Nuclear Imaging Approach to Plaque Characterization

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Contents

• Overview of plaque nuclear imaging
• $^{18}$F-FDG PET/CT in plaque characterization
• $^{18}$F-sodium fluoride PET/CT in plaque characterization
• $^{18}$F-GP1 PET/CT in plaque characterization
• Other tracers
Cardiovascular Atherosclerotic Disease

• Leading cause of death in western countries

• Korea: cause of death in 35%

• Preventing acute coronary events and their sequelae

• Identifying patients at increased risk → intensive care

• Various kinds of risk stratification systems: low hazard rate
Vulnerable Plaque Concept

Different Types of Vulnerable Plaque

- Future Culprit Plaque, high-risk plaque, unstable plaque
- All thrombosis-prone plaques and plaques with a high probability of undergoing rapid progression, thus becoming culprit plaques

Vulnerable Plaque - Major Criteria

- Active Inflammation
- A thin cap with a large lipid core
- Endothelial denudation with superficial platelet aggregation
- Fissured/injured plaque
- Severe stenosis
Vulnerable Plaque - Minor Criteria

- Superficial calcified nodules
- Yellow color
- Intraplaque hemorrhage
- Endothelial dysfunction
- Expansive (positive) remodeling
Molecular Targets for Nuclear Imaging

Superficial platelet aggregation

# Nuclear Imaging

<table>
<thead>
<tr>
<th>Process</th>
<th>Target</th>
<th>Probe</th>
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<tbody>
<tr>
<td><strong>Inflammation</strong></td>
<td>Macrophages</td>
<td>$^{99m}$Tc-MCP-1 [1]</td>
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<tr>
<td></td>
<td>Chemokine (C-C motif) receptor 2 (Ccr2)</td>
<td>$^{11}$C-choline [2]</td>
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<td>Choline metabolic activity</td>
<td>$^{18}$F-fluorocholine [3]</td>
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<td>Translocator protein (TSPO)</td>
<td>$^{123}$I-DPA-713 [4]</td>
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<td>Somatostatin receptor subtype 2</td>
<td>$^{11}$C-PK11195 [5]</td>
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<td>Phosphatidyl serine receptor</td>
<td>$^{64}$Cu-DOTATATE [6, 7]</td>
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<td>Foam cell, M1 macrophage</td>
<td>$^{111}$In-PS200 [9]</td>
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<td><strong>Glucose metabolic activity</strong></td>
<td>$^{18}$F-FDG [10]</td>
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<td>M2 macrophage</td>
<td>$^{18}$F-FDM [11]</td>
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<td>Mannose receptor</td>
<td>$^{99m}$Tc-/$^{123}$I-IL-2 [12]</td>
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<td>Lymphocyte</td>
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<td><strong>Lipid core and fibrous cap formation</strong></td>
<td>Lipoprotein(OxLDL)</td>
<td>$^{123}$I-AHP [13]</td>
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<td>LOX-1 (scavenger receptor)</td>
<td>$^{99m}$Tc-LOX-1-mAb [14]</td>
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<td>Fatty acid synthesis</td>
<td>$^{11}$C-Acetate [15]</td>
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<td><strong>Apoptosis</strong></td>
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<td>Caspase-3</td>
<td>$^{18}$F-isatin derivatives [17]</td>
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<td>Membrane alteration</td>
<td>$^{18}$F-ML-10 [18]</td>
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<td><strong>Angiogenesis</strong></td>
<td>VEGF receptor</td>
<td>$^{89}$Zr-VEGF-mAb [19]</td>
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<td>Integrin-$\alpha$, $\beta_3$</td>
<td>$^{18}$F-galacto-RGD [20]</td>
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<td><strong>Hypoxia</strong></td>
<td>Hypoxia</td>
<td>$^{18}$F-FMISO [22]</td>
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<td><strong>Proteolysis</strong></td>
<td>MMPs</td>
<td>$^{99m}$Tc-/$^{111}$In-/$^{123}$I-/$^{18}$F-MMP inhibitors [23]</td>
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<td>$^{99m}$Tc-MT1-MMP-mAb [24]</td>
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<td><strong>Thrombosis</strong></td>
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<td>Tissue factor (TF)</td>
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<tr>
<td><strong>Calcification</strong></td>
<td>Mineral deposition/active calcification</td>
<td>$^{18}$F-NaF [27, 28]</td>
</tr>
</tbody>
</table>

¹⁸F-FDG PET/CT

- Glucose analogue
- High uptake in active inflammatory cells such as macrophage
- Whole body hybrid imaging
- Quantification
- Clinically available
CT coronal

PET/CT coronal

PET/CT axial

Histopathology axial

Calcified plaque

High FDG uptake

Low FDG uptake

FDG uptake (TBR)

Macrophage Density

$R = 0.70, P < .001$

Clinical Results

• Aortic FDG uptake: predictor for future CVD events, incremental predictive value above the coronary artery calcium and Framingham Risk Score

• Carotid FDG uptake: predictor for recurrent ipsilateral cerebrovascular events

• FDG PET in drug clinical trial

Experienced subsequent CVD event

Carotid imaging

Did not experience subsequent CVD event

Aortic imaging

FDG PET/CT in Drug Trial


Samsung Medical Center
Limitations

• Lack of large prospective clinical trials
• Various kinds of quantitation methods
• Significant overlap in values
• Low spatial resolution of PET: coronary plaque
• Myocardial physiological uptake
• Motion artifact: respiration, cardiac motion
$^{18}$F-Sodium Fluoride PET/CT

- To identify areas of calcification, active calcification and micro-calcification of vulnerable plaque
- Low myocardial background uptake, clinically available
- Clinical results
  - High uptake in culprit coronary plaques
  - High uptake associated with high-risk features on IVUS
  - High correlation with clinical CV risk, coronary artery calcium score
- Limitations: lack of good clinical outcome studies

$^{18}$F-Sodium Fluoride PET/CT
18F-Sodium Fluoride PET/CT

Figure 3

10-Year Framingham Risk Scores for Control Subjects and Patients With Atherosclerosis Who Did and Did Not Have Increased 18F-NaF Uptake

Error bars denote the SD of the mean. 18F-NaF = 18F-sodium fluoride; CHD = coronary heart disease; CVD = cardiovascular disease.

# FDG vs. NaF PET/CT

<table>
<thead>
<tr>
<th>18F-Fluoride uptake (n = 27)</th>
<th>18F-FDG uptake (n = 34)</th>
<th>Arterial calcification (n = 34)</th>
<th>Total no. of patients (n = 45)</th>
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<tbody>
<tr>
<td>PET-positive</td>
<td>PET-positive</td>
<td>CT-positive</td>
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<tr>
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<td>CT-negative</td>
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<tr>
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<td>PET-negative</td>
<td>CT-positive</td>
<td>1</td>
</tr>
<tr>
<td>PET-negative</td>
<td>PET-positive</td>
<td>CT-negative</td>
<td>7</td>
</tr>
<tr>
<td>PET-negative</td>
<td>PET-positive</td>
<td>CT-negative</td>
<td>1</td>
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<tr>
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<tr>
<td>PET-negative</td>
<td>PET-negative</td>
<td>CT-negative</td>
<td>9</td>
</tr>
</tbody>
</table>

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**Graph 1**: Comparison of TBRmax between 18F-FDG and 18F-NaF. The graph shows a significant increase in TBRmax for 18F-NaF compared to 18F-FDG. * indicates statistical significance.

**Graph 2**: Comparison of Hounsfield units (HU) for calcium density at baseline and follow-up. The graph shows a significant increase in Hounsfield units for both 18F-FDG and 18F-NaF at follow-up. * indicates statistical significance.

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FDG vs. NaF PET/CT

A $^{18}$F-sodium fluoride

B $^{18}$F-fluorodeoxyglucose

Novel PET Imaging

- $^{68}$Ga-DOTATATE: somatostatin receptor on inflammatory cells, associated with coronary calcium score, CV risk
- $^{11}$C-PK11195 (targeting translocator protein receptors), $^{18}$F-fluoromethylcholine (FMCH), $^{18}$F-fluorodeoxymannose (FDM): activated macrophage, preclinical results on stroke, carotid, aorta
- $^{68}$Ga-NOTA-RGD and $^{18}$F-Galacto-RGD: neoangiogenesis
- $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO): hypoxia
- $^{18}$F-GP1: activated platelet

18F-GP1 PET/CT

- High affinity for glycoprotein IIb/IIIa (GPIIb/IIIa) receptor of activated platelet
- Vulnerable plaque in atherosclerosis: endothelial denudation with superficial platelet aggregation
- Originally developed for venous thrombosis imaging
- Promising imaging modality for vulnerable plaque imaging
- Available in Korea
  - Cooperation between Bayer and AMC
  - Ongoing phase I clinical trial
  - Planned phase II-III clinical trial

Pre-clinical Study

Microtiter plates coated with human GPIIa/IIIb

Autoradiography of human left ventricular thrombus

Pre-clinical Study

In vitro blood flow model

PET imaging of $^{18}$F-GP1 thrombus binding in the in vitro blood flow model

Pre-clinical Study

18F-GP1 PET of arterial thrombi in cynomolgus monkeys.

Pre-clinical Study

$^{18}$F-GP1 PET of both arterial and venous thrombi in cynomolgus monkeys.

Clinical Study

• Interim analysis of an open-label, single center phase I study

• Patients with deep vein thrombosis (DVT, n=4), pulmonary embolism (PE, n=5) or arterial thromboembolism (ATE, n=6: one cerebral infarction, and 5 subjects after endovascular abdominal aortic aneurysm repair) who had acute thromboembolic focus/foci confirmed by standard imaging modalities

• $^{18}$F-GP1 dynamic PET/CT, no drug-related adverse events
Clinical Study

• Results by visual assessment
  - Patient-based sensitivity: 100% (15/15)
  - Lesion-based sensitivity: 100% in DVT (18/18), 75% in PE (18/24), 86% in ATE (6/7)

• Quantitative results
  - SUV ratio (SUVR): lesion vs. reference tissue
    - DVT: 5.89 ± 2.71 (SUV_{max}), 4.97 ± 1.85 (SUVR)
    - PE: 4.99±2.35 (SUV_{max}), 4.24±2.01 (SUVR)
    - ATE: 5.07±1.95 (SUV_{max}), 5.34±2.17 (SUVR)
  - Clinically unexpected additional thromboembolic lesions: 47% (7/15)

Summary

• Carotid and aortic FDG uptake is associated with future cardiovascular and cerebrovascular events. However, further large prospective clinical trial is necessary.
• Coronary NaF uptake is associated with vulnerable coronary plaque. However, further clinical outcome study is necessary.
• FDG and NaF uptakes reflect different pathology of atherosclerotic plaque.
• $^{18}$F-GP1 PET/CT may be a promising imaging modality for DVT, PE or ATE with a high sensitivity, which deserves further study for plaque characterization.
Thank you for your attention!