Coronary heart disease: what’s new?

Noninvasive imaging of the vulnerable plaque in 2012

Federico Conrotto
Definition of Vulnerable Plaque

The susceptibility of a plaque to rupture

Circulation 1989; 79: 733-43
JACC 2006; 47 Suppl 8: C13-8
Plaque rupture as the basis of ACS

From autopsy studies in patients who had died of cardiac causes, the most common underlying plaque morphology was a ruptured thin-cap fibroatheroma.
Representative Lesion Morphologies for Progressive Human Coronary Atherosclerosis

A. Pathologic Intima Thickening
   - LP
   - CD68

B. Fibroatheroma “Early” Core
   - NC
   - CD68

C. Fibroatheroma “Late” Core
   - NC
   - CD68

D. Thin Cap Fibroatheroma
   - CD68

Most Culprit Lesions Cause Insignificant Luminal Narrowing Prior to Onset of MI
A Prospective Natural-History Study of Coronary Atherosclerosis

<table>
<thead>
<tr>
<th>Lesion hazard ratio (95% CI)</th>
<th>P value</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCFA (all)</td>
<td>3.90 (2.25–6.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TCFA + MLA ≤4 mm²</td>
<td>6.55 (3.43–12.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TCFA + PB ≥70%</td>
<td>10.83 (5.55–21.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TCFA + PB ≥70% + MLA ≤4 mm²</td>
<td>11.05 (4.39–27.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Noninvasive imaging of the vulnerable plaque

Plaque morphology and plaque composition (identification of the “vulnerable plaques”)

Plaque progression/regression.

Monitor the effects of drugs on diseased arteries
Imaging

Imaging of atherosclerosis: carotid intima–media thickness

Lines were estimated from the statistical model based on 12 carotid artery sites. Gray shading indicates 95% confidence intervals.
A.L. 56 aa
Hypertension, dislipidemia
Transient ischemic attack
Detection of carotid vulnerable plaque on doppler examination

Carotid endarterectomy
Noninvasive Characterization of Plaque Morphology

Computed tomography angiography:
Calcium, plaque attenuation and PVR

MRI: plaque morphology and intraplaque hemorrhage

Positron emission tomography
Noninvasive Characterization of Plaque Morphology

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Positron emission tomography
Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups
Acute Coronary Syndrome

Positive remodeling
NCP plaque (also including areas of 30 HU)
Spotty calcification (pink arrows)
Stable Angina

Negatively remodeled
No NCP 30 HU or spotty calcification
Plaque Characteristics in ACS and SAP
Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary Syndrome

2-year ACS Risk
22% PVR + LAP
Vs
0.5% No PVR nor LAP

J Am Coll Cardiol 2009;54:49–57
Computed Tomographic Angiography
Characteristics of Atherosclerotic Plaques
Subsequently Resulting in Acute Coronary Syndrome

Table:

<table>
<thead>
<tr>
<th></th>
<th>Cutoff Value</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remodeling Index (%)</td>
<td>116.5</td>
<td>72.7</td>
<td>61.9</td>
<td>25.0</td>
<td>69.0</td>
</tr>
<tr>
<td>Total Plaque Volume (mm³)</td>
<td>63.13</td>
<td>72.7</td>
<td>68.3</td>
<td>28.6</td>
<td>93.5</td>
</tr>
<tr>
<td>LAP Volume (mm³)</td>
<td>0.99</td>
<td>90.0</td>
<td>66.7</td>
<td>32.3</td>
<td>97.7</td>
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<tr>
<td>Max LAP Area/Plaque Area (%)</td>
<td>11.39</td>
<td>63.6</td>
<td>76.2</td>
<td>31.8</td>
<td>92.3</td>
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</table>
Computed Tomographic Angiography–Verified Plaque Characteristics and Slow-Flow Phenomenon During Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N = 80)</th>
<th>Control Group (n = 40)</th>
<th>SF Group (n = 40)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>CCTA findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive remodeling index</td>
<td>1.4 (1.2–1.6)</td>
<td>1.2 (1.0–1.5)</td>
<td>1.5 (1.3–1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum CT value, HU</td>
<td>34 (18–75)</td>
<td>45 (29–86)</td>
<td>23.5 (9.5–40)</td>
<td>0.001</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>69 ± 11</td>
<td>69 ± 12</td>
<td>69 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>CPC</td>
<td>27 (34)</td>
<td>2 (5)</td>
<td>25 (63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ULA</td>
<td>9 (11)</td>
<td>5 (13)</td>
<td>4 (10)</td>
<td>NS</td>
</tr>
</tbody>
</table>

D: Color map indicating HU levels.
E: Image showing a region of interest.
F: Detailed image with measured HU values:
- CPC 156 HU
- CPC 325 HU
- Lumen 262 HU
- LAP 17 HU

J Am Coll Cardiol Intv 2012;5:636–43
Serial Coronary CT Angiography–Verified Changes in Plaque Characteristics as an End Point

Evaluation of Effect of Statin Intervention

Baseline cross-sectional images

Follow-up cross-sectional images
CT LIMITATIONS

1. Suboptimal resolution
2. Various imaging or technical parameters may significantly influence the soft plaque measurements
3. Heavy plaque calcification
4. No characterization of plaque erosions
5. Radiation burden
6. No Primary prevention studies
Noninvasive Characterization of Plaque Morphology

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Positron emission tomography
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Quantitative Evaluation of Carotid Plaque Composition by In Vivo MRI
1. severity of stenotic lesions
2. spatial distribution
3. composition

154 asymptomatic patients
50% to 80% carotid stenosis

Thin or ruptured fibrous cap (HR: 17.0; p 0.001)
IPH (HR: 5.2; p 0.005)
Larger mean necrotic core area (HR: 1.6; p 0.01 per 10-mm² increment)

Plaque features predictive of subsequent transient ischemic attack or stroke during a mean follow-up of 3 years

Intraluminal haemorrhages as the trigger of plaque vulnerability

Jean-Baptiste Michel¹, Renu Virmani², Eloïsa Arbustini³, and Gerard Pasterkamp⁴

These microvessels are fragile because of lack of support by smooth muscle cells and focal discontinuity of the endothelial lining.
Haemorrhagic/necrotic core

- RBC
- Leucocytes
- Platelets
- Plasma

- Membranes
- Haemoglobin
- Neutrophils

- Fe
- MPO
- Elastase
- Plasmin

- Cholesterol crystals
- Oxidation
- Proteolysis
Presence of Intraplaque Hemorrhage Stimulates Progression of Carotid Atherosclerotic Plaques: A High-Resolution Magnetic Resonance Imaging Study

Norihide Takaya, Chun Yuan, Baocheng Chu, Tobias Saam, Nayak L. Polissar, Gail P. Jarvik, Carol Isaac, Judith McDonough, Cynthia Natiello, Randy Small, Marina S. Ferguson and Thomas S. Hatsukami

Lipid-rich necrotic core without hemorrhage

Type I hemorrhage

Type II hemorrhage
Images of progression of atherosclerosis with intraplaque hemorrhage in right carotid artery.

Table 3. Percent change of volume and wall thickness

<table>
<thead>
<tr>
<th></th>
<th>Hemorrhage Group (n=14)</th>
<th>Control Group (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen volume</td>
<td>-8.5±12.2</td>
<td>1.5±7.9</td>
<td>0.014</td>
</tr>
<tr>
<td>Wall volume</td>
<td>6.8±7.9</td>
<td>-0.15±5.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Outer wall volume</td>
<td>1.5±6.2</td>
<td>0.2±4.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Lipid-rich necrotic core volume</td>
<td>28.4±29.7</td>
<td>-5.2±17.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium volume</td>
<td>0.3±38.4</td>
<td>3.4±26.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Maximum wall thickness</td>
<td>8.3±11.3</td>
<td>-3.2±10.7</td>
<td>0.009</td>
</tr>
<tr>
<td>Minimum wall thickness</td>
<td>3.9±21.3</td>
<td>-5.6±23.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean wall thickness</td>
<td>8.5±8.8</td>
<td>-1.6±4.74</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD.
**Advantages**

✓ Technique Non-invasive
✓ Any exposition to radiation
✓ Adequate spatial resolution for large vessels (i.e. aorta, carotid, and femoral arteries)

**Limitations**

✓ Limited temporal resolution hampering its application in the coronary circulation
Noninvasive Characterization of Plaque Morphology

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Noninvasive Characterization of Plaque Morphology

Computed tomography angiography:
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Positron emission tomography
Increased FDG Uptake in Vascular Inflammatory Diseases

Increased FDG uptake has been reported in:
- Takayasu's arteritis,
- Giant cell arteritis,
- Polymyalgia rheumatica
- Nonspecific aortitis
- Patients with atherosclerosis
Inflammation and Plaque Progression
Basis for FDG-PET Imaging of Inflamed Atherosclerotic Plaques

Macrophages:
• Have high basal metabolic rates
• Rely on external glucose source as fuel (macrophages do not store glycogen)
• Increase glucose consumption further when activated.

FDG uptake by inflamed tissues is 10-20 times that of most other tissues.

FDG uptake is often higher in inflammatory tissue than in tumor cells.
Increased FDG Uptake Observed in Symptomatic Carotid Disease

Circulation. 2002;105:2708-2711
In Vivo 18F-Fluorodeoxyglucose Positron Emission Tomography Imaging Provides a Noninvasive Measure of Carotid Plaque Inflammation in Patients
Aortic 18F-FDG uptake 70% of the patients
- Calcifications were often seen in patients
- Calcification and 18F-FDG uptake were present at the same site in only 2%
Arterial wall uptake of fluorodeoxyglucose on PET imaging in stable cancer disease patients indicates higher risk for cardiovascular events.

Abstract

BACKGROUND:
We aimed to evaluate the additional information of 18 fluorodeoxyglucose (FDG) arterial uptake with respect to other conventional cardiovascular risk factors and arterial calcifications in patients with stable cancer.

METHODS AND RESULTS:
We compared the rate of cardiovascular events in 2 groups of patients with (n = 45) and without (n = 56) enhanced arterial 18FDG uptake, matched for the main clinical parameters. The extent and intensity of 18FDG uptake were quantified. A calcification index was also determined. About one third of the selected patients had a history of cardiovascular events and thus could be defined as "vulnerable patients." Old cardiovascular events (>6 months before or after positron emission tomography [PET]) and recent cardiovascular events (<6 months before or after PET) were significantly more frequent in the high-FDG uptake group than in the low-FDG uptake group (48% vs 15%, respectively [P = .0006], and 30% vs 1.8%, respectively [P = .0002]). The extent of 18FDG arterial uptake was the unique factor significantly related to the occurrence of a recent event by either logistic regression or discriminant analysis (P = .004 for all). Conversely, calcium index was the single factor related to old events (P = .004 and P = .002, respectively).

CONCLUSIONS:
Extensive arterial 18FDG uptake might be an indicator of an evolving atherosclerotic process and should be mentioned in PET/computed tomography reports.

18F-FDG PET/CT identifies patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease
Feasibility of FDG Imaging of the Coronary Arteries

Comparison Between Acute Coronary Syndrome and Stable Angina

- **ACS Recently Stented**: 2.61 (IQR=2.27-3.45)
- **Stable Recently Stented**: 1.74 (IQR=1.14-2.0)
- **Stable Remotely Stented**: 1.43 (IQR=1.09-1.75)

- **ACS Aorta**: 3.30 (2.73-4.00)
- **Stable Aorta**: 2.43 (2.00-2.90)
- **ACS Left Main Coronary Artery**: 2.48 (2.30-2.93)
- **Stable Left Main Coronary Artery**: 2.00 (1.71-2.44)
Conclusions: Arterial lesions with increased 18F-FDG uptake represent transient phenomena. This data is important for the interpretation of findings of clinical trials using arterial 18F-FDG uptake as an imaging biomarker to monitor pharmacological intervention.
**BACKGROUND**

Unstable, vulnerable plaques are associated with increased microembolisation during interventions (carotid or coronary).

Has been shown that trans femoral TAVI is associated with >70% incidence of new cerebral lesion following the procedure as evaluated by diffusion-weighted magnetic resonance imaging.

Imaging modalities able to identify aortic high risk plaque could select high risk patients.

In this subset of patients anti embolic system device could be used.

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J Am Coll Cardiol 2010; 55: 1427-32
Circulation 2010; 121: 870-8
Circulation 2012;126(10):1245-55.
Aim

Detection of vulnerable plaque using 18FDG PET/CT and correlation with aortic calcification in patients scheduled for transcatheter aortic valve implantation
METHODS

Eight patients scheduled for Trans Cathether Aortic Valve Implantation underwent 18FDG PET/CT.

16 patients without aortic stenosis who underwent 18FDG PET/CT for neoplasm were reviewed.

PET/CT images of the aorta were reviewed for focal 18F-FDG activity that followed arterial contours on the fused images in 3 orthogonal planes. The intensity of 18 F-FDG uptake was quantified by measuring the maximum standardized uptake value (SUVmax). We considered significant a SUV max > 2.5

The thoracic aorta was divided into 3 segments of analysis: ascending (extending from the aortic root to the origin of the innominate artery), arch (from the origin of the innominate artery to the origin of the left subclavian artery), and descending (from the origin of the left subclavian artery to the level of the diaphragm).

The presence of calcifications was identified in a quantitative manner; calcifications were defined as regions with multiple attenuation greater than 130 Hounsfield units in the thoracic aortic wall on CT.
# Population characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Proportion)</th>
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<tbody>
<tr>
<td>TAVI</td>
<td>n=8</td>
</tr>
<tr>
<td>Female</td>
<td>4/8 (50%)</td>
</tr>
<tr>
<td>Age</td>
<td>82.4 (69-87)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4/8 (50%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1/8 (12.5%)</td>
</tr>
<tr>
<td>Patient</td>
<td>Gender</td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>CS♀</td>
<td>87y</td>
</tr>
<tr>
<td>MT♀</td>
<td>81y</td>
</tr>
<tr>
<td>CG♀</td>
<td>84y</td>
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<tr>
<td>GS♂</td>
<td>85y</td>
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<td>CC♂</td>
<td>69y</td>
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<td>VA♀</td>
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<tr>
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<tr>
<td>LB♂</td>
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<tr>
<td></td>
<td>18F-FDG</td>
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<tr>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>VV ♂, 81y</td>
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<td>RG ♂, 80y</td>
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<td>DG ♂, 69y</td>
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<td>GA ♂, 70y</td>
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<tr>
<td>GR ♀, 82y</td>
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</tr>
<tr>
<td>CG ♀, 84y</td>
<td>-</td>
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<tr>
<td>FG ♀, 81y</td>
<td>+</td>
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## Analysis per segment

<table>
<thead>
<tr>
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<th>TAVI N=8 (%)</th>
<th>No TAVI N=16 (%)</th>
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<tr>
<td><strong>FDG</strong></td>
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<tr>
<td>Asc</td>
<td>1 (12.5)</td>
<td>4 (25)</td>
<td>0.85</td>
</tr>
<tr>
<td>Arch</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Disc</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Tot</td>
<td>1 (4.1)</td>
<td>4 (8.3)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

|                  |              |                  |      |
| **Calcification**|              |                  |      |
| Asc              | 5 (62.5)     | 2 (6.2)          | 0.039|
| Arch             | 8 (100)      | 10 (62.5)        | 0.13 |
| Disc             | 8 (100)      | 7 (43.7)         | 0.025|
| Tot              | 21 (87.5)    | 19 (39.6)        | <0.001|
Conclusion

Aortic 18F-FDG uptake is rare in patients > 80y

No relationship between arterial 18F-FDG uptake and calcification

High calcification rate

(TAVI patients > No TAVI patients)
Advantages

✓ Morphological and metabolic information
✓ FDG is widely available
✓ FDG uptake reflects atherosclerotic plaque inflammation

Limitations

✓ Limited spatial resolution (Requires CT or MRI for co-registration)
✓ Radiation burden
✓ Cost
✓ Meaning of FDG uptake?
Conclusions

Non invasive detection of plaque vulnerability in vivo is becoming a reality.

There is an ongoing evidence that the presence of vulnerable plaques is associated with an increased risk of subsequent acute ischemic events.

Therefore, before these methods can be implemented into daily clinical routine, their diagnostic and predictive accuracy need to be evaluated in large groups of patients.

We need to learn which of the different morphological, molecular, biological features of vulnerable plaques are clinically relevant to the outcome of patients.
"The real voyage of discovery consists not in seeking new landscapes, but in having new eyes."

Marcel Proust