td>51.4%</td>
<td>33.3%</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>18.9%</td>
<td>2.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>△ Angle in lesion</td>
<td>16 (14, 21)</td>
<td>9 (6, 14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OCT Max Ca angle, °</td>
<td>301 (247, 347)</td>
<td>64 (0, 123)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Ca angle, °</td>
<td>166 (134, 202)</td>
<td>48 (0, 81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Max Ca thickness, mm</td>
<td>1.18 (0.94, 1.3)</td>
<td>0.21 (0, 0.75)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Distribution of CN Lesions

- Total (n = 889)
- CN (n = 37)

A "Vulnerable" Plaque Stems From a Mismatch of Stress and Strength
Inflammatory Differences in Plaque Erosion and Rupture in STEMI

45 STEMI <6 hrs

Thrombectomy

OCT diagnose to 23 Rupture vs 15 Intact fibrous cap (IFC)

1. Cytokine array
2. ELISA
3. mRNA expression

Intact fibrous cap
TSP (thrombospondin) to impairs endothelial cell adhesion, motility etc.

EGF (epidermal growth factor)

Rupture
I-TAC (interferon-inducible T cell alpha chemoattractant)
MMP9 (matrix metalloprotein)

Role of local inflammation

Histopathologic Characteristics of Atherosclerotic Coronary Disease and Implications of the Findings for the Invasive and Noninvasive Detection of Vulnerable Plaques

Narula et al JACC 2013
Shear Stress Approaches: Endothelial, Wall and Plaque

- Genetic Predisposition
- Systemic Cardiovascular RF
- Microvascular Dysfunction
- Endothelial Dysfunction
- Plaque Rupture

High WSS:
- Plasmin
- MMP-1, -3, -9, -10, -13
- Plaque Area
- Necrotic Core
- Fibrous
- Fibro-Fatty
- Excessive Expansive Remodeling

Low WSS:
- VCAM-1 and ICAM-1
- MMP-2, -9, -12
- Cathepsins K and S
- Oxidative stress
- eNOS and KLF-2

Normal Coronary Artery
Early Atherosclerotic Lesion
Thin-cap Large NC

Inflammation
- hs-CRP
- suPAR
- Gluthathione
Anatomy-Physiology Interaction: Endothelial Wall Shear Stress

Choi GW et al. JACC Imaging 2015
Endothelial Shear Stress

Severe Endothelial Dysfunction and Low Shear Stress

• PPVs of shear+IVUS can reach 40-50%

PH Stone et al Circulation 2012
Papafaklis et al. Int J Cardiology 2016
2 years later: ESS has normalized over the scaffold, and a 210 um layer of neointima has developed.
High Plaque Structural Stress (PSS) to predict Rupture

- 4053 VH-IVUS frames from 32 fibroatheroma with rupture in VIVA study and 32 fibroatheroma without rupture by OCT from stable angina pts.
- Plaque rupture was used as an endpoint.
- PSS was calculated using Finite element analysis (FEA) by considering plaque composition, plaque geometry, and lumen geometry.

<table>
<thead>
<tr>
<th>VH-IVUS parameter</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen area, mm²</td>
<td>0.46</td>
</tr>
<tr>
<td>Lumen eccentricity</td>
<td>0.32</td>
</tr>
<tr>
<td>Necrotic core ≥10%</td>
<td>0.12</td>
</tr>
<tr>
<td>Dense calcium ≥10%</td>
<td>-0.12</td>
</tr>
</tbody>
</table>
High WSS and OCT Features of Plaque Vulnerability

WSS

- Upstream 2
- Upstream 1
- MLA
- Downstream 1
- Downstream 2

Toba H, Otake H et al. Circulation. 2017
Identification of a culprit lesion

ACCS

<table>
<thead>
<tr>
<th>Anatomical assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
</tr>
<tr>
<td>OCT, NIRS-IVUS, IVUS</td>
</tr>
</tbody>
</table>

Stable CAD

<table>
<thead>
<tr>
<th>Functional assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR</td>
</tr>
</tbody>
</table>

WHAT TO DO WITH FUNCTIONALLY INSIGNIFICANT VULNERABLE PLAQUE?

Don’t Treat Them!
Combining Hemodynamics + Atherosclerotic Plaque Characteristics: Stress-Strain

- $\text{FFR}_{\text{CT}} \rightarrow$ Stenosis severity, Diffuseness, Volume-to-Mass
- Axial Plaque Stress $\rightarrow$ Coronary geometry, Diffuseness
- Wall Shear Stress $\rightarrow$ Coronary geometry, Local physiology, Plaque composition
- Radial Plaque Stress $\rightarrow$ Unexplored

- **Axial Plaque Stress and Wall Shear Stress do NOT correlate with $\text{FFR}_{\text{CT}}$**

Combining Hemodynamics + Atherosclerotic Plaque Characteristics: Stress-Strain

11 centers, 228 lesions

- Stenosis (%)
  - Non-Culprit
  - Culprit

- Hounsfield Unit (LAP)
  - Non-Culprit
  - Culprit

- Remodeling Index (Positive Remodeling)
  - Non-Culprit
  - Culprit

- Plaque Composition

- Lesion Geometry
  (Stenosis severity, Radius gradient)

- Hemodynamic Force

- Plaque Strength

- Plaque Stress

- Delta FFR_{CT}
  - Non-Culprit
  - Culprit

- Axial Plaque Stress
  - Non-Culprit
  - Culprit

- Wall Shear Stress
  - Non-Culprit
  - Culprit

- Wall Shear Stress (Positive Remodeling)
Vulnerable Plaque Detection by CT?

Caixeta et al, JACC Img 2016
Atherosclerotic Plaque Characterization

1. Stenosis (%DS, %AS, MLD, MLA)
2. Non-obstructive stenoses
3. Plaque burden (volume, area, thickness)
4. Plaque composition (non-calcified, calcified)
5. “Spotty calcifications”
6. “Lipid dense” intraplaque core (low attenuation)
7. Arterial remodeling (positive, negative, intermediate)
8. Absolute material density (dual energy CT)

Thomsen C and Abdulla J, Eur Heart J Cardiovasc Imaging 2016
Danad I et al. JACC Cardiovasc Imaging 2015
Plaque Stress: Hemodynamics - FFR

CT: Severe Stenosis  FFR\text{CT}: \text{Lesion-specific Ischemia}  FFR: Ischemia

Norgaard BL et al. JACC 2014
$\text{FFR}_{\text{CT}}$
### FFR<sub>CT</sub>: Three (3) Prospective Multicenter Trials

<table>
<thead>
<tr>
<th></th>
<th>DISCOVER-FLOW</th>
<th>DeFACTO</th>
<th>NXT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>Min (JACC)</td>
<td>Min (JAMA)</td>
<td>Norgaard (JACC)</td>
</tr>
<tr>
<td>Primary end point</td>
<td>Per pt. diag accuracy</td>
<td>Per pt. diag accuracy; lower limit 95% CI 0.7</td>
<td>Per pt. AUC</td>
</tr>
<tr>
<td>Study sites/ countries</td>
<td>4 / 3</td>
<td>17 / 5</td>
<td>10 / 8</td>
</tr>
<tr>
<td>Site expertise qualification</td>
<td>FFR</td>
<td>CT or FFR</td>
<td>CT plus FFR</td>
</tr>
<tr>
<td>CT training of site</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>FFR training of site</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CT quality check</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CT results reading</td>
<td>Core lab</td>
<td>Core lab</td>
<td>Site</td>
</tr>
<tr>
<td>FFR results report</td>
<td>Site</td>
<td>Site</td>
<td>Site with core lab overview</td>
</tr>
<tr>
<td>Vessel size for inclusion</td>
<td>≥ 2.0 mm</td>
<td>≥ 1.5 mm</td>
<td>≥ 2.0 mm</td>
</tr>
<tr>
<td>Software version*</td>
<td>V 1.0 manual</td>
<td>V 1.2 partial automation ~6 hrs</td>
<td>V 1.4 automation; &lt;4 hours</td>
</tr>
</tbody>
</table>

Koo et al. JACC 2011  
Min JK et al. JAMA 2012  
Norgaard BL et al. JACC 2014
Molecular Imaging: PET/CT

Joshi et al, Lancet 2014
None of the available IC imaging techniques can show all the features of plaque vulnerability.
OCT and IVUS characteristics

OCT

A. Lipid plaque
- Plaque rupture: 100%
- Plaque erosion: 43.3%
- Calcified nodule: 55.6%

B. TCFA
- Plaque rupture: 97.0%
- Plaque erosion: 3.7%
- Calcified nodule: 11.1%

C. Microchannel
- Plaque rupture: 54.2%
- Plaque erosion: 13.8%
- Calcified nodule: 22.2%

IVUS

A. Eccentric plaque
- Plaque rupture: 31.9%
- Plaque erosion: 73.3%
- Calcified nodule: 11.1%

B. Positive remodeling
- Plaque rupture: 76.4%
- Plaque erosion: 30.0%
- Calcified nodule: 0%

C. Negative remodeling
- Plaque rupture: 4.2%
- Plaque erosion: 26.7%
- Calcified nodule: 55.6%

Higuma et al, JACC Interv, 2015
Rationale for Multimodality Imaging

Structural imaging alone provides insufficient positive predictive value for lesion progression and stent complications.

Hybrid approaches are needed

---

**Table 1** Advantages and limitations of the existing invasive imaging modalities and the available hybrid imaging techniques

<table>
<thead>
<tr>
<th>Imaging modalities</th>
<th>Features associated with increased plaque vulnerability</th>
<th>Fast analysis</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lumen dimensions</td>
<td>Plaque burden and positive remodelling</td>
<td>Lipid component</td>
</tr>
<tr>
<td>IVUS + X-ray</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>OCT + X-ray</td>
<td>+++</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>IVUS + CTCA</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>OCT + CTCA</td>
<td>+++</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>NIRS-IVUS</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>IVUS-OCT</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>OCT-NIRF</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>IVUS-NIRF</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>OCT-NIRS</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>IVUS-IVPA</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>IVUS-FLIm</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

Extensive applications in the study of the role of ESS in atherosclerotic evolution.

Implemented to evaluate the efficacy of CTCA in assessing plaque morphology.

Limited applications in the study of the association between plaque characteristics and the local hemodynamic forces.

Commercially available.

In vivo validation.

First in man studies.

Under development.

Ex vivo validation.

In vivo validation.
Novel invasive imaging approaches emerging

OCT-NIRAF ( Autofluorescence )

Thrombus
Rupture

NIRS-IVUS

NIRS-OCT images

Normalized NIRAF intensity

Calcium
Lipid

1 mm

Tearney Lab, MGH

proximal
PROSPECT II Study
PROSPECT ABSORB RCT

900 pts with ACS after successful PCI
3 vessel IVUS + NIRS (blinded)
≥1 IVUS lesion with ≥65% plaque burden present?

Yes (N=300)
ABSORB BVS + GDMT (N~150)
Routine angio/3V IVUS-NIRS FU at 2 years

No (n=600)
GDMT (N=150)
Clinical FU for up to 15 years
Patient 'Signed Off' by Heart Team for PCI

iFR in all 3 major epicardial vessels*

- iFR < 0.86
- iFR 0.86-0.93
- iFR > 0.93

**FFR**

- FFR ≤ 0.80
- FFR > 0.80

- Implantation of SYNERGY™ stent(s)
- No stent implantation in lesion

Optimization by IVUS guidance (modified MUSIC Criteria)

Optimal medical therapy with a strict control of LDL (≤1.8 mmol)

*FFR with adenosine, iFR/FFR in side branches, all at discretion of the operator.
To evaluate the relationship between non-obstructive lipid-rich plaque and a new coronary events.

Suspected Index Culprit Lesion -or- Index Culprit Lesion

Send to Core Lab

Core Lab will un-blind NIRS data

N = 3000
Large LRP
(Max LCBI 4mm ≥ 250)

N = 6000
Small/No LRP
(Max LCBI 4mm < 250)

2yr Follow-Up

N = 3000

N = 3000

2yr Follow-Up

Terminate upon Discharge
Identification of Vulnerable Patient

- 704 culprit lesions in 704 pts evaluated by OCT
- 17.5% of STEMI, 20% of NSTEMI
- Predictor of Lipid rich plaque (ACS, non-statin, DM)

Zhang, et al TCT2016
CONCLUSIONS

- TCFAs are considered the vulnerable plaques
- Plaque rupture is the main cause of thrombosis, while erosion occurs less and calcified nodule is uncommon
- Multimodality non-invasive and invasive imaging and/or physiology is the key
- Identification and treatment of vulnerable plaque still seem to be an achievable goal
Artificial intelligence can predict heart attack better than doctors.

- Each year 20 million deaths attributed to cardiovascular diseases including strokes, heart attacks, and coronary artery disease.
- Computers can now be used to predict heart attacks.
- Computer better predicts the diseases weigh the risk factors of each patient which include age, blood pressure, and cholesterol.
- Computer artificial intelligence can predicts cardiovascular diseases with 75% accuracy.
- Scientists hope that providing more data to the artificial intelligence algorithms such as genetic or other lifestyle factors will further enhance the prediction results.